

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211243Orig1s004

Trade Name: SPRAVATO

Generic or Proper Name: (esketamine)

Sponsor: Janssen Pharmaceuticals Inc.

Approval Date: July 31, 2020

Indication: SPRAVATO® is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 211243/S-004

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Patricia K. Treichler, RAC
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Treichler:

Please refer to your supplemental new drug application (sNDA) dated October 2, 2019, received October 2, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spravato (esketamine) nasal spray.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 2, 2019.

This Prior Approval supplemental new drug application provides for the following changes: 1) modifications to the approved risk evaluation and mitigation strategy (REMS) and 2) a new indication for the depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We are waiving the pediatric studies requirement for ages 0 to 8 years because necessary studies are impossible or highly impracticable. This is because of the rare incidence of the condition in this pediatric population. Furthermore, study enrollment in this patient population is also considered highly impracticable due to the limited number of patients in this age group.

We are deferring submission of your pediatric studies for ages 9 to <18 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

- 3915-1 Double-blind, double-dummy, randomized, active-controlled dose-response efficacy and safety study in pediatric subjects with major depressive disorder ages 9 to <18.

Final Protocol Submission: 05/2017 (submitted)

Study Completion: 06/2022

Final Report Submission: 11/2022

- 3915-2 Double-blind, double-dummy, randomized, active-controlled study in pediatric subjects with major depressive disorder ages 9 to <18.

Final Protocol Submission: 07/2022

Study Completion: 04/2025

Final Report Submission: 09/2026

- 3915-3 Open-label safety study in pediatric subjects with major depressive disorder ages 9 to <18

Final Protocol Submission: 07/2023

Study Completion: 04/2026

Final Report Submission: 09/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Submit the protocol(s) to your IND 129516, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for SPRAVATO (esketamine) was originally approved on March 5, 2019, and the most recent modification was approved on June 25, 2019. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of changing the requirements for the certified healthcare setting based on inpatient or outpatient setting in the REMS document; aligning the patient enrollment form, REMS website, and REMS Program Overview with these requirements; and replacing the single healthcare setting enrollment form with setting specific enrollment forms.

Your proposed modified REMS, submitted on October 9, 2019, and amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 5, 2019.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Program Implementation (2-year assessment only)
 - a. Date when the SPRAVATO REMS website became live and fully operational
 - b. Date when inpatient and outpatient healthcare settings could become certified
 - c. Date when pharmacies could become certified
 - d. Date when outpatients could become enrolled
 - e. Date when the REMS Coordinating Center was and fully operational with new

2. REMS Program Operation and Performance Data (per reporting period and cumulatively)

a. REMS Website

- i. Number of visits and unique visits to the REMS Program website
- ii. Number of REMS materials downloaded or printed for each material

b. REMS Coordinating Center

- i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, inpatient healthcare settings, outpatient healthcare settings, wholesaler/distributors, other)
- ii. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) and by reporter (authorized representative, healthcare setting, patient/caregiver, other)
- iii. Summary of frequently asked questions (FAQ) by stakeholder type
- iv. Summary report of REMS-related problems identified and resulting corrective actions

3. REMS Enrollment Statistics (per reporting period and cumulatively)

a. Certified Inpatient and Outpatient Healthcare Settings

- i. Number of newly enrolled and active inpatient and outpatient healthcare settings (active settings are those that have received shipments of SPRAVATO) stratified by type of healthcare setting (i.e., group practice, independent practice, outpatient clinic, hospital-inpatient, hospital emergency department, mental health facility, other), and geographic region (defined by the U.S. Census)
- ii. Number of outpatient healthcare settings that dispensed/provided SPRAVATO for administration stratified by the healthcare setting type and geographic region (defined by the U.S. Census); outpatient healthcare settings that dispense/provide SPRAVATO administration are defined as having at least one patient with at least one treatment of SPRAVATO as evidenced by submission of a *Patient Monitoring Form*
- iii. Healthcare settings that were unable to become certified and reasons why

b. Certified Pharmacies

- i. Number of newly enrolled and active pharmacies (active pharmacies defined as those that have received SPRAVATO) stratified by type of pharmacy (i.e., Retail, Specialty, other) and geographic region (defined by the U.S. Census)
 - ii. Pharmacies that were unable to become certified and reasons why
 - c. Contracted Wholesalers/Distributors
 - i. Number of newly contracted and active wholesalers/distributors (active wholesalers/distributors defined as those that have shipped SPRAVATO)
 - ii. Number of contracted wholesalers/distributors that shipped SPRAVATO
 - d. Enrolled Outpatients
 - i. Number of newly enrolled and active outpatients (outpatients who have administered at least one dose of SPRAVATO) stratified by age, sex, and geographic region (defined by the U.S. Census)
- 4. SPRAVATO Utilization Data
 - a. The number of devices distributed to certified inpatient healthcare settings, outpatient healthcare settings, and pharmacies
 - b. Number of treatments administered at certified outpatient healthcare settings (first treatment session and subsequent treatment sessions) stratified by:
 - i. Healthcare Setting type
 - ii. Prescriber specialty, professional degree/credentials, geographic region (defined by the U.S. Census)
 - iii. Patient demographics (e.g., age, sex, geographic region (Defined by the U.S. Census))
- 5. REMS Compliance (per reporting period and cumulatively, starting with the 1-year Assessment)
 - a. Provide a summary report of non-compliance identified, including but not limited to:
 - i. Provide a copy of the SPRAVATO REMS Compliance Assessment Action Plan including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what

circumstances a stakeholder would be suspended or decertified from the REMS

- ii. Provide a copy of the audit plan for each stakeholder
- iii. Report of audit findings for each stakeholder group (certified Healthcare Settings, certified Pharmacies, and contracted wholesalers/distributors)
 - The number of audits expected, and the number of audits performed
 - The number and types of deficiencies noted for each group of audited stakeholders
 - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within 1 month of audit
 - For any that did not complete the CAPA within 1 month of the audit, describe actions taken
 - Include a unique identification (ID) for each stakeholder that had deviations to track deviations by stakeholder over time
 - Documentation of completion of training for relevant staff
 - The existence of documented processes and procedures for complying with the REMS Program, including ensuring that patients are not given SPRAVATO for home use
 - Verification for each audited stakeholder's site that the designated authorized representative remains the same; if different, include the number of new authorized representatives and verification of the sites' recertification
 - Any of elements stated in 5. b-d. of this Assessment Plan that are noted as observations in the audit
 - Any other SPRAVATO REMS non-compliance, source of report, and resulting corrective actions
- b. Healthcare Settings (for each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken):

- i. The number and type of certified Healthcare Settings for which noncompliance with the REMS Program is detected
- ii. The number and type of non-certified Healthcare Settings that administered SPRAVATO and the number of incidents for each
- iii. The number of times a Healthcare Setting (certified or non-certified) or a Pharmacy (certified or non-certified) dispensed SPRAVATO for use outside of the certified Healthcare Setting
- iv. Number of times SPRAVATO was distributed, transferred, or loaned from one Healthcare Setting (certified or non-certified) to another
- v. The number of certified Healthcare Settings suspended or de-certified for non-compliance with REMS Program requirements and reasons for such actions
- vi. The number of patients who received a SPRAVATO administration in an outpatient setting that were not enrolled
- vii. Number of patients treated in an outpatient setting who were not observed for at least 2 hours after administration based on the *Patient Monitoring Form*:
 - Number of events
 - Number of outpatient healthcare settings
 - Number of events per patient and per administration
 - Number of patients who refused to comply with the 2 hours monitoring after administration
- c. Certified Pharmacies (for each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken):
 - i. The number of certified Pharmacies for which non-compliance with the REMS Program is detected
 - ii. The number and type of non-certified Pharmacies that dispensed SPRAVATO and the number of incidents for each
 - iii. The number of certified Pharmacies suspended or de-certified for non-compliance with REMS Program requirements and reasons for such actions

- d. Wholesalers/Distributors (for each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken):
 - i. The number of contracted wholesalers/distributors for which non-compliance with the REMS Program is detected
 - ii. The number and type of non-contracted wholesalers/distributors that shipped SPRAVATO and the number of incidents for each
 - iii. The number of instances where contracted wholesalers/distributors shipped SPRAVATO directly to non-certified Healthcare Settings, noncertified Pharmacies, or directly to Patients
 - iv. The number of contracted wholesalers/distributors suspended for non-compliance with REMS Program requirements and reasons for such actions

Safe Use Behaviors

6. *Patient Monitoring Forms* – Outpatient Use Only (per reporting period and cumulatively)
 - a. Number of SPRAVATO REMS *Patient Monitoring Forms* received as of the assessment report cut-off date by the number of active outpatients
 - b. Number of *Patient Monitoring Forms* not received within 60 calendar days from the date of submission of the *Patient Enrollment Form*; include outreach activities performed to collect the forms and the reasons why the forms were not submitted
 - c. Number of *Patient Monitoring Forms* outstanding from previous reporting periods
 - d. Any other evidence that safe use was not demonstrated (patient was not monitored for sufficient period or appropriate monitoring was not done)

Health Outcomes and/or Surrogates of Health Outcomes

7. Safety Surveillance (per reporting period and cumulatively)
 - a. Known, or suspected adverse events related to abuse or misuse of SPRAVATO, as well as known or suspected cases of sedation, dissociation, and changes in vital signs (e.g., an increase in blood pressure) are to be reported regardless of outcome. Root cause analyses of whether REMS Program processes for patient monitoring were followed are to be included; sources of the reports are to include but are not limited to:

i. The SPRAVATO REMS *Patient Monitoring Form* – Outpatient Use Only

- Number of patients with sedation or dissociation and whether they required medical intervention and number of patients with a blood pressure increase reported on the *Patient Monitoring Forms*, including:
 - Number of patients with sedation, dissociation, or a blood pressure increase reported on the *Patient Monitoring Form* stratified by the total dose administered
 - Provide the number of patients where the time to resolution of sedation and dissociation symptoms was greater than 2 hours
- Number of patient treatment sessions with sedation or dissociation, whether the events required medical intervention, and number of treatment sessions with a blood pressure increase reported on the *Patient Monitoring Forms*, including:
 - Those events that resulted in monitoring greater than 2 hours in each treatment session; include the mean, median, and range of time to resolution
 - Number of treatment sessions with sedation, dissociation, or a blood pressure increase reported on the *Patient Monitoring Form* stratified by the total dose administered.
- Number of patients with serious adverse events reported on the *Patient Monitoring Forms*
- Number of patients who were considered ready for discharge prior to the 2-hour monitoring period reported on the *Patient Monitoring Forms*; provide the time in minutes from start of SPRAVATO administration to when the patient is considered ready for discharge; include the mean, median, and range
- Number of patients who were ready for discharge after the 2-hour monitoring period reported on the *Patient Monitoring Forms*
- Number of adverse events reported on the *Patient Monitoring Form* stratified by the total dose administered
- Number of adverse events linked to patients who were not monitored for 2 hours

- Trend analysis of whether adverse events decrease or increase over time
- ii. Adverse events reported in the REMS registry
- iii. Spontaneous adverse event reports
 - Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
 - Include a line listing of all serious adverse event cases that includes manufacturer control number, narrative, assessment of causality, and source of the report
- iv. Literature searches
- v. Social media
- vi. National databases that include poison center calls as well as data regarding drug diversion
- b. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, or communication
- 8. Knowledge, Attitudes, and Behavior (KAB) stakeholder surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report) to assess stakeholders' understanding of the risks of serious adverse outcomes from sedation and dissociation as a result of SPRAVATO administration and from the abuse and misuse of SPRAVATO and the REMS requirements to ensure safe use for patients; stakeholders include:
 - a. Authorized representatives and healthcare providers within the certified Healthcare Settings
 - b. Enrolled Patients
- 9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

1. An evaluation of how the benefit-risk profile will or will not change with the new indication.
2. A determination of the implications of a change in the benefit-risk profile for the current REMS.
3. *If the new indication for use introduces unexpected risks*, a description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
4. *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*, a statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
5. *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use*, provision of as many of the currently listed assessment plan items as is feasible.
6. *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use*, submit an adequate rationale to support the modification including a provision of the reason(s) why the proposed REMS modification is necessary; the potential effect on the serious risk(s) for which the REMS was required, potential effect on patient access to the drug, and potential effect on the associated health care delivery system burden; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing

the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211243 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,
AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 211243 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 211243/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 211243/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 211243/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 211243/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 211243

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Shin-Ye (Sandy) Chang, Regulatory Project Manager, at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Acting Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - Instructions for Use
- REMS

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/

TIFFANY R FARCHIONE
07/31/2020 06:36:13 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO® safely and effectively. See full prescribing information for SPRAVATO®.

SPRAVATO® (esketamine) nasal spray, CIII

Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)
- Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)
- SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)

RECENT MAJOR CHANGES

Indications and Usage (1)	07/2020
Dosage and Administration (2.3, 2.6)	07/2020
Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	07/2020

INDICATIONS AND USAGE

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults. (1)
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. (1)

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO. (1)
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

DOSAGE AND ADMINISTRATION

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)

- Assess blood pressure prior to and after administration. (2.1)
- *TRD* Evidence of therapeutic benefit should be evaluated at the end of the 4-week induction phase to determine need for continued treatment. (2.2)
- *Depressive symptoms in MDD with acute suicidal ideation or behavior:* Evidence of therapeutic benefit should be evaluated after 4 weeks to determine need for continued treatment. Treatment beyond 4 weeks has not been systematically evaluated. (2.3)
- See Full Prescribing Information for recommended dosage. (2.2, 2.3)
- See Full Prescribing Information for important administration instructions. (2.4)

DOSAGE FORMS AND STRENGTHS

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

CONTRAINDICATIONS

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- *Increases in Blood Pressure* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant):

- TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)
- Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation

- Patients are at risk for sedation after administration of SPRAVATO *[see Warnings and Precautions (5.1)]*.

Dissociation

- Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO *[see Warnings and Precautions (5.2)]*.

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting *[see Warnings and Precautions (5.1, 5.2)]*.

Abuse and Misuse

- SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse *[see Warnings and Precautions (5.3)]*.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS *[see Warnings and Precautions (5.4)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

SPRAVATO[®] is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated [*see Clinical Studies (14.2)*]. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Important Considerations Prior to Initiating and During Therapy

SPRAVATO must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of SPRAVATO and post-administration observation under supervision.

Blood Pressure Assessment Before and After Treatment

- Assess blood pressure prior to dosing with SPRAVATO [*see Warnings and Precautions (5.6)*].
- If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATO treatment [*see Warnings and Precautions (5.6)*]. Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk [*see Contraindications (4)*].
- After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes (which corresponds with the C_{max}) and subsequently as clinically warranted.
- If blood pressure is decreasing and the patient appears clinically stable for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor [*see Warnings and Precautions (5.6)*].

Food and Liquid Intake Recommendations Prior to Administration

Because some patients may experience nausea and vomiting after administration of SPRAVATO [*see Adverse Reactions (6.1)*], advise patients to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.

Nasal Corticosteroid or Nasal Decongestant

Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before SPRAVATO [see *Clinical Pharmacology* (12.3)].

2.2 Treatment-Resistant Depression

Administer SPRAVATO in conjunction with an oral antidepressant (AD).

The recommended dosage of SPRAVATO for the treatment of TRD in adults is shown in Table 1. Dosage adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

Table 1: Recommended Dosage for SPRAVATO for TRD

		Adults
Induction Phase	<u>Weeks 1 to 4:</u>	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	<u>Weeks 5 to 8:</u>	
	Administer once weekly	56 mg or 84 mg
	<u>Week 9 and after:</u>	
	Administer every 2 weeks or once weekly*	56 mg or 84 mg

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

2.3 Depressive Symptoms in Patients with Major Depressive Disorder with Acute Suicidal Ideation or Behavior

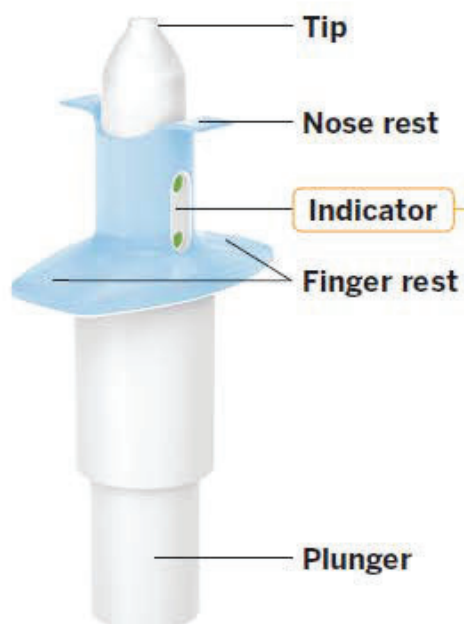
Administer SPRAVATO in conjunction with an oral antidepressant (AD).

The recommended dosage of SPRAVATO for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. After 4 weeks of treatment with SPRAVATO, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of SPRAVATO, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior.

2.4 Administration Instructions

SPRAVATO is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device. Follow these administration instructions and read the *Instructions for Use* before administration:

Nasal Spray Device

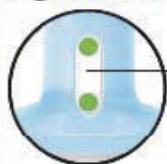


Each device delivers two sprays containing a total of 28 mg of esketamine.

Indicator

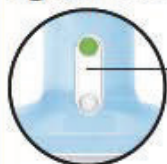
One device contains 2 sprays.
(1 spray for each nostril)

2 green dots (0 mg delivered)



Device full

1 green dot



One spray delivered

No green dots

Two sprays (28 mg) delivered



Device empty

Step 1 Get ready

Before first device only:



Instruct patient to blow nose **before first device only**.



Confirm required number of devices.

56 mg = 2 devices

84 mg = 3 devices

Step 2 Prepare device



Healthcare professional:

- Check expiration date ('EXP'). If expired, get a new device.
- Peel blister and remove device.



Healthcare professional:

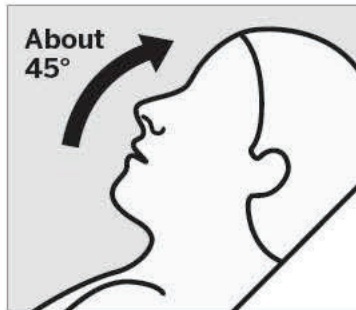
- **Do not prime device.** This will result in a loss of medication.
- Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.
- Hand device to patient.

Step 3 Prepare patient



Instruct the patient to:

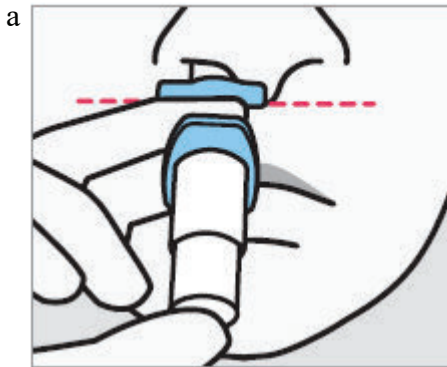
- Hold device as shown with the thumb gently supporting the plunger.
- **Do not** press the plunger.



Instruct the patient to:

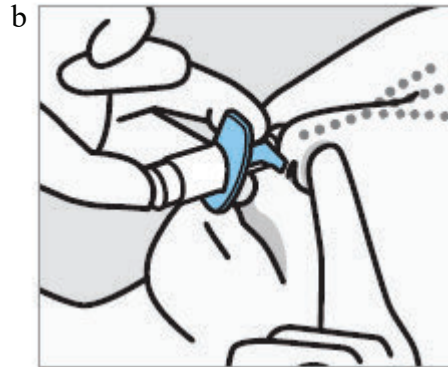
- Recline head at about **45 degrees** during administration to keep medication inside the nose.

Step 4 Patient sprays once into each nostril



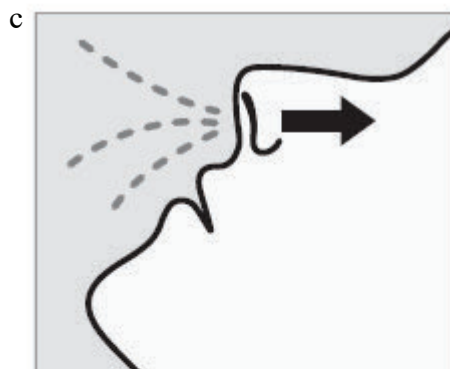
Instruct the patient to:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.



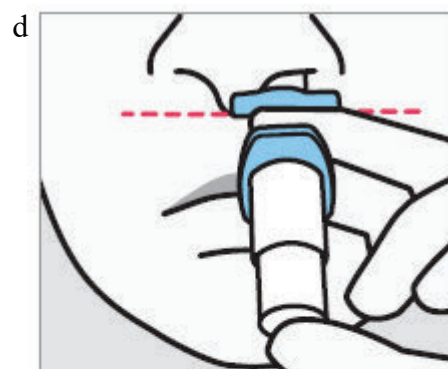
Instruct the patient to:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.



Instruct the patient to:

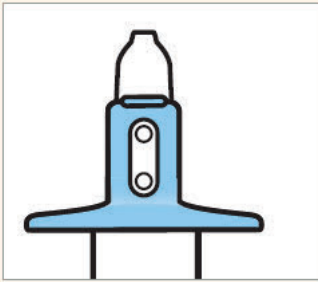
- **Sniff gently** after spraying to keep medication inside nose.



Instruct the patient to:

- Switch hands to insert tip into the **second nostril**.
- Repeat Step 4 to deliver second spray.

Step 5 Confirm delivery and rest



Healthcare professional:

- Take device from patient.
- **Check that indicator shows no green dots.** If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm device is empty.

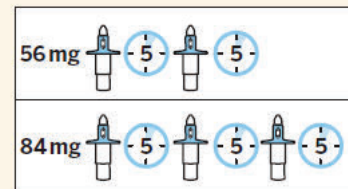


Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device.**
- If liquid drips out, dab nose with a tissue.

 **Do not blow nose.**

Next device



Healthcare professional:

- **Repeat Steps 2-5 for the next device.**

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.

Disposal

Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations.

2.5 Post-Administration Observation

During and after SPRAVATO administration at each treatment session, observe the patient for at least 2 hours until the patient is safe to leave [see *Warnings and Precautions* (5.1, 5.2, 5.6, 5.8)]. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

2.6 Missed Treatment Session(s)

If a patient misses treatment session(s), provided there is no worsening of their depressive symptoms, the patient should continue the current dosing schedule.

For patients who miss treatment session(s) during maintenance treatment and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule (e.g., if doses missed during weekly dosing, revert to twice weekly dosing).

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg esketamine.

4 CONTRAINDICATIONS

SPRAVATO is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation [see *Warnings and Precautions* (5.6)]
- History of intracerebral hemorrhage [see *Warnings and Precautions* (5.6)]
- Hypersensitivity to esketamine, ketamine, or any of the excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Sedation

In clinical trials, 48% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) [see *Adverse Reactions* (6.1)], and 0.3% to 0.4% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/S score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see *Dosage and Administration* (2.4)].

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants [see *Drug Interaction* (7.1)].

SPRAVATO is available only through a restricted program under a REMS [see *Warnings and Precautions* (5.4)].

5.2 Dissociation

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale) [see *Adverse Reactions* (6.1)]. Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see *Dosage and Administration* (2.4)].

SPRAVATO is available only through a restricted program under a REMS [see *Warnings and Precautions* (5.4)].

5.3 Abuse and Misuse

SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence [see *Drug Abuse and Dependence* (9)].

SPRAVATO is available only through a restricted program under a REMS [see *Warnings and Precautions* (5.4)].

5.4 SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse [see *Boxed Warning and Warnings and Precautions* (5.1, 5.2, 5.3)].

Important requirements of the SPRAVATO REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO is:
 - Only dispensed and administered in healthcare settings.
 - Patients treated in outpatient settings (e.g. medical offices and clinics) must be enrolled in the program.
 - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO [see *Dosage and Administration* (2.4)].
- Pharmacies must be certified in the REMS and must only dispense SPRAVATO to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies is available at www.SPRAVATOREMS.com or 1-855-382-6022.

5.5 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the

number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

Table 2: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range (Years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

* SPRAVATO is not approved in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.6 Increase in Blood Pressure

SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 4 hours [see *Adverse Reactions* (6.1)].

Approximately 8% to 19% of SPRAVATO-treated patients and 1% to 4% of placebo-treated patients experienced an increase of greater than or equal to 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage) [see *Contraindications* (4)]. Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks.

Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO administration (as a general guide: >140/90 mmHg) a decision to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO administration [see *Dosage and Administration* (2.1, 2.4)]. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs) [see *Drug Interactions* (7.2, 7.3)].

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

5.7 Cognitive Impairment

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

5.8 Impaired Ability to Drive and Operate Machinery

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive [see *Clinical Studies* (14.3)]. The effects of SPRAVATO 84 mg were comparable to placebo at 6 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of the studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions.

Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO.

5.9 Ulcerative or Interstitial Cystitis

Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients [*see Adverse Reactions (6)*]. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

5.10 Embryo-fetal Toxicity

Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Sedation [*see Warnings and Precautions (5.1)*]
- Dissociation [*see Warnings and Precautions (5.2)*]
- Increase in Blood Pressure [*see Warnings and Precautions (5.6)*]
- Cognitive Impairment [*see Warnings and Precautions (5.7)*]
- Impaired Ability to Drive and Operate Machinery [*see Warnings and Precautions (5.8)*]
- Ulcerative or Interstitial Cystitis [*see Warnings and Precautions (5.9)*]
- Embryo-fetal Toxicity [*see Warnings and Precautions (5.10)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment-Resistant Depression

SPRAVATO was evaluated for safety in 1709 adults diagnosed with treatment-resistant depression (TRD) [*see Clinical Studies (14.1)*] from five Phase 3 studies (3 short-term and 2 long-term studies) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 479 (30%) received at least 6 months of treatment, and 178 (11%) received at least 12 months of treatment.

Adverse Reactions Leading to Discontinuation of Treatment

In short-term studies in adults <65 years old (Study 1 pooled with another 4-week study), the proportion of patients who discontinued treatment because of an adverse reaction was 4.6% in patients who received SPRAVATO plus oral AD compared to 1.4% for patients who received placebo nasal spray plus oral AD. For adults ≥65 years old, the proportions were 5.6% and 3.1%, respectively. In Study 2, a long-term maintenance study, the discontinuation rates because of an adverse reaction were similar for patients receiving SPRAVATO plus oral AD and placebo nasal spray plus oral AD in the maintenance phase, at 2.6% and 2.1%, respectively. Across all Phase 3 studies, adverse reactions leading to SPRAVATO discontinuation in more than 2 patients were (in order of frequency): anxiety (1.2%), depression (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in patients treated with SPRAVATO plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Table 3 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with placebo nasal spray plus oral AD.

Table 3: Adverse Reactions Occurring in ≥2% of Adult TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD		
	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
Cardiac disorders		
Tachycardia*	6 (2%)	1 (0.5%)
Ear and labyrinth disorders		
Vertigo*	78 (23%)	6 (3%)
Gastrointestinal disorders		
Nausea	98 (28%)	19 (9%)
Vomiting	32 (9%)	4 (2%)
Diarrhea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Constipation	11 (3%)	3 (1%)
General disorders and administration site conditions		
Feeling drunk	19 (5%)	1 (0.5%)
Feeling abnormal	12 (3%)	0 (0%)

Investigations		
Blood pressure increased*	36 (10%)	6 (3%)
Nervous system disorders		
Dizziness*	101 (29%)	17 (8%)
Sedation*	79 (23%)	21 (9%)
Headache*	70 (20%)	38 (17%)
Dysgeusia*	66 (19%)	30 (14%)
Hypoesthesia*	63 (18%)	5 (2%)
Lethargy*	37 (11%)	12 (5%)
Dysarthria*	15 (4%)	0 (0%)
Tremor	12 (3%)	2 (1%)
Mental impairment	11 (3%)	2 (1%)
Psychiatric disorders		
Dissociation*	142 (41%)	21 (9%)
Anxiety*	45 (13%)	14 (6%)
Insomnia	29 (8%)	16 (7%)
Euphoric mood	15 (4%)	2 (1%)
Renal and urinary disorders		
Pollakiuria	11 (3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort*	23 (7%)	11 (5%)
Throat irritation	23 (7%)	9 (4%)
Oropharyngeal pain	9 (3%)	5 (2%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)

*

The following terms were combined:

Anxiety includes: agitation; anticipatory anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panic attack; tension

Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension

Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment

Dizziness includes: dizziness; dizziness exertional; dizziness postural; procedural dizziness

Dysarthria includes: dysarthria; slow speech; speech disorder

Dysgeusia includes: dysgeusia; hypogeusia

Headache includes: headache; sinus headache

Hypoesthesia includes: hypoesthesia; hypoesthesia oral, hypoesthesia teeth, pharyngeal hypoesthesia

Lethargy includes: fatigue; lethargy

Nasal discomfort includes: nasal crusting; nasal discomfort; nasal dryness; nasal pruritus

Sedation includes: altered state of consciousness; hypersomnia; sedation; somnolence

Tachycardia includes: extrasystoles; heart rate increased; tachycardia

Vertigo includes: vertigo; vertigo positional

Depressive Symptoms in Patients with Major Depressive Disorder with Acute Suicidal Ideation or Behavior

SPRAVATO was evaluated for safety in 262 adults for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior [see *Clinical Studies (14.2)*] from two Phase 3 studies (Study 3 and Study 4) and one Phase 2 study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 184 (81%) received all eight doses over a 4-week treatment period.

Adverse Reactions Leading to Discontinuation of Treatment

In short-term studies in adults (pooled Study 3 and Study 4), the proportion of patients who discontinued treatment because of an adverse reaction was 6.2% for patients who received SPRAVATO plus oral AD compared to 3.6% for patients who received placebo nasal spray plus oral AD. Adverse reactions leading to SPRAVATO discontinuation in more than 1 patient were (in order of frequency): dissociation-related events (2.6%), blood pressure increased (0.9%), dizziness-related events (0.9%), nausea (0.9%), and sedation-related events (0.9%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in patients treated with SPRAVATO plus oral AD (incidence $\geq 5\%$ and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. Table 4 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD and greater than patients treated with placebo nasal spray plus oral AD.

Table 4: Adverse Reactions Occurring in $\geq 2\%$ of Adult Patients with MDD and Acute Suicidal Ideation or Behavior Treated with SPRAVATO + Oral AD and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

	SPRAVATO + Oral AD (N=227)	Placebo + Oral AD (N=225)
Cardiac disorders		
Tachycardia*	8 (4%)	2 (1%)
Ear and labyrinth disorders		
Vertigo	14 (6%)	1 (0.4%)
Gastrointestinal disorders		
Nausea	61 (27%)	31 (14%)
Vomiting	26 (11%)	12 (5%)
Constipation	22 (10%)	14 (6%)
Dry mouth	8 (4%)	6 (3%)
Toothache	5 (2%)	2 (1%)
General disorders and administration site conditions		
Feeling drunk	8 (4%)	1 (0.4%)
Feeling of relaxation	5 (2%)	3 (1%)

Investigations		
Blood pressure increased*	34 (15%)	14 (6%)
Musculoskeletal and connective tissue disorders		
Myalgia	5 (2%)	1 (0.4%)
Nervous system disorders		
Dizziness*	103 (45%)	34 (15%)
Sedation*	66 (29%)	27 (12%)
Dysgeusia*	46 (20%)	29 (13%)
Hypoesthesia*	30 (13%)	4 (2%)
Lethargy*	10 (4%)	4 (2%)
Confusional state	5 (2%)	0 (0%)
Psychiatric disorders		
Dissociation*	108 (48%)	30 (13%)
Anxiety*	34 (15%)	20 (9%)
Euphoric mood	17 (7%)	1 (0.4%)
Intentional self-injury	7 (3%)	3 (1%)
Dysphoria	5 (2%)	0 (0%)
Renal and urinary disorders		
Pollakiuria*	5 (2%)	2 (1%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	10 (4%)	3 (1%)
Throat irritation	9 (4%)	5 (2%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis*	11 (5%)	5 (2%)

* The following terms were combined:
Anxiety includes: agitation; anxiety; anxiety disorder; fear; irritability; nervousness; panic attack; psychomotor hyperactivity; tension
Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
Dissociation includes: depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; hallucination; hallucination, auditory; hallucination, visual; hallucinations, mixed; hyperacusis; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred
Dizziness includes: dizziness; dizziness exertional; dizziness postural
Dysgeusia includes: dysgeusia; hypogeusia
Hyperhidrosis includes: cold sweat; hyperhidrosis
Hypoesthesia includes: hypoesthesia; hypoesthesia oral; intranasal hypoesthesia; pharyngeal hypoesthesia
Lethargy includes: fatigue; lethargy; psychomotor retardation
Pollakiuria includes: micturition urgency; pollakiuria
Sedation includes: sedation; somnolence; stupor
Tachycardia includes: heart rate increased; sinus tachycardia; tachycardia

Sedation

Sedation was evaluated by adverse event reports and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). In the MOAA/S, 5 means "responds readily to name spoken in normal tone" and 0 means "no response after painful trapezius squeeze." Any decrease in

MOAA/S from pre-dose is considered to indicate the presence of sedation, and such a decrease occurred in a higher number of patients on SPRAVATO than placebo during the short-term TRD studies. Dose-related increases in the incidence of sedation (MOAA/S score <5) were observed in a fixed-dose TRD study [see *Warnings and Precautions (5.1)*]. Table 5 presents the incidence of sedation (MOAA/S score <5) in a fixed-dose study with adult patients <65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

Table 5: Incidence of Sedation (MOAA/S Score <5) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD		Placebo + Oral AD	SPRAVATO + Oral AD
		56 mg	84 mg		28 to 84 mg
Number of patients*	N=112	N=114	N=114	N=63	N=72
Sedation (MOAA/S score <5)	11%	50%	61%	19%	49%

* Patients who were evaluated with MOAA/S

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, there was a higher incidence of sedation (MOAA/S score <5) in patients treated with SPRAVATO plus oral AD compared to patients treated with placebo plus oral AD, similar to the TRD study results in Table 5.

Dissociation/Perceptual Changes

SPRAVATO can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADSS). A CADSS total score of more than 4 indicates the presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on SPRAVATO compared to placebo during the short-term TRD studies. Dose-related increases in the incidence of dissociative symptoms (CADSS total score >4 and change >0) were observed in a fixed-dose TRD study [see *Warnings and Precautions (5.2)*]. Table 6 presents the incidence of dissociation (CADSS total score >4 and change >0) in a fixed-dose study with adult patients <65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

Table 6: Incidence of Dissociation (CADSS Total Score >4 and Change >0) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD		Placebo + Oral AD	SPRAVATO + Oral AD
		56 mg	84 mg		28 to 84 mg
Number of patients*	N=113	N=113	N=116	N=65	N=72
CADSS total score >4 and change >0	5%	61%	69%	12%	75%

* Number of patients who were evaluated with CADSS

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral AD also demonstrated a higher number (84%) with dissociation (CADSS total score >4 and change >0) compared to patients treated with placebo plus oral AD (16%).

Increase in Blood Pressure

The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients with TRD receiving SPRAVATO plus oral antidepressants [see *Warnings and Precautions* (5.6)]. Table 7 presents increases in blood pressure in short-term trials with patients <65 years of age and ≥65 years of age with TRD.

Table 7: Increases in Blood Pressure in Double-blind, Randomized, Placebo-Controlled, Short-Term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD in Adult Patients

	Patients <65 years		Patients ≥65 years	
	SPRAVATO + Oral AD N=346	Placebo + Oral AD N=222	SPRAVATO + Oral AD N=72	Placebo + Oral AD N=65
Systolic blood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolic blood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥40 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results in Table 7.

Nausea and Vomiting

SPRAVATO can cause nausea and vomiting. Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Rates of reported nausea and vomiting decreased over time across dosing sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment. Table 8 presents the incidence and severity of nausea and vomiting in a short-term study with patients with TRD.

Table 8: Incidence and Severity of Nausea and Vomiting in a Double-blind, Randomized, Placebo-Controlled, Fixed-Dose Study in Adult Patients with TRD

Treatment (+ Oral AD)		Nausea		Vomiting	
		All	Severe	All	Severe
SPRAVATO 56 mg	115	31 (27%)	0	7 (6%)	0
SPRAVATO 84 mg	116	37 (32%)	4 (3%)	14 (12%)	3 (3%)
Placebo Nasal Spray	113	12 (11%)	0	2 (2%)	0

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients demonstrated similar incidence and severity of reported nausea and vomiting compared to the TRD study results described above.

Sense of Smell

Sense of smell was assessed over time; no difference was observed between patients treated with SPRAVATO plus oral AD and those treated with placebo nasal spray plus oral AD during the double-blind maintenance phase of Study 2 [see *Clinical Studies (14.1)*].

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation [see *Warnings and Precautions (5.1)*]. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

7.2 Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure [see *Warnings and Precautions (5.6)*]. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

7.3 Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure [see *Warnings and Precautions (5.6)*]. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at

1-844-405-6185 or online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.

Risk Summary

SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women (*see Data*). Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. There are risks to the mother associated with untreated depression in pregnancy (*see Clinical Considerations*). If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

Published studies in pregnant primates demonstrate that the administration of drugs that block *N*-methyl-*D*-aspartate (NMDA) receptors during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans [*see Use in Specific Populations (8.2)*].

In an embryo-fetal reproduction study in rabbits, skeletal malformations were noted at maternally toxic doses when ketamine was intranasally administered with a No Observed Adverse Effect Level (NOAEL) at estimated esketamine exposures 0.3 times the exposures at the maximum recommended human dose (MRHD) of 84 mg/day. In addition, intranasal administration of esketamine to pregnant rats during pregnancy and lactation at exposures that were similar to those at the MRHD resulted in a delay in sensorimotor development in pups during the preweaning period and a decrease in motor activity in the post-weaning period.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Data

Animal Data

Based on published data, when female monkeys were treated intravenously with racemic ketamine at anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. This period of brain development translates into the third trimester of human pregnancy. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

Racemic ketamine was administered intranasally to pregnant rats during the period of organogenesis at doses of 15, 50, and 150 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for embryo-fetal toxicity in rats was the highest dose of 150 mg/kg/day. Estimating 50% of the exposure to be from esketamine, the NOAEL associated with esketamine plasma exposure (AUC) is 12-times the AUC exposure at the MRHD of 84 mg/day. In pregnant rabbits, racemic ketamine was administered intranasally from gestational day 6 to 18 at doses of 10, 30, and 100 mg/kg/day. The high dose was lowered from 100 to 50 mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal malformations were observed at doses ≥ 30 mg/kg/day, which were maternally toxic. The NOAEL for skeletal malformations was associated with a plasma esketamine exposure (AUC) that was 0.3 times the AUC exposure at MRHD of 84 mg/day.

Administration of esketamine to pregnant rats during pregnancy and lactation at intranasal doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat) produced AUC exposures 0.07, 0.5, and 0.7 times the MRHD of 84 mg/day, respectively. Maternal toxicity was observed at doses ≥ 15 mg/kg/day. In addition, a dose-dependent delay in the age of attainment of Preyer response reflex was observed in pups at all doses during the preweaning period. This sensory/motor developmental measure was tested starting on postnatal day (PND) 9, and the effect normalized by PND 19 in treatment groups as compared with PND 14 for the majority of the control animals. There is no NOAEL for this delay in sensory/motor response observed in pups during the preweaning period. During the postweaning period, a decrease in motor activity was observed at doses ≥ 15 mg/kg which is 0.5-times the human exposure at the MRHD of 84 mg/day. The NOAEL for maternal toxicity and decreased motor activity during the postweaning period was 4.5 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-times the AUC exposure at MRHD of 84 mg/day.

8.2 Lactation

Risk Summary

Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity (*see Data*). Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

Data

Published juvenile animal studies demonstrate that the administration of drugs that block NMDA receptors, such as ketamine, during the period of rapid brain growth or synaptogenesis, results in

widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but this window may extend out to approximately 3 years of age in humans.

8.3 Females and Males of Reproductive Potential

Contraception

Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman [see *Warnings and Precautions* (5.10) and *Use in Specific Populations* (8.1)]. However, it is not clear how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO.

8.4 Pediatric Use

The safety and effectiveness of SPRAVATO in pediatric patients have not been established. Clinical studies of SPRAVATO in pediatric patients have not been conducted.

8.5 Geriatric Use

Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO, (N=1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients [see *Clinical Pharmacology* (12.3)].

The efficacy of SPRAVATO for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥ 65 years of age. SPRAVATO was initiated at 28 mg twice weekly and could be titrated to 56 mg or 84 mg administered twice-weekly. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

8.6 Hepatic Impairment

The mean esketamine AUC and $t_{1/2}$ values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function [see *Clinical Pharmacology* (12.3)]. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended [see *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SPRAVATO contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

9.2 Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be “spaced out”. Monitoring for signs of abuse and misuse is recommended.

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a Schedule III controlled substance and has known abuse potential. In this study, the mean “Drug Liking at the Moment” and “Take Drug Again” scores for single doses of intranasal SPRAVATO (84 mg and 112 mg – the maximum recommended dose and 1.3 times the maximum recommended dose, respectively) were similar to these scores in the intravenous ketamine (0.5 mg/kg infused over 40 minutes) control group. However, these scores were greater in the SPRAVATO and ketamine groups compared to the placebo group. The 112 mg dose of intranasal SPRAVATO was associated with significantly higher scores for “Hallucinating,” “Floating,” “Detached,” and “Spaced Out” than the 84 mg dose of intranasal SPRAVATO and the intravenous ketamine dose.

9.3 Dependence

Physical dependence has been reported with prolonged use of ketamine. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dosage reduction of a drug. There were no withdrawal symptoms captured up to 4 weeks after cessation of esketamine treatment. Withdrawal symptoms have been reported after the discontinuation of frequently used (more than weekly) large doses of ketamine for long periods of time. Such withdrawal symptoms are likely to occur if esketamine were similarly abused. Reported symptoms of withdrawal associated with daily intake of large doses of ketamine include craving, fatigue, poor appetite, and anxiety. Therefore, monitor SPRAVATO-treated patients for symptoms and signs of physical dependence upon the discontinuation of the drug.

Tolerance has been reported with prolonged use of ketamine. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of

a drug is required to produce the same effect that was once obtained at a lower dose). Similar tolerance would be expected with prolonged use of esketamine.

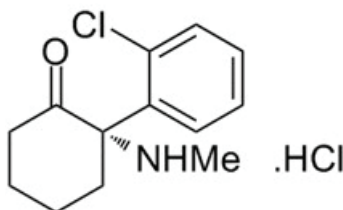
10 OVERDOSAGE

Management of Overdosage

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Contact a Certified Poison Control Center for the most up to date information on the management of overdose (1-800-222-1222 or www.poison.org).

11 DESCRIPTION

SPRAVATO® contains esketamine hydrochloride, a non-competitive *N*-methyl-*D*-aspartate (NMDA) receptor antagonist. Esketamine is the S-enantiomer of racemic ketamine. The chemical name is (*S*)-2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride. Its molecular formula is C₁₃H₁₆ClNO.HCl and its molecular weight is 274.2. The structural formula is:



Esketamine hydrochloride is a white or almost white crystalline powder that is freely soluble in water and in methanol, and soluble in ethanol.

SPRAVATO nasal spray is intended for nasal administration. Esketamine hydrochloride is contained as a solution in a stoppered glass vial within the nasal spray device. Each device delivers two sprays with a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine) in 0.2 mL of a clear, colorless aqueous solution with a pH of 4.5.

The inactive ingredients are citric acid monohydrate, edetate disodium, sodium hydroxide, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of SPRAVATO (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. A large increase in heart rate (i.e., >10 bpm) was observed in both intranasal and intravenous esketamine treatment groups. The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeutic dose of esketamine.

12.3 Pharmacokinetics

Esketamine exposure increases with dose from 28 mg to 84 mg. The increase in $C_{\max}$ and AUC values was less than dose-proportional between 28 mg and 56 mg or 84 mg, but it was nearly dose proportional between 56 mg and 84 mg. No accumulation of esketamine in plasma was observed following twice a week administration.

Absorption

The mean absolute bioavailability is approximately 48% following nasal spray administration.

The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session.

The inter-subject variability of esketamine ranges from 27% to 66% for $C_{\max}$ and 18% to 45% for AUC_{∞} . The intra-subject variability of esketamine is approximately 15% for $C_{\max}$ and 10% for AUC_{∞} .

Distribution

The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.

Protein binding of esketamine was approximately 43% to 45%.

The brain-to-plasma ratio of noresketamine is 4- to 6-times lower than that of esketamine.

Elimination

After $C_{\max}$ was reached following intranasal administration, the decline in plasma esketamine concentrations was biphasic, with rapid decline for the initial 2 to 4 hours and a mean terminal half-life ($t_{1/2}$) that ranged from 7 to 12 hours. The mean clearance of esketamine is approximately 89 L/hour following intravenous administration. The elimination of the major metabolite, noresketamine, from plasma is slower than esketamine. The decline of noresketamine plasma concentrations is biphasic, with rapid decline for the initial 4 hours and a mean terminal $t_{1/2}$ of approximately 8 hours.

Metabolism

Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. Noresketamine is metabolized via CYP-dependent pathways and certain subsequent metabolites undergo glucuronidation.

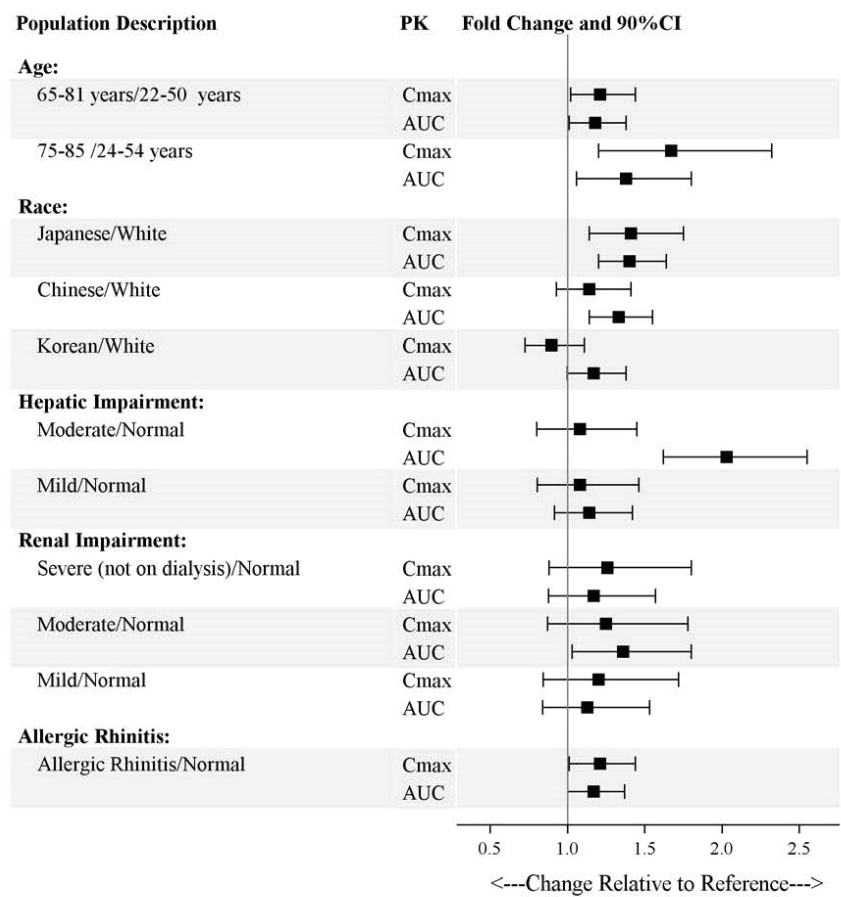
Excretion

Less than 1% of a dose of nasal esketamine is excreted as unchanged drug in urine. Following intravenous or oral administration, esketamine-derived metabolites were primarily recovered in urine ($\geq 78\%$ of a radiolabeled dose) and to a lesser extent in feces ($\leq 2\%$ of a radiolabeled dose).

Specific Populations

Exposures of esketamine in specific populations are summarized in Figure 1. No significant differences in the pharmacokinetics of SPRAVATO nasal spray were observed for sex and total body weight (>39 to 170 kg) based on population PK analysis. There is no clinical experience with SPRAVATO nasal spray in patients on renal dialysis or with severe (Child-Pugh class C) hepatic impairment.

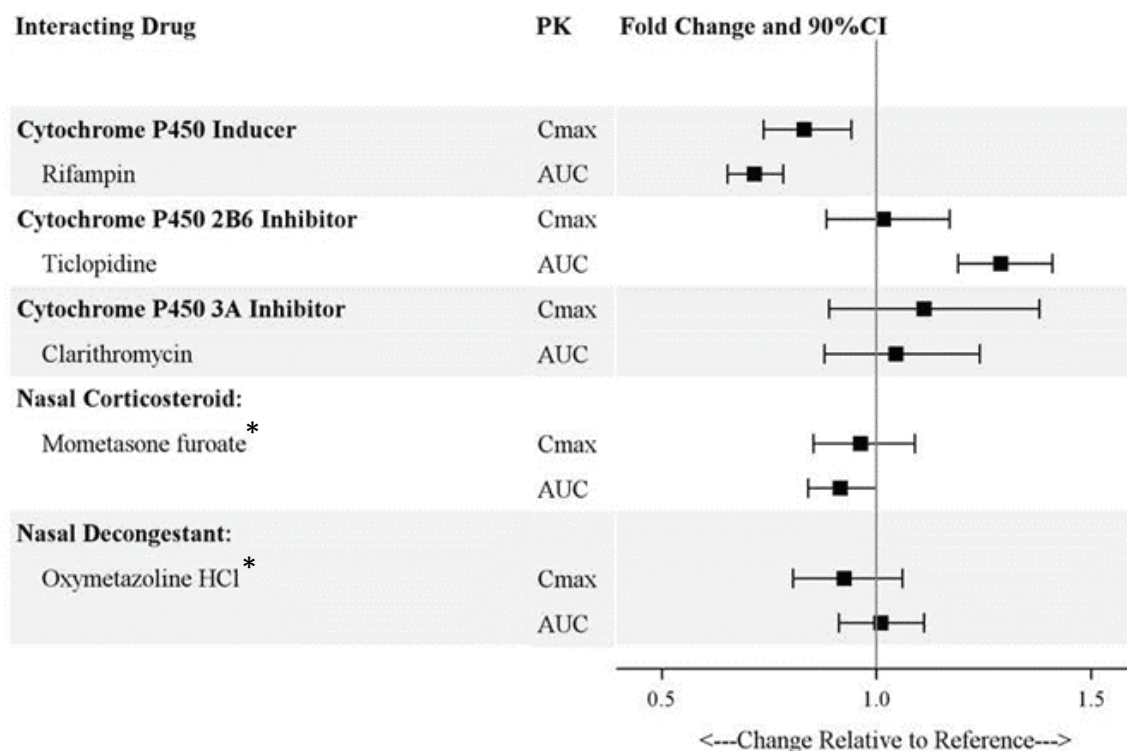
Figure 1: Effect of Specific Populations on the Pharmacokinetics of Esketamine



Drug Interaction Studies

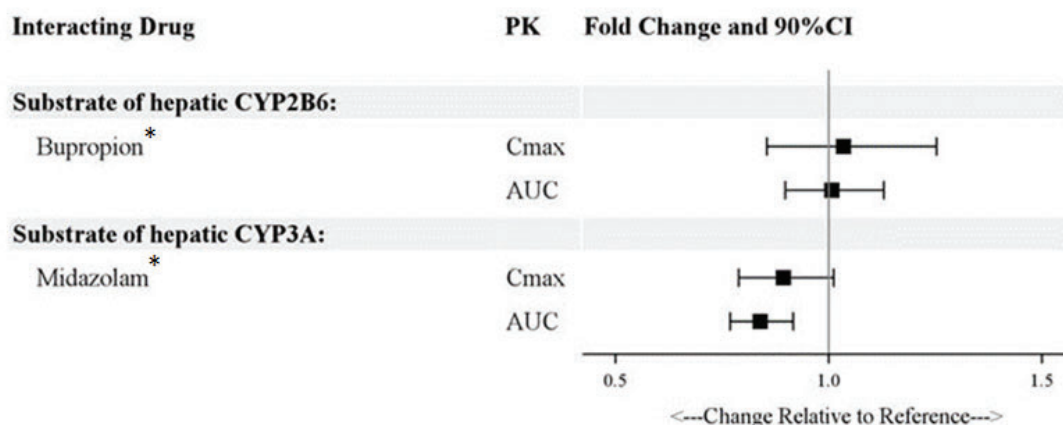
The effect of other drugs on the exposures of intranasally administered esketamine are summarized in Figure 2. The effect of SPRAVATO on the exposures of other drugs are summarized in Figure 3. Based on these results, none of the drug-drug interactions are clinically significant.

Figure 2: Effect of Co-administered Drugs on the Pharmacokinetics of Esketamine



* Administered 1 hour before intranasal esketamine

Figure 3: Effect of Esketamine on the Pharmacokinetics of Co-Administered Drugs



* The potential for cytochrome P450 induction by esketamine was assessed. Intranasal esketamine (84 mg) was administered twice weekly for 2 weeks. Bupropion or midazolam was administered at baseline and 24 hours after the last dose of esketamine.

In Vitro Studies

Enzyme Systems: Esketamine has modest induction effects on CYP2B6 and CYP3A4 in human hepatocytes. Esketamine and its major metabolites do not induce CYP1A2. Esketamine and its major circulating metabolites did not show inhibition potential against CYPs and UGTs, except for a weak reversible inhibition of noresketamine on CYP3A4.

Transporter Systems: Esketamine is not a substrate of transporters P-glycoprotein (P-gp; multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3. Esketamine and its major circulating metabolites do not inhibit these transporters or multi-drug and toxin extrusion 1 (MATE1) and MATE2-K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Once-daily intranasal administration of esketamine at doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat) did not increase the incidence of tumors in a 2-year rat carcinogenicity study. At the highest dose, the AUC exposure to esketamine was lower than the human exposure (AUC) at the maximum recommended human dose (MRHD) of 84 mg. Once-daily subcutaneous administration of esketamine up to 75 mg/kg/day (reduced to 40 mg/kg/day during week 17) did not increase the incidence of tumors in a 6-month study in transgenic (Tg.rasH2) mice.

Mutagenesis

Esketamine was not mutagenic with or without metabolic activation in the Ames test. Genotoxic effects with esketamine were seen in a screening *in vitro* micronucleus test in the presence of

metabolic activation. However, intravenously-administered esketamine was devoid of genotoxic properties in an *in vivo* bone marrow micronucleus test in rats and an *in vivo* Comet assay in rat liver cells.

Impairment of Fertility

Esketamine was administered intranasally to both male and female rats before mating, throughout the mating period, and up to day 7 of gestation at doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat), which are approximately 0.05, 0.3, and 0.6-times the maximum recommended human dose (MRHD) of 84 mg/day based on mean AUC exposures, respectively. Estrous cycle irregularities were observed at the high dose of 45 mg/kg/day and increased time to mate was observed at doses ≥ 15 mg/kg/day without an overall effect on mating or fertility indices. The No Observed Adverse Effect Level (NOAEL) for mating and fertility is 45 mg/kg/day which is 0.6 times the esketamine exposures at MRHD of 84 mg/day.

13.2 Animal Toxicology and/or Pharmacology

Neurotoxicity

In a single-dose neuronal toxicity study where esketamine was administered intranasally to adult female rats, there were no findings of neuronal vacuolation in the brain up to an estimated dose equivalent of 45 mg/kg for a 200-gram rat with a safety margin of 1.8 and 4.5 times the clinical exposures for AUC and $C_{\max}$, respectively, to the MRHD of 84 mg/day. In a second single-dose neurotoxicity study conducted with intranasally administered esketamine to adult female rats, there were no findings of neuronal necrosis up to a dose equivalent of 270 mg/kg for a 200-gram rat which has a safety margin of 18-fold and 23-fold, respectively, to AUC and $C_{\max}$ exposures at the MRHD of 84 mg/day. Neuronal vacuolation was not examined in this study.

In a single-dose neuronal toxicity study in adult rats, subcutaneously administered racemic ketamine caused neuronal vacuolation in layer I of the retrosplenial cortex of the brain without neuronal necrosis at a dose of 60 mg/kg. The NOAEL for vacuolation in this study was 15 mg/kg. Estimating 50% of the exposure to be from esketamine, the NOAEL for neuronal vacuolation is 1.6-times and 4.5-times and the NOAEL for neuronal necrosis is 10-times and 16-times exposures, respectively, for AUC and $C_{\max}$ to the clinical exposure at the MRHD of 84 mg/day. The relevance of these findings to humans is unknown.

14 CLINICAL STUDIES

14.1 Treatment-Resistant Depression

Short-Term Study

SPRAVATO was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), Phase 3 study (Study 1; NCT02418585) in adult patients 18 to <65 years old with treatment-resistant depression (TRD). Patients in Study 1 met DSM-5 criteria for major depressive disorder (MDD) and in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients in Study 1 were randomized to receive twice weekly doses of intranasal SPRAVATO (flexible dose; 56 mg or 84 mg) or intranasal placebo. All patients also

received open-label concomitant treatment with a newly initiated daily oral antidepressant (AD) (duloxetine, escitalopram, sertraline, or extended-release venlafaxine as determined by the investigator based on patient's prior treatment history). SPRAVATO could be titrated up to 84 mg starting with the second dose based on investigator discretion.

The demographic and baseline disease characteristics of patients in Study 1 were similar for the SPRAVATO and placebo nasal spray groups. Patients had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. The newly initiated oral AD was an SSRI in 32% of patients and an SNRI in 68% of patients.

In Study 1, the primary efficacy measure was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. SPRAVATO plus a newly initiated oral AD demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral AD (see Table 9).

Table 9: Primary Efficacy Results for Change from Baseline in MADRS Total Score at Week 4 in Patients with TRD in Study 1

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from Baseline to end of Week 4	LS Mean Difference (95% CI)*
SPRAVATO (56 mg or 84 mg) + Oral AD [†]	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	-

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval; AD=antidepressant

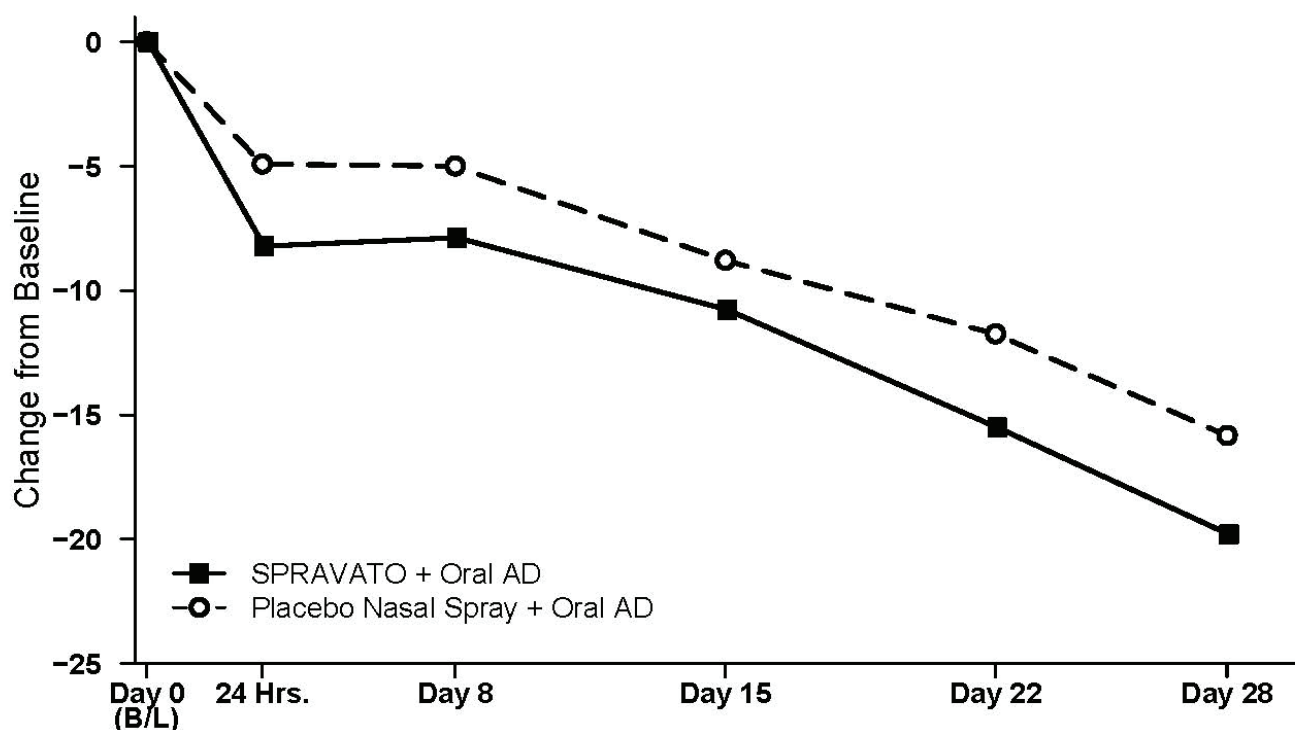
* Difference (SPRAVATO + Oral AD minus Placebo nasal spray + Oral AD) in least-squares mean change from baseline

[†] SPRAVATO + Oral AD was statistically significantly superior to placebo nasal spray + oral AD

Time Course of Treatment Response

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. At Day 28, 67% of the patients randomized to SPRAVATO were receiving 84 mg twice weekly.

Figure 4: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1* (Full Analysis Set)



* Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

Treatment-Resistant Depression – Long-term Study

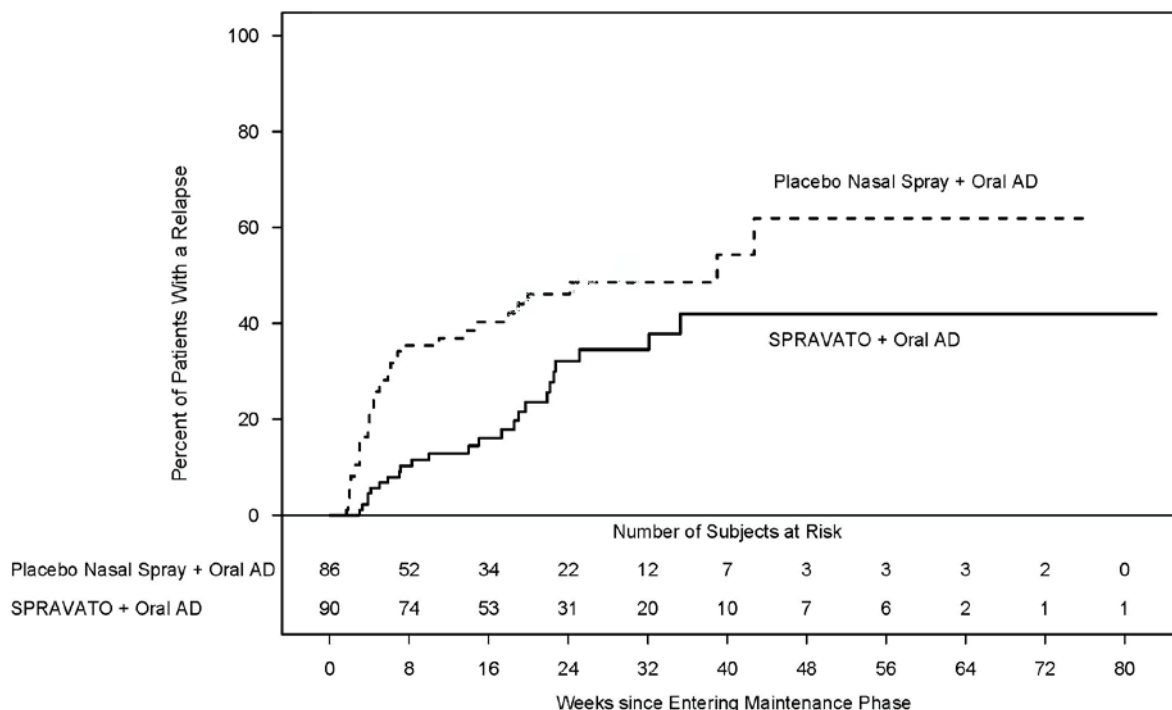
Study 2 (NCT02493868) was a long-term randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to SPRAVATO. Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly-dosed SPRAVATO (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase.

Stable remission was defined as a MADRS total score ≤ 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction $\geq 50\%$ for the last 2 weeks of optimization and not in remission. After at least 16 initial weeks of treatment with SPRAVATO and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with SPRAVATO or switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

The demographic and baseline disease characteristics of the two groups were similar. Patients had a median age of 48 years (range 19 to 64 years) and were 66% female, 90% Caucasian, and 4% Black.

Patients in stable remission who continued treatment with SPRAVATO plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (see Figure 5).

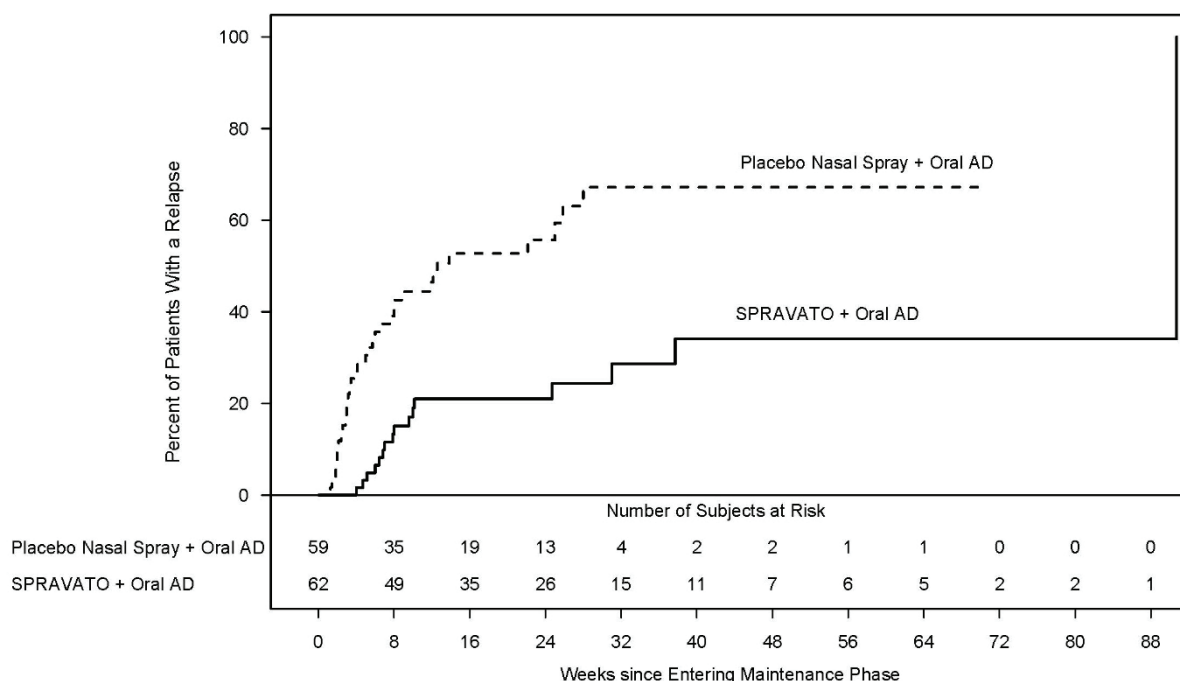
Figure 5: Time to Relapse in Patients with TRD in Stable Remission in Study 2* (Full Analysis Set)



* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on weighted estimates was 0.49 (95% CI: 0.29, 0.84). However, the hazard ratio did not appear constant throughout the trial.

Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time to relapse of depressive symptoms than patients on placebo nasal spray plus oral AD (see Figure 6).

Figure 6: Time to Relapse in Patients in Stable Response in Patients with TRD in Study 2* (Full Analysis Set)



* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55).

In Study 2, based on depressive symptomatology, the majority of stable remitters (69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remitters received weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to SPRAVATO, 39% received the 56 mg dose and 61% received the 84 mg dose.

14.2 Depressive Symptoms in Patients with Major Depressive Disorder with Acute Suicidal Ideation or Behavior

SPRAVATO was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Study 3 (NCT03039192) and Study 4 (NCT03097133), in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, patients received treatment with SPRAVATO 84 mg or placebo nasal spray twice-weekly for 4 weeks. After the first dose, a one-time dose reduction to SPRAVATO 56 mg was allowed for patients unable to tolerate the 84 mg dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD) (AD monotherapy or AD plus augmentation therapy) as determined by the investigator. After completion of the 4-week treatment period with SPRAVATO/placebo, study follow-up continued through Day 90.

The baseline demographic and disease characteristics of patients in Study 3 and Study 4 were similar between the SPRAVATO plus standard of care or placebo nasal spray plus standard of care treatment groups. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation therapy, and 6% received both AD monotherapy/AD plus augmentation therapy.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In Study 3 and Study 4, SPRAVATO plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care (see Table 10).

Table 10: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies 3 and 4)

Study No.	Treatment Group [§]	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline to 24 hr Post First Dose (SE)	LS Mean Difference (95% CI) [†]
Study 3	SPRAVATO 84 mg + SOC [‡]	111	41.3 (5.87)	-15.9 (1.04)	-3.8 (-6.56; -1.09)
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.0 (1.02)	-
Study 4	SPRAVATO 84 mg + SOC [‡]	113	39.4 (5.21)	-16.0 (1.02)	-3.9 (-6.60; -1.11)
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.2 (1.05)	-

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval; SOC=standard of care.

§ SOC treatment included an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (antidepressant monotherapy or antidepressant monotherapy plus augmentation therapy).

† Difference (SPRAVATO + SOC minus placebo nasal spray + SOC) in least-squares mean change from baseline.

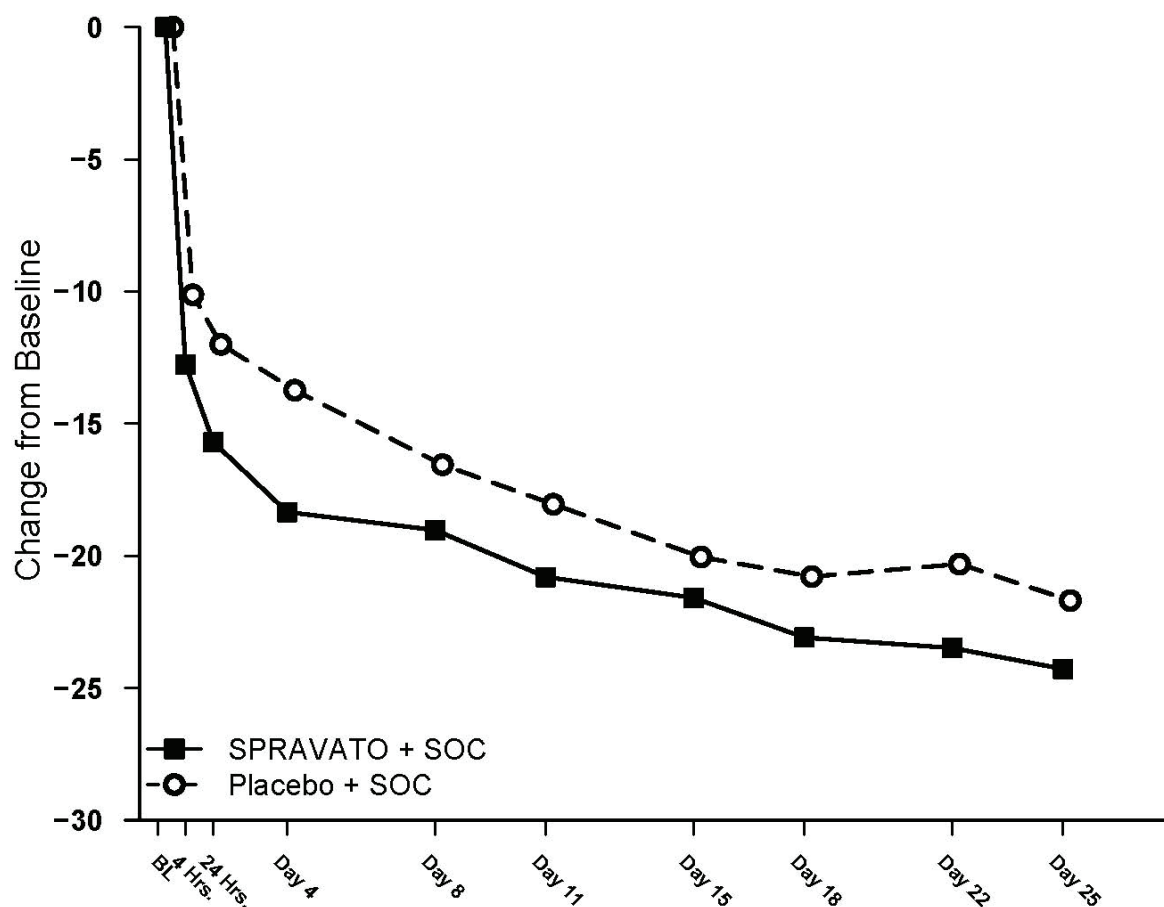
‡ SPRAVATO + SOC were statistically significantly superior to placebo nasal spray + SOC.

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). The CGI-SS-r is a one-item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior. In Study 3 and Study 4, SPRAVATO plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r.

Time Course of Treatment Response

In both Study 3 and Study 4, SPRAVATO's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, 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 25. Figure 7 depicts time course of the primary efficacy measure of change in MADRS total score from Study 3.

Figure 7: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study 3 (Full Analysis Set)



* Note: In Study 3, after the first dose, a one-time dose reduction to SPRAVATO 56 mg was allowed for patients unable to tolerate the 84 mg dose. Approximately 19% of patients had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

14.3 Special Safety Studies

Effects on Driving

Two studies were conducted to assess the effects of SPRAVATO on driving skills; one study in adult patients with major depressive disorder (Study 5) and one study in healthy subjects (Study 6). On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.

A single-blind, placebo-controlled study in 25 adult patients with major depressive disorder evaluated the effects of a single 84 mg dose of intranasal SPRAVATO on next day driving and the effect of repeated administration of 84 mg of intranasal SPRAVATO on same-day driving performance (Study 5). For the single dose treatment phase, an ethanol-containing beverage was used as a positive control. The SDLP after administration of single 84 mg dose of SPRAVATO nasal spray was similar to placebo 18 hours post-dose. For the multiple dose treatment phase, the SDLP after repeated administration of 84 mg intranasal SPRAVATO was similar to placebo 6 hours post-dose on Day 11, Day 18, and Day 25.

A randomized, double-blind, cross-over, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84-mg dose of esketamine nasal spray on driving (Study 6). Mirtazapine (30 mg) was used as a positive control. Driving performance was assessed at 8 hours after SPRAVATO or mirtazapine administration. The SDLP 8 hours after SPRAVATO nasal spray administration was similar to placebo. Two subjects discontinued the driving test after receiving SPRAVATO because of a perceived inability to drive after experiencing post-dose adverse reactions; one subject reported pressure behind the eyes and paresthesia of the hands and feet, the other reported headache with light sensitivity and anxiety.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPRAVATO® nasal spray is available as an aqueous solution of esketamine hydrochloride in a stoppered glass vial within a nasal spray device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine (supplied as 32.3 mg of esketamine hydrochloride).

SPRAVATO is available in the following presentations:

- 56 mg Dose Kit: Unit-dose carton containing two 28 mg nasal spray devices (56 mg total dose) (NDC 50458-028-02).
- 84 mg Dose Kit: Unit-dose carton containing three 28 mg nasal spray devices (84 mg total dose) (NDC 50458-028-03).

Within each kit, each 28 mg device is individually packaged in a sealed blister (NDC 50458-028-00).

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].

Disposal

SPRAVATO nasal spray devices must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule III drug product, and per applicable federal, state, and local regulations.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Sedation and Dissociation

Inform patients that SPRAVATO has potential to cause sedation, dissociative symptoms, perception disturbances, dizziness, vertigo, and anxiety. Advise patients that they will need to be observed by a healthcare provider until these effects resolve [*see Boxed Warning, Warnings and Precautions (5.1, 5.2)*].

Potential for Abuse, Misuse, and Dependence

Advise patients that SPRAVATO is a federally controlled substance because it can be abused or lead to dependence [see *Warnings and Precautions* (5.3), *Drug Abuse and Dependence* (9)].

SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)

SPRAVATO is available only through a restricted program called the SPRAVATO REMS [see *Warnings and Precautions* (5.4)]. Inform the patient of the following notable requirements:

- Patients treated in outpatient healthcare settings (e.g. medical offices and clinics) must be enrolled in the SPRAVATO REMS Program prior to administration.
- SPRAVATO must be administered under the direct observation of a healthcare provider.
- Patients must be monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO.

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted [see *Boxed Warning* and *Warnings and Precautions* (5.5)].

Increases in Blood Pressure

Advise patients that SPRAVATO can cause increases in blood pressure. Inform patients that after treatment sessions they should be advised that they may need to be observed by a healthcare provider until these effects resolve [see *Warnings and Precautions* (5.6)].

Impaired Ability to Drive and Operate Machinery

Caution patients that SPRAVATO may impair their ability to drive or operate machinery. Instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination such as driving a motor vehicle or operating machinery until the next day after a restful sleep. Advise patients that they will need someone to drive them home after each treatment session [see *Warnings and Precautions* (5.8)].

Pregnancy

Advise pregnant women and women of reproductive potential of the potential risk to a fetus. Advise patients to notify their healthcare provider if they are pregnant or intend to become pregnant during treatment with SPRAVATO. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPRAVATO during pregnancy. [See *Use in Specific Populations* (8.1)].

Lactation

Advise women not to breastfeed during treatment with SPRAVATO [see *Use in Specific Populations* (8.2)].

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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MEDICATION GUIDE
SPRAVATO® (sprah vah' toe) CIII
(esketamine)
nasal spray

What is the most important information I should know about SPRAVATO?

SPRAVATO can cause serious side effects, including:

- **Sedation and dissociation.** SPRAVATO may cause sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation).
 - Tell your healthcare provider right away if you feel like you cannot stay awake or if you feel like you are going to pass out.
 - Your healthcare provider must monitor you for serious side effects for at least 2 hours after taking SPRAVATO. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Abuse and misuse.** There is a risk for abuse and physical and psychological dependence with SPRAVATO treatment. Your healthcare provider should check you for signs of abuse and dependence before and during treatment with SPRAVATO.
 - Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
 - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **SPRAVATO Risk Evaluation and Mitigation Strategy (REMS).** Because of the risks for sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program called the SPRAVATO Risk Evaluation and Mitigation Strategy (REMS) Program. SPRAVATO can only be administered at healthcare settings certified in the SPRAVATO REMS Program. Patients treated in outpatient healthcare settings (e.g. medical offices and clinics) must be enrolled in the program.
- **Increased risk of suicidal thoughts and actions.** Antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **especially within the first few months of treatment or when the dose is changed. SPRAVATO is not for use in children.**
 - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of having suicidal thoughts and actions. These include people who have (or have a family history of) depression or a history of suicidal thoughts and actions.

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
- Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Tell your healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:

- | | |
|-----------------------------------|---|
| ○ suicide attempts | ○ worsening depression |
| ○ thoughts about suicide or dying | ○ other unusual changes in behavior or mood |

What is SPRAVATO?

SPRAVATO is a prescription medicine used along with an antidepressant taken by mouth to treat:

- adults with treatment-resistant depression (TRD)
- depressive symptoms in adults with major depressive disorder (MDD) with suicidal thoughts or actions

SPRAVATO is not for use as a medicine to prevent or relieve pain (anesthetic). It is not known if SPRAVATO is safe and effective as an anesthetic medicine.

It is not known if SPRAVATO is safe and effective for use in preventing suicide or in reducing suicidal thoughts or actions. SPRAVATO is not for use in place of hospitalization if your healthcare provider determines that hospitalization is needed, even if improvement is experienced after the first dose of SPRAVATO.

It is not known if SPRAVATO is safe and effective in children.

Do not take SPRAVATO if you:

- have blood vessel (aneurysmal vascular) disease (including in the brain, chest, abdominal aorta, arms and legs)
- have an abnormal connection between your veins and arteries (arteriovenous malformation)
- have a history of bleeding in the brain
- are allergic to esketamine, ketamine, or any of the other ingredients in SPRAVATO. See the end of this Medication Guide for a complete list of ingredients in SPRAVATO.

If you are not sure if you have any of the above conditions, talk to your healthcare provider before taking SPRAVATO.

Before you take SPRAVATO, tell your healthcare provider about all of your medical conditions, including if you:

- have heart or brain problems, including:
 - high blood pressure (hypertension)
 - slow or fast heartbeats that cause shortness of breath, chest pain, lightheadedness, or fainting
 - history of heart attack
 - history of stroke
 - heart valve disease or heart failure
 - history of brain injury or any condition where there is increased pressure in the brain
- have liver problems
- have ever had a condition called “psychosis” (see, feel, or hear things that are not there, or believe in things that are not true).
- are pregnant or plan to become pregnant. SPRAVATO may harm your baby. You should not take SPRAVATO if you are pregnant.
 - Tell your healthcare provider right away if you become pregnant during treatment with SPRAVATO.
 - If you are able to become pregnant, talk to your healthcare provider about methods to prevent pregnancy during treatment with SPRAVATO.
 - There is a pregnancy registry for women who are exposed to SPRAVATO during pregnancy. The purpose of the registry is to collect information about the health of women exposed to SPRAVATO and their baby. If you become pregnant during treatment with SPRAVATO, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.
- are breastfeeding or plan to breastfeed. You should not breastfeed during treatment with SPRAVATO.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking SPRAVATO with certain medicines may cause side effects.

Especially tell your healthcare provider if you take central nervous system (CNS) depressants, psychostimulants, or monoamine oxidase inhibitors (MAOIs) medicines. Ask your healthcare provider if you are not sure if you take these medicines. Your healthcare provider can tell you if it is safe to take SPRAVATO with your other medicines.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I take SPRAVATO?

- You will take SPRAVATO nasal spray yourself, under the supervision of a healthcare provider in a healthcare setting. Your healthcare provider will show you how to use the SPRAVATO nasal spray device.
- Your healthcare provider will tell you how much SPRAVATO you will take and when you will take it.
- Follow your SPRAVATO treatment schedule exactly as your healthcare provider tells you to.
- During and after each use of the SPRAVATO nasal spray device, you will be checked by a healthcare provider who will decide when you are ready to leave the healthcare setting.
- You will need to plan for a caregiver or family member to drive you home after taking SPRAVATO.
- If you miss a SPRAVATO treatment, your healthcare provider may change your dose and treatment schedule.
- Some people taking SPRAVATO get nausea and vomiting. You should not eat for at least 2 hours before taking SPRAVATO and not drink liquids at least 30 minutes before taking SPRAVATO.
- If you take a nasal corticosteroid or nasal decongestant medicine, take these medicines at least 1 hour before taking SPRAVATO.

What should I avoid while taking SPRAVATO?

- **Do not** drive, operate machinery, or do anything where you need to be completely alert after taking SPRAVATO. **Do not** take part in these activities until the next day following a restful sleep. See “**What is the most important information I should know about SPRAVATO?**”

What are the possible side effects of SPRAVATO?

SPRAVATO may cause serious side effects, including:

- See “**What is the most important information I should know about SPRAVATO?**”
- **Increased blood pressure.** SPRAVATO can cause a temporary increase in your blood pressure that may last for about 4 hours after taking a dose. Your healthcare provider will check your blood pressure before taking SPRAVATO and for at least 2 hours after you take SPRAVATO. Tell your healthcare provider right away if you get chest pain, shortness of breath, sudden severe headache, change in vision, or seizures after taking SPRAVATO.
- **Problems with thinking clearly.** Tell your healthcare provider if you have problems thinking or remembering.
- **Bladder problems.** Tell your healthcare provider if you develop trouble urinating, such as a frequent or urgent need to urinate, pain when urinating, or urinating frequently at night.

The most common side effects of SPRAVATO when used along with an antidepressant taken by mouth include:

- | | |
|---|---|
| • feeling disconnected from yourself, your thoughts, feelings and things around you | • decreased feeling of sensitivity (numbness) |
| • dizziness | • feeling anxious |
| • nausea | • lack of energy |
| • feeling sleepy | • increased blood pressure |
| • spinning sensation | • vomiting |
| | • feeling drunk |
| | • feeling very happy or excited |

If these common side effects occur, they usually happen right after taking SPRAVATO and go away the same day.

These are not all the possible side effects of SPRAVATO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about SPRAVATO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about SPRAVATO that is written for healthcare providers.

What are the ingredients in SPRAVATO?

Active ingredient: esketamine hydrochloride

Inactive ingredients: citric acid monohydrate, edetate disodium, sodium hydroxide, and water for injection

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

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For more information, go to www.SPRAVATO.com or call 1-800-526-7736.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s004

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

SPRAVATO (esketamine) REMS Program

I. Administrative Information

Application Number: NDA 211,243

Application Holder: Janssen Pharmaceuticals, Inc.

Initial REMS Approval: 3/2019

Most recent REMS Update: 7/2020

II. REMS Goal

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 patients are informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring.
- Enrolling all patients who receive treatment in an outpatient healthcare setting in a registry to further characterize the risks and support safe use.

III. REMS Requirements

Janssen Pharmaceuticals, Inc. must ensure that healthcare settings, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare settings that dispense SPRAVATO for outpatient use must:

- | | |
|---------------------------------|--|
| To become certified to dispense | <ol style="list-style-type: none">1. Have a prescriber onsite during SPRAVATO administration and monitoring.2. Have healthcare provider(s) onsite to monitor patients.3. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.4. Have the authorized representative review the SPRAVATO prescribing information and REMS Program Overview.5. Have the authorized representative enroll in the REMS Program by completing the Outpatient Healthcare Setting Enrollment Form and submitting it to the REMS Program.6. Establish processes and procedures to enroll the patient in the REMS Program.7. Establish processes and procedures to counsel the patient on the need for enrollment, monitoring, and risks of sedation and dissociation, and changes in vital signs. |
|---------------------------------|--|

8. Establish processes and procedures to verify the patient is enrolled in the REMS Program before each administration and that SPRAVATO is not dispensed for use outside the certified healthcare setting.
9. Establish processes and procedures to complete and submit the [Patient Monitoring Form](#) after each administration within 7 calendar days.
10. Train all relevant staff involved in prescribing, dispensing and administering SPRAVATO on 1) Counseling the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.
11. Establish processes and procedures to identify all staff involved in prescribing, dispensing, and administering SPRAVATO and ensure they are trained on 1) Counseling the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs; 2) Patient administration under the supervision of a healthcare provider; 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.

Before treatment initiation (first dose)	12. Counsel the patient on the risks and need for monitoring for resolution of sedation and dissociation and changes in vital signs. 13. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS Program.
Before administering	14. Counsel the patient on the need for monitoring for resolution of sedation and dissociation, and changes in vital signs. 15. Verify the patient is enrolled in the REMS Program through the processes and procedures established as a requirement of the REMS Program.
During and after administering, for at least 2 hours	16. Assess the patient for administration of SPRAVATO and resolution of sedation and dissociation, and changes in vital signs.
After administering, within 7 calendar days	17. Document and submit to the REMS Program using the Patient Monitoring Form.
To maintain certification to dispense	18. Have any new authorized representative enroll in the REMS Program by completing the Outpatient Healthcare Setting Enrollment Form.
At all times	19. Not dispense SPRAVATO for use outside the certified healthcare setting. 20. Not distribute, transfer, loan, or sell SPRAVATO. 21. Maintain records documenting staff's completion of training.

22. Maintain records that all processes and procedures are in place and are being followed.
23. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date administered.
24. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

2. Healthcare settings that dispense SPRAVATO for inpatient use (including emergency departments within certified healthcare settings) must:

To become certified to dispense	1. Have a prescriber onsite during SPRAVATO administration and monitoring. 2. Have healthcare provider(s) onsite to monitor patients. 3. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting. 4. Have the authorized representative review the SPRAVATO prescribing information and REMS Program Overview. 5. Have the authorized representative enroll in the REMS Program by completing and submitting the Inpatient Healthcare Setting Enrollment Form. 6. Establish processes and procedures to counsel the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs. 7. Establish processes and procedures to verify SPRAVATO is not dispensed for use outside the certified healthcare setting. 8. Train all relevant staff involved in prescribing, dispensing and administering SPRAVATO on 1) Counseling the patient on the need for monitoring, risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.
Before administering	9. Counsel the patient on the need for monitoring for resolution of sedation and dissociation, and changes in vital signs and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities
During and after administering, for at least 2 hours	10. Assess the patient for administration of SPRAVATO and resolution of sedation and dissociation, and changes in vital signs.

To maintain certification to dispense	11. Have any new authorized representative enroll in the REMS Program by completing the Inpatient Healthcare Setting Enrollment Form .
At all times	12. Not dispense SPRAVATO for use outside the certified healthcare setting. 13. Not distribute, transfer, loan, or sell SPRAVATO. 14. Maintain records documenting staff's completion of training. 15. Maintain records that all processes and procedures are in place and are being followed. 16. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date administered. 17. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

3. Patients who are prescribed SPRAVATO:

Before treatment initiation (first dose)	1. Receive counseling from a healthcare provider on risks and the need for monitoring for resolution of sedation and dissociation, and changes in vital signs. 2. For outpatients: Enroll in the REMS Program by completing the Patient Enrollment Form with a healthcare provider. Enrollment information will be provided to the REMS Program.
During treatment, before each dose	3. Receive counseling from a healthcare provider on the need for monitoring for resolution of sedation and dissociation; and change in vital signs.
During treatment, during and after administration for at least 2 hours	4. Be monitored for taking SPRAVATO, resolution of sedation and dissociation, and changes in vital signs at the healthcare setting.

4. Pharmacies that dispense SPRAVATO must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program. 3. Establish processes and procedures to verify that a healthcare setting is certified in the REMS Program before dispensing SPRAVATO. 4. Train all relevant staff involved in dispensing that SPRAVATO must only be dispensed to a certified healthcare setting.
Before dispensing	5. Verify that the healthcare setting is certified through the processes and procedures established as a requirement of the REMS Program.

At all times	6. Not distribute, transfer, loan or sell SPRAVATO except to certified dispensers. 7. Not dispense SPRAVATO for use outside a certified healthcare setting. 8. Maintain records documenting staff's completion of training. 9. Maintain records that all processes and procedures are in place and are being followed. 10. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date dispensed. 11. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.
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5. Wholesalers-distributors that distribute SPRAVATO must:

To be able to distribute	1. Establish processes and procedures to ensure that SPRAVATO is distributed only to certified healthcare settings and certified pharmacies. 2. Train all relevant staff involved in distributing on the REMS Program requirements.
At all times	3. Distribute only to certified healthcare settings and certified pharmacies. 4. Maintain and submit records of all shipments of SPRAVATO. 5. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

Janssen Pharmaceuticals, Inc. must provide training to health care settings that dispense SPRAVATO.

The training includes the following educational material: [REMS Program Overview](#). The training must be provided online and in hardcopy format by mail or fax.

To support REMS Program operations, Janssen Pharmaceuticals, Inc. must:

1. Establish and maintain a REMS Program website, www.SPRAVATOREMS.com. The REMS Program website must include the capability to complete healthcare setting and pharmacy certification online, patient enrollment online, the capability to provide patient monitoring information online, and to print the Prescribing Information, Medication Guide and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS program website. The REMS program website must not link back to the promotional product website(s).
2. Make the REMS program website fully operational and all REMS materials available through the website and coordinating center.
3. Establish and maintain a REMS coordinating center for REMS participants at 1-855-382-6022.

4. Establish and maintain a validated and secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
5. Ensure healthcare settings and pharmacies are able to enroll and certify in the REMS Program online or by fax.
6. Ensure healthcare providers in outpatient healthcare settings are able to enroll patients by fax and online.
7. Ensure outpatient healthcare settings are able to submit the [Patient Monitoring Form](#) by fax and online.
8. Notify healthcare settings and pharmacies within 7 calendar days after they become certified in the REMS.
9. Provide the [Outpatient Healthcare Setting Enrollment Form](#), [Inpatient Healthcare Setting Enrollment Form](#), [Pharmacy Enrollment Form](#), [REMS Program Overview](#) and Prescribing Information to REMS participants who (1) attempt to dispense SPRAVATO and are not yet certified, or (2) inquire about how to become certified.
10. Provide public access to a database of certified healthcare settings and pharmacies.
11. Provide certified pharmacies access to the database of certified healthcare settings.
12. Provide certified healthcare settings access to the database of certified pharmacies and enrolled patients.
13. Provide authorized wholesalers-distributors access to a database of certified pharmacies and healthcare settings.
14. Establish and maintain a registry, which includes a reporting and collection system for all patients treated in outpatient healthcare settings, to provide information on the incidence of adverse outcomes from sedation and dissociation.
15. Ensure that once a report suggestive of adverse outcomes from sedation or dissociation is received, Janssen Pharmaceuticals, Inc. follows up with the healthcare provider to obtain all required data for the registry.

To ensure REMS participants' compliance with the REMS program, Janssen Pharmaceuticals, Inc. must:

16. Notify outpatient healthcare settings if [Patient Monitoring Forms](#) have not been received by the REMS Program in the last 60 calendar days from the date of submission of the [Patient Enrollment Form](#).
17. Ensure every 60 calendar days from the date of submission of the [Patient Enrollment Form](#) that all expected monitoring forms are received for each patient.
18. Verify annually that the authorized representative's name and information correspond to the authorized healthcare setting or pharmacy. If the authorized representative changes at any time, the healthcare setting or pharmacy must be required to re-certify with a new authorized representative.
19. Maintain adequate records to demonstrate that REMS requirements have been met, including but not limited to records of: drug distribution and dispensing; certification of healthcare settings and pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
20. Establish a plan for addressing non-compliance with the REMS Program requirements.

21. Monitor pharmacies, healthcare settings, and wholesalers/distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
22. Audit 15% or 50 healthcare settings (whichever is greater), 15% or 50 pharmacies (whichever is greater), and data from all wholesalers-distributors that have ordered/dispensed SPRAVATO at 12 months from date of first commercial distribution and annually thereafter to ensure that all REMS processes are in place, functioning and support the REMS requirements. To be audited, healthcare setting must have received at least one shipment of SPRAVATO in the past 12 months and not have been previously audited in the past 3 years.
23. Take reasonable steps to improve implementation of and compliance with the requirements in the SPRAVATO REMS Program based on monitoring and evaluation of the SPRAVATO REMS Program.

IV. REMS Assessment Timetable

Janssen Pharmaceuticals, Inc. must submit REMS assessments at 6 months and 12 months from the date of initial approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Janssen Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the SPRAVATO REMS:

Enrollment Forms

Healthcare Setting:

1. [Outpatient Healthcare Setting Enrollment Form](#)
2. [Inpatient Healthcare Setting Enrollment Form](#)

Patient:

3. [Patient Enrollment Form](#)

Pharmacy:

4. [Pharmacy Enrollment Form](#)

Training and Educational Materials

Healthcare Setting:

5. [REMS Program Overview](#)

Pharmacy:

6. [REMS Program Overview](#)

Patient Care Forms

7. [Patient Monitoring Form](#)

Other Materials

8. [REMS Program Website](#)

INSTRUCTIONS:

1. Review the *SPRAVATO® Prescribing Information* and the *SPRAVATO® REMS Program Overview*
2. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

**This form is intended only for Outpatient Medical Offices and Clinics.
Emergency departments within hospitals are certified through the Inpatient Healthcare Setting enrollment.**

* Indicates Required Field

Healthcare Setting Information

Healthcare Setting Name*:

Healthcare Setting Address 1*:

Address Line 2:

City*:

State*:

ZIP*:

Healthcare Setting Telephone Number*:

Healthcare Setting Website URL:

DEA License Number* (associated with the Healthcare Setting address):

Name of DEA License Holder (if different from Healthcare Setting Name):

DEA License Expiration Date (MM/DD/YYYY)*:

Healthcare Setting Type*:
(select all that apply)

- ☐ Mental Health Facility ☐ Outpatient Clinic ☐ Independent Practice ☐ Group Practice
☐ Other: _____

If your healthcare setting is **an independent (private) practice, or group practice, or outpatient clinic**, how does your practice intend to acquire SPRAVATO® for patients? (Select all that apply)

- ☐ By sending a patient-specific prescription for SPRAVATO® CIII (controlled substance) to a REMS-certified pharmacy, have that pharmacy deliver patient-name product to your practice, and follow all required State and Federal DEA laws and regulations.
☐ By acquiring SPRAVATO® CIII (controlled substance) as bulk supply directly from a SPRAVATO® REMS-qualified distributor, and follow all required State and Federal DEA laws and regulations.

For each additional healthcare setting where SPRAVATO® will be delivered, dispensed, and administered within your healthcare system for which the same Authorized Representative will be responsible, you will **need to** complete page 3.

Your healthcare setting information will be shared with Janssen's patient support and distribution partners, to allow your healthcare setting to purchase product.

Your healthcare setting information (name, location, and phone number) will be listed on a location finder, as a certified healthcare setting, available to healthcare professionals and patients seeking treatment with SPRAVATO®. **If you do not want your information listed, please call SPRAVATO® REMS at 1-855-382-6022.**

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Outpatient Healthcare Setting Enrollment Form

* Indicates Required Field

Healthcare Setting Authorized Representative Information

First Name*:	MI:	Last Name*:
Credentials*: ☐ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other: _____		
Telephone Number*:	EXT:	Fax*:
Email Address*:		

Healthcare Setting Alternate Contact

First Name:	Last Name:
Telephone Number:	EXT:
Fax:	Email Address:

Healthcare Setting Authorized Representative Agreement

I am the Authorized Representative designated by my Healthcare Setting to oversee implementation and coordinate the activities of the SPRAVATO® REMS. By signing this form, I agree, on behalf of myself and my Healthcare Setting, to comply with all REMS Requirements:

- I will:**
- Review the SPRAVATO® Prescribing Information and REMS Program Overview.
 - Enroll in the SPRAVATO® REMS by completing this form *and* submitting this form to the SPRAVATO® REMS.
 - Have a prescriber onsite during SPRAVATO® administration and monitoring.
 - Have a healthcare provider(s) onsite to monitor each patient for at least 2 hours following administration of SPRAVATO® for resolution of sedation and dissociation, and changes in vital signs.
 - Establish processes and procedures** and **train** all relevant staff involved in prescribing, dispensing, and administering SPRAVATO® to ensure that the following takes place in my Healthcare Setting:
 - Prior to the patient receiving SPRAVATO®, a healthcare provider counsels the patient on the need for enrollment, monitoring, risks of sedation and dissociation, and changes in vital signs.
 - All patients are enrolled in the SPRAVATO® REMS by completing and submitting the *Patient Enrollment Form* with their prescriber.
 - Verify the patient is enrolled in the REMS before dispensing SPRAVATO® for patient administration.
 - The patient administers SPRAVATO® under the direct supervision of a healthcare provider.
 - A healthcare provider monitors every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose.
 - A *Patient Monitoring Form* is submitted to the SPRAVATO® REMS for every patient within 7 days following administration of every dose.
 - Notify the SPRAVATO® REMS in advance if patient treatment will be transferred from one REMS-certified Healthcare Setting to another REMS-certified Healthcare Setting.
 - SPRAVATO® is not dispensed for use outside the Healthcare Setting.
 - If the authorized representative changes, have the new authorized representative re-certify the Outpatient Healthcare Setting into the REMS by completing the *Outpatient Healthcare Setting Enrollment Form*.
 - Not distribute, transfer, loan, or sell SPRAVATO®.
 - Maintain records documenting staff's completion of training.
 - Maintain records that all processes and procedures are in place and are being followed.
 - Maintain records of all shipments of SPRAVATO® received and dispensing information including the patient name, dose, number of devices, and date administered.
 - Comply with audits carried out by Janssen Pharmaceuticals, Inc., or a third party acting on behalf of Janssen Pharmaceuticals, Inc., to ensure that all processes and procedures are in place and are being followed.

Name (please print):

Authorized Representative Signature*:	Date*:
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Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Use this form to add each additional healthcare setting location for which the same Authorized Representative will be responsible.

** Indicates Required Field*

Additional Healthcare Setting			
Authorized Representative First Name*:	MI:	Last Name*:	
Authorized Representative Email:			
Healthcare Setting Name*:			
Healthcare Setting Address 1*:		Address Line 2:	
City*:	State*:	ZIP*:	
Healthcare Setting Telephone Number*:		Healthcare Setting Website URL:	
DEA License Number* (associated with the Healthcare Setting address):	Name of DEA License Holder (if different from Healthcare Setting Name):		DEA License Expiration Date (MM/DD/YYYY)*:
Healthcare Setting Type*: ☐ Mental Health Facility ☐ Outpatient Clinic ☐ Independent Practice ☐ Group Practice (select all that apply) ☐ Other: _____			
If your healthcare setting is an independent (private) practice, or group practice, or outpatient clinic , how does your practice intend to acquire SPRAVATO® for patients? (Select all that apply)			
☐ By sending a patient-specific prescription for SPRAVATO® CIII (controlled substance) to a REMS-certified pharmacy, have that pharmacy deliver patient-name product to your practice, and follow all required State and Federal DEA laws and regulations.			
☐ By acquiring SPRAVATO® CIII (controlled substance) as bulk supply directly from a SPRAVATO® REMS-qualified distributor, and follow all required State and Federal DEA laws and regulations.			
Additional Alternate Contact Information			
First Name:		Last Name:	
Telephone Number:	EXT:	Fax:	Email Address:
Your healthcare setting information will be shared with Janssen's patient support and distribution partners, to allow your outpatient healthcare setting to purchase product. Your healthcare setting information (name, location, and phone number) will be listed on a location finder, as a certified outpatient healthcare setting, available to healthcare professionals and patients seeking treatment with SPRAVATO®. If you <u>do not want</u> your information listed, please call SPRAVATO® REMS at 1-855-382-6022.			

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

INSTRUCTIONS:

1. Review the *SPRAVATO® Prescribing Information* and the *SPRAVATO® REMS Program Overview*
2. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

As an Inpatient Healthcare Setting (with inpatient units, emergency department, etc.), your Inpatient Pharmacy, operating under the same Drug Enforcement Administration (DEA) license and physical location, will be considered certified once this form is completed/submitted. A separate pharmacy enrollment is not required.

** Indicates Required Field*

Healthcare Setting Information

Healthcare Setting Name*:

Healthcare Setting Address 1*:

Address Line 2:

City*:

State*:

ZIP*:

Healthcare Setting Telephone Number*:

Healthcare Setting Website URL:

DEA License Number* (associated with the Healthcare Setting address):

Name of DEA License Holder (if different from Healthcare Setting Name):

DEA License Expiration Date (MM/DD/YYYY)*:

Healthcare Setting Type*:
(select all that apply)

- ☐ Hospital-Emergency Department ☐ Hospital-Inpatient ☐ Mental Health Facility
☐ Other: _____

Your healthcare setting information will be shared with Janssen's patient support and distribution partners, to allow your healthcare setting to purchase product.

Your healthcare setting information (name, location, and phone number) will be listed on a location finder, as a certified healthcare setting, available to healthcare professionals and patients seeking treatment with SPRAVATO®. **If you do not want your information listed, please call SPRAVATO® REMS at 1-855-382-6022.**

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Phone: 1-855-382-6022

www.SPRAVATOREMS.com

Fax: 1-877-778-0091

Inpatient Healthcare Setting Enrollment Form

* Indicates Required Field

Healthcare Setting and Pharmacy Authorized Representative Information			
First Name*:		MI:	Last Name*:
Credentials*: ☐ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other: _____			
Telephone Number*:	EXT:	Fax*:	Email Address*:
Healthcare Setting and Pharmacy Alternate Contact			
First Name:		Last Name:	
Telephone Number:	EXT:	Fax:	Email Address:
Healthcare Setting and Pharmacy Authorized Representative Agreement			
I am the Authorized Representative designated by my Healthcare Setting to oversee implementation and coordinate the activities of the SPRAVATO® REMS. By signing this form, I agree, on behalf of myself and my Healthcare Setting, to comply with all REMS requirements: I will: - Review the SPRAVATO® Prescribing Information and REMS Program Overview. - Enroll in the SPRAVATO® REMS by completing this form <i>and</i> submitting this form to the SPRAVATO® REMS. - Have a prescriber onsite during SPRAVATO® administration and monitoring. - Have a healthcare provider(s) onsite to monitor each patient for at least 2 hours following administration of SPRAVATO® for resolution of sedation and dissociation, and changes in vital signs. Establish processes and procedures and train all relevant staff involved in prescribing, dispensing, and administering SPRAVATO® to ensure that the following takes place in my Healthcare Setting: - A healthcare provider counsels the patient prior to receiving SPRAVATO® on the need for monitoring due to risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities. - The patient administers SPRAVATO® under the direct supervision of a healthcare provider. - A healthcare provider monitors every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose. - SPRAVATO® is not dispensed for use outside the Healthcare Setting. - If the authorized representative changes, have the new authorized representative re-certify the Inpatient Healthcare Setting into the REMS by completing the <i>Inpatient Healthcare Setting Enrollment Form</i>. - Not distribute, transfer, loan, or sell SPRAVATO®. - Maintain records documenting staff's completion of training. - Maintain records that all processes and procedures are in place and are being followed. - Maintain records of all shipments of SPRAVATO® received and dispensing information including the patient name, dose, number of devices, and date administered. - Comply with audits carried out by Janssen Pharmaceuticals, Inc., or a third party acting on behalf of Janssen Pharmaceuticals, Inc., to ensure that all processes and procedures are in place and are being followed.			
Name (please print):			
Authorized Representative Signature*:			Date*:

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

INSTRUCTIONS:

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments

1. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

This section is to be completed by the Prescriber

* Indicates required field

Healthcare Setting Information

Healthcare Setting Name*:		
Healthcare Setting DEA License Number* (associated with the Healthcare Setting address):		
Address 1*:	Address 2:	
City*:	State*:	ZIP*:
Phone*:	Fax*:	

Prescriber Information

First Name*:		Last Name*:	
Credentials*: ☐ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other _____ Specialty*: ☐ Psychiatry ☐ Internal Medicine ☐ Family Practice ☐ Other _____			Prescriber DEA License Number*:
Phone*:	Fax:	Email*:	
Prescriber Signature*:			Date*:

Referring Healthcare Provider – if different from Prescriber

First Name:	Last Name:
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Relevant Clinical Information

Has the patient previously been treated with ketamine or esketamine for major depressive disorder, treatment-resistant depression, pain syndromes, or any other condition?*	☐ Yes ☐ No
If YES, list all pre-existing conditions treated with ketamine or esketamine: _____ _____	
List all pre-existing medical and psychiatric conditions*: _____ _____	
List concomitant medications (e.g., adjunctive depression medications, sedative hypnotics, psychostimulants, monoamine oxidase inhibitors [MAOIs])*: _____ _____	

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

This section is to be completed by the Patient

Your healthcare provider will help you complete this form and provide you with a copy.

*** Indicates required field**

Patient Information

First Name*:	MI:	Last Name*:	Birthdate* (MM/DD/YYYY):	Sex*: ☐ Male ☐ Female ☐ Other
Email*: (Email is required for online enrollment only)			Phone Number*:	
Address 1*:			Address 2:	
City*:			State*:	ZIP*:

Patient Agreement

By signing this form, I understand and acknowledge that:

Before my treatment begins, I will:

- Enroll in the SPRAVATO® REMS by completing this *Patient Enrollment Form* with my healthcare provider. Enrollment information will be submitted to the SPRAVATO® REMS.
- Receive counseling on safety risks and the need for monitoring to observe for resolution of sedation and dissociation, and for any changes in vital signs.

During treatment, and after administration I will:

- Use the SPRAVATO® nasal spray myself under the direct observation of a healthcare provider.
- Be observed at the healthcare setting where I get SPRAVATO® for at least 2 hours after each treatment until the healthcare provider determines I am ready to leave the healthcare setting.

I understand:

- Sedation and dissociation can result from treatment with SPRAVATO® and I must stay after each treatment. Until these effects resolve, I may feel:
 - sleepy and/or
 - disconnected from myself, my thoughts, feelings and things around me.
- I should make arrangements to safely get home.
- I should not drive or use heavy machinery for the rest of the day on which I receive SPRAVATO®.
- I should contact my doctor or inform him/her at my next visit if I believe I have a side effect or reaction from SPRAVATO®.
- In order to receive SPRAVATO® as an outpatient, I am required to be enrolled in the REMS, and my information will be stored in a database of all outpatients who receive SPRAVATO® in the United States.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may contact me or my prescriber via phone, mail, fax, or email to support administration of the REMS.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may use, disclose, and share my personal health information for the purpose of the operations of the REMS, including enrolling me into the REMS and administering the REMS, coordinating the dispensing of SPRAVATO®, and releasing and disclosing my personal health information to the Food and Drug Administration (FDA), as necessary, and as otherwise required by law.

Patient Name (please print):

Patient Signature*:

Date*:

INSTRUCTIONS:

1. Review the *SPRAVATO® Prescribing Information* and the *SPRAVATO® REMS Program Overview*
2. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

If you are an Inpatient Pharmacy (support inpatient units, emergency department, etc.) and operate under the same DEA license and physical location with your Inpatient Healthcare Setting, your pharmacy will be considered certified once the Inpatient Healthcare Setting Enrollment form is completed/submitted, and you do not require a separate pharmacy enrollment form. This form is intended only for pharmacies that dispense to outpatient facilities.

* Indicates Required Field

Pharmacy Information

Name of Pharmacy*:			
Pharmacy Address 1*:		Address Line 2:	
City*:		State*:	ZIP*:
Pharmacy Telephone Number*:	DEA License Number* (On file with distributor account)		DEA Expiration Date* (MM/DD/YYYY):
Pharmacy Type*(select all that apply) ☐ Community/Retail ☐ Specialty ☐ Other:_____			
Your pharmacy information will be shared with Janssen's patient support and distribution partners, to allow your pharmacy to purchase product.			

Pharmacy Shipping Address, if different from above

Pharmacy Address (address must match the DEA address associated with your Pharmacy's DEA License Number):		Address Line 2:	
City:		State:	ZIP:

Pharmacy Authorized Representative Information

First Name*:		Last Name*:		Title*:
Telephone Number*:	Ext:	Fax*:	Email Address*:	

Pharmacy Alternate Contact

First Name:		Last Name:		
Telephone Number:	Ext:	Fax:	Email Address:	

Pharmacy Authorized Representative Agreement

I am the Authorized Representative designated by my pharmacy to carry out the certification process and oversee implementation and coordinate the activities of the SPRAVATO® REMS. By completing this form, I agree, on behalf of the pharmacy, to comply with all REMS requirements:

I will:

- Review the SPRAVATO® Prescribing Information and REMS Program Overview.
- Enroll in the SPRAVATO® REMS by completing this *Pharmacy Enrollment Form* and submitting this form to the SPRAVATO® REMS.
- **Establish processes and procedures** and **train** all relevant staff involved in dispensing SPRAVATO® on the following:
 - SPRAVATO® can only be dispensed to a certified healthcare setting.
 - SPRAVATO® must never be dispensed directly to a patient for home use.
 - Before dispensing SPRAVATO®, verify the healthcare setting is certified.
 - Not distribute, transfer, loan, or sell SPRAVATO® except to certified dispensers.
 - If the authorized representative changes, have the new authorized representative re-certify the Pharmacy into the REMS by completing the *Pharmacy Enrollment Form*.
- Maintain records documenting staff's completion of training.
- Maintain records that all REMS processes and procedures are in place and are being followed.
- Maintain records of all shipments of SPRAVATO® received and dispensing information including patient name, dose, number of devices, and date dispensed.
- Comply with audits carried out by Janssen Pharmaceuticals, Inc., or third party acting on behalf of Janssen Pharmaceuticals, Inc., to ensure that all processes and procedures are in place and are being followed.

Authorized Representative Signature*:	Date:
---------------------------------------	-------

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

SPRAVATO® REMS Program Overview **(Risk Evaluation and Mitigation Strategy)**

This overview describes the SPRAVATO® REMS requirements and responsibilities of inpatient healthcare settings, outpatient healthcare settings, pharmacies, and patients.

If you have any questions regarding the SPRAVATO® REMS, please visit www.SPRAVATOREMS.com or call 1-855-382-6022



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What is the SPRAVATO® REMS (Risk Evaluation and Mitigation Strategy)?

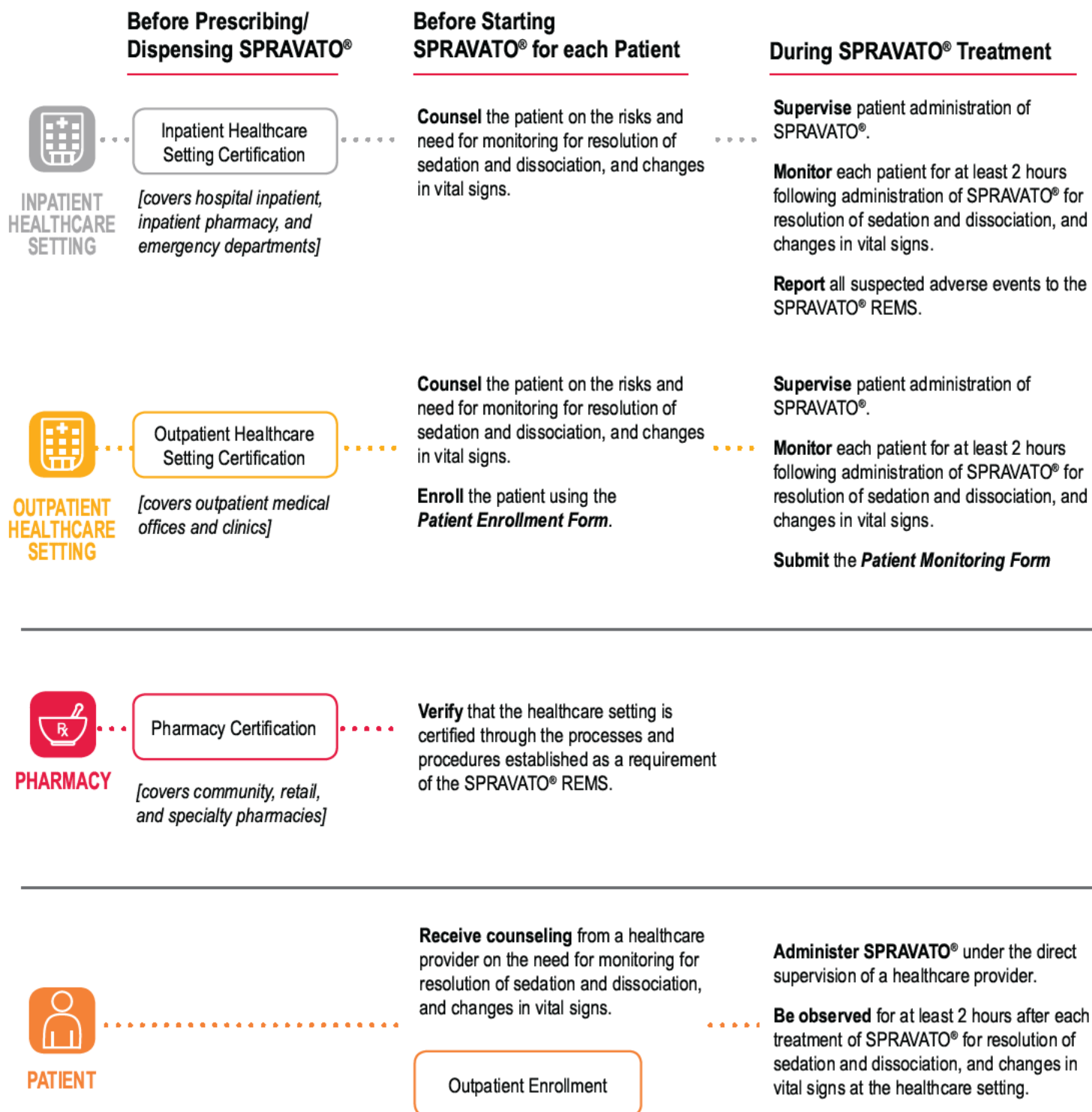
A REMS is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

SPRAVATO® is available only through a restricted distribution program called the SPRAVATO® REMS because of the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO® administration, and abuse and misuse of SPRAVATO®. SPRAVATO® is intended for use only in a certified Healthcare Setting.

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours. SPRAVATO® must never be dispensed directly to a patient for home use.



How does the SPRAVATO® REMS work?



What are the Requirements of the SPRAVATO® REMS?

- In order for patients to receive SPRAVATO®, healthcare settings, pharmacies, and patients must comply with all requirements of the SPRAVATO® REMS



INPATIENT HEALTHCARE SETTING REQUIREMENTS

Become Certified*:

1. **Designate** an Authorized Representative to oversee implementation and coordinate the activities of the SPRAVATO® REMS
2. **Review** the following materials:
 - SPRAVATO® Prescribing Information
 - SPRAVATO® REMS Program Overview (this document)
3. Have the Authorized Representative **complete** and **submit** the **Inpatient Healthcare Setting Enrollment Form** at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091
4. Once submitted, you will be notified of certification in the SPRAVATO® REMS and you will receive information on additional requirements necessary to order and receive SPRAVATO®

Before treating a patient:

1. **Establish** processes and procedures and train all relevant staff involved in prescribing, dispensing, and administering SPRAVATO®
2. Have a healthcare provider **counsel** the patient prior to receiving SPRAVATO® on the need for monitoring due to risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities.

*As an Inpatient Healthcare Setting (with inpatient units, emergency department, etc.), your Inpatient Pharmacy, operating under the same Drug Enforcement Administration (DEA) license and physical location, will be considered certified once the **Inpatient Healthcare Setting Enrollment Form** is completed/submitted. **A separate pharmacy enrollment is not required.**

At All Times:

1. **Ensure** relevant staff are trained and follow all established processes and procedures to comply with SPRAVATO® REMS requirements†
2. **Have a prescriber onsite** during SPRAVATO® administration and monitoring
3. **Have a healthcare provider monitor** every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose
4. **Ensure** SPRAVATO® is not dispensed for use outside the Healthcare Setting
5. **Maintain** records documenting staff completion of training
6. **Maintain** records of all shipments of SPRAVATO® received and dispensing information including the patient name, dose, number of devices, and date administered
7. **Comply** with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed

† To review all SPRAVATO® REMS Inpatient Healthcare Setting requirements see the **Inpatient Healthcare Setting Enrollment Form**



OUTPATIENT HEALTHCARE SETTING REQUIREMENTS

Become Certified:

1. **Designate** an Authorized Representative to oversee implementation and coordinate the activities of the SPRAVATO® REMS
2. **Review** the following materials:
 - SPRAVATO® Prescribing Information
 - SPRAVATO® REMS Program Overview (this document)
3. Have the Authorized Representative **complete** and **submit** the **Outpatient Healthcare Setting Enrollment Form** at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091.
4. Once submitted, you will be notified of certification in the SPRAVATO® REMS and you will receive information on additional requirements necessary to order and receive SPRAVATO®

Before treating a patient:

1. **Establish** processes and procedures and train all relevant staff involved in prescribing, dispensing, and administering SPRAVATO® to comply with all SPRAVATO® REMS requirements
2. Have a healthcare provider **counsel** the patient prior to receiving SPRAVATO® on the need for enrollment, monitoring, risks of sedation and dissociation, and changes in vital signs
3. Have a prescriber **enroll** the patient by completing and submitting the **Patient Enrollment Form** to the SPRAVATO® REMS
4. **Verify** the patient is enrolled in the SPRAVATO® REMS before dispensing SPRAVATO® for patient administration

At All Times:

1. **Ensure** relevant staff are trained and follow all established processes and procedures to comply with all SPRAVATO® REMS requirements*
2. Have a **prescriber onsite** during SPRAVATO® administration and monitoring
3. Have the patient **administer** SPRAVATO® under the direct supervision of a healthcare provider
4. Have a **healthcare provider(s) onsite** to monitor each patient for at least 2 hours following administration of SPRAVATO® for resolution of sedation and dissociation, and changes in vital signs after every dose
5. **Document** and **submit** a **Patient Monitoring Form** for every patient within 7 days following administration of every dose of SPRAVATO®
6. **Notify** the SPRAVATO® REMS in advance if patient treatment will be transferred from one REMS-certified Healthcare Setting to another REMS-certified Healthcare Setting
7. **Ensure** SPRAVATO® is not dispensed for use outside the Healthcare Setting
8. **Maintain** records documenting staff completion of training
9. **Maintain** records of all shipments of SPRAVATO® received and dispensing information including the patient name, dose, number of devices, and date administered
10. **Comply** with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed

*To review all SPRAVATO® REMS Outpatient Healthcare Setting requirements see the **Outpatient Healthcare Setting Enrollment Form**



PHARMACY REQUIREMENTS - FOR OUTPATIENT DISPENSING ONLY

Become Certified:

1. **Designate** an Authorized Representative to oversee implementation and coordinate the activities of the SPRAVATO® REMS
2. **Review** the following materials:
 - SPRAVATO® Prescribing Information
 - SPRAVATO® REMS Program Overview (this document)
3. Have the Authorized Representative **complete** and **submit** the **Pharmacy Enrollment Form** at www.SPRAVATOrems.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091
4. Once submitted, you will be notified of certification in the SPRAVATO® REMS and you will receive information on additional requirements necessary to order and receive SPRAVATO®

Before Dispensing:

1. **Establish** processes and procedures and train all relevant staff involved in dispensing SPRAVATO® to comply with all SPRAVATO® REMS requirements
2. **Verify** the healthcare setting is certified before dispensing SPRAVATO®

At All Times:

1. **Ensure** relevant staff are trained and follow all established processes and procedures to comply with all SPRAVATO® REMS requirements*
2. **Ensure** SPRAVATO® is never dispensed directly to a patient for home use
3. **Ensure** SPRAVATO® is only dispensed to a certified healthcare setting
4. **Maintain** records documenting staff's completion of training
5. **Maintain** records of all shipments of SPRAVATO® received and dispensing information including the patient name, dose, number of devices, and date dispensed
6. **Comply** with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed

*To review all SPRAVATO® REMS Pharmacy requirements see the **Pharmacy Enrollment Form**



PATIENT REQUIREMENTS

Before Treatment:

1. **Receive** counseling from a healthcare provider on risks and the need for monitoring for resolution of sedation and dissociation, and changes in vital signs
2. **Outpatient Only:**
Enroll in the SPRAVATO® REMS Program by completing the **Patient Enrollment Form** with a healthcare provider. Enrollment information will be provided to the SPRAVATO® REMS Program

During Treatment:

1. **Administer** SPRAVATO® nasal spray under the direct observation of a healthcare provider
2. **Be observed** at the healthcare setting where SPRAVATO® is received for at least 2 hours after each treatment until the healthcare provider determines the patient is ready to leave the healthcare setting

At All Times*:

1. **Make arrangements** to safely get home after receiving SPRAVATO®, if leaving the healthcare setting
2. **Do not** drive or use heavy machinery for the rest of the day after receiving SPRAVATO®
3. **Contact the healthcare provider** or inform the healthcare provider at the next visit if a side effect or reaction from SPRAVATO® occurs

*To review all SPRAVATO® REMS requirements for patients receiving SPRAVATO® in an Outpatient Healthcare Setting, see the **Patient Enrollment Form**

SPRAVATO® REMS Resources



INPATIENT HEALTHCARE SETTING

- *Inpatient Healthcare Setting Enrollment Form*
- *REMS Program Overview*
- *Prescribing Information*



OUTPATIENT HEALTHCARE SETTING

- *Outpatient Healthcare Setting Enrollment Form*
- *Patient Enrollment Form*
- *Patient Monitoring Form*
- *REMS Program Overview*
- *Prescribing Information*



PHARMACY

- *Pharmacy Enrollment Form*
- *REMS Program Overview*
- *Prescribing Information*

Contact the SPRAVATO® REMS

Phone: 1-855-382-6022

Fax: 1-877-778-0091

Hours of Operation: Monday- Friday 8:00 AM - 8:00 PM ET

Visit www.SPRAVATOREMS.com

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Please see the Prescribing Information for more information.

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Reference ID:

8
Reference ID: 4649523

Patient Monitoring Form - Outpatient Use Only

INSTRUCTIONS:

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATorems.com or by fax (1-877-778-0091).

*Indicates Required Field

Patient Information (PRINT)			
First Name*:	MI:	Last Name*:	Birthdate* (MM/DD/YYYY): Sex*: ☐ Male ☐ Female ☐ Other
Concomitant Medication			
Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?			
Benzodiazepines*	☐ Yes ☐ No		
Non-benzodiazepine sedative hypnotics*	☐ Yes ☐ No		
Psychostimulants*	☐ Yes ☐ No		
Monoamine oxidase inhibitors (MAOIs)*	☐ Yes ☐ No		
Healthcare Provider Conducting Patient Monitoring (PRINT)			
First Name*:		Last Name*:	
Telephone*:		Email*:	
Healthcare Setting Information (PRINT)			
Healthcare Setting Name*:			
Healthcare Setting Address 1*:		Healthcare Setting Address 2:	
City*:	State*:	ZIP*:	
Patient Treatment Session Information (Administration and Monitoring)			
Treatment Date*	Date (MM/DD/YYYY): _____		
Dose Administered*	☐ 56 mg ☐ 84 mg ☐ Other: _____		
Treatment Duration*	Total time _____ minutes (from 1st device administration to completion of monitoring) Patient must be monitored for at least 2 hours		
REMS Evaluation Question*	If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring? _____ minutes from start of administration		
Monitoring of Vital Signs*	Vital signs were in acceptable range prior to: • administration? ☐ Yes ☐ No • treatment session completion? ☐ Yes ☐ No		
Monitoring of Blood Pressure*	Prior to administration _____ mmHg	40 mins post-administration _____ mmHg	Prior to treatment session completion _____ mmHg
Did the patient experience Sedation and/or Dissociation			
Sedation*: ☐ Yes ☐ No		Dissociation*: ☐ Yes ☐ No	
Onset of symptoms from start of administration* ☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins ☐ >120 mins		Onset of symptoms from start of administration* ☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins ☐ >120 mins	
Resolution of symptoms within 2 hours?* ☐ Yes ☐ No Specify total time to resolution*: _____ min		Resolution of symptoms within 2 hours?* ☐ Yes ☐ No Specify total time to resolution*: _____ min	
Medication(s) given for sedation?* ☐ Yes ☐ No •If YES, name and dose of medication(s): _____ _____ _____		Medication(s) given for dissociation?* ☐ Yes ☐ No •If YES, name and dose of medication(s): _____ _____ _____	

* Indicates Required Field

Patient Information (PRINT)			
First Name*:	MI:	Last Name*:	Birthdate* (MM/DD/YYYY): Sex*: ☐ Male ☐ Female ☐ Other
Healthcare Provider Conducting Patient Monitoring (PRINT)			
First Name*:	Last Name*:		
Phone*:	Email:		
Serious Adverse Events (PRINT)			
A serious adverse event (SAE) for this SPRAVATO® REMS is <u>defined</u> as any event that results in/is: Hospitalization Disability or permanent damage Death Life-threatening Important medical event – defined as any event that may jeopardize the patient or may require intervention to prevent one of the above outcomes			
<i>All non-serious adverse events or product quality complaints that are <u>not defined above</u>, should be reported to: Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.</i>			
Did the patient experience a serious adverse event?* ☐ Yes ☐ No If YES, describe below.			
Event resulted in the following: (check all that apply)	Event Timing	Event Description (Please list one event per row)	Event Resolution
☐ Hospitalization ☐ Disability or permanent damage ☐ Death ☐ Life-threatening ☐ Important Medical Event	☐ During treatment sessions ☐ Between treatment sessions		☐ Yes ☐ No ☐ Unknown
	Date of Event (MM/DD/YYYY)		
☐ Hospitalization ☐ Disability or permanent damage ☐ Death ☐ Life-threatening ☐ Important Medical Event	☐ During treatment sessions ☐ Between treatment sessions		☐ Yes ☐ No ☐ Unknown
	Date of Event (MM/DD/YYYY)		
☐ Hospitalization ☐ Disability or permanent damage ☐ Death ☐ Life-threatening ☐ Important Medical Event	☐ During treatment sessions ☐ Between treatment sessions		☐ Yes ☐ No ☐ Unknown
	Date of Event (MM/DD/YYYY)		
Janssen Pharmaceuticals, Inc., Safety Department may follow up to obtain more information about these events.			

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SPRAVATO® REMS

(Risk Evaluation and Mitigation Strategy)

What is the SPRAVATO® REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

SPRAVATO® (esketamine) nasal spray CIII is available only through a restricted distribution program called the REMS because of the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO® abuse and misuse of SPRAVATO®. SPRAVATO® is intended for use only in a certified Healthcare Setting.

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, and patients must be monitored by a healthcare provider for at least 2 hours. SPRAVATO® must never be dispensed directly to a patient.

Program Requirements



Inpatient Healthcare Setting

Inpatient Healthcare Settings must be certified in the SPRAVATO® REMS in order to treat patients with SPRAVATO®

[Inpatient Healthcare
Setting Certification ▶](#)

Outpatient Healthcare Setting

Outpatient Healthcare Settings must be certified in the SPRAVATO® REMS in order to treat patients with SPRAVATO®

[Outpatient Healthcare
Setting Certification ▶](#)

Pharmacy

Pharmacies must be certified in the SPRAVATO® REMS in order to dispense SPRAVATO®

[Pharmacy
Certification ▶](#)

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Inpatient Healthcare Settings

SPRAVATO® REMS Inpatient Healthcare Setting Enrollment

Inpatient Healthcare Settings must be certified in the SPRAVATO® REMS in order to treat patients with

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, and adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and all SPRAVATO. SPRAVATO® is intended for use only in a certified Healthcare Setting.

Inpatient Healthcare Settings are NOT required to enroll patients or submit *Patient Monitoring Forms* to the

As an Inpatient Healthcare Setting (with inpatient units, emergency department, etc.), your Inpatient Pharmacy, with the same Drug Enforcement Administration (DEA) license and physical location, will be considered certified once the *Setting Enrollment Form* is completed/submitted. A separate pharmacy enrollment is not required.

Inpatient Healthcare Settings are required to report all suspected adverse events to the SPRAVATO® REMS

How does my Inpatient Healthcare Setting become certified in the SPRAVATO® REMS?



Step 1: Designate an Authorized Representative to oversee implementation and compliance with the REMS requirements.



Step 2: Review the following materials:

- *SPRAVATO® Prescribing Information*
- *SPRAVATO® REMS Program Overview*

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Outpatient Healthcare Settings

SPRAVATO® REMS Outpatient Healthcare Setting Enrollment

Outpatient Healthcare Settings must be certified in the SPRAVATO® REMS in order to prescribe pr

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, du
adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and abu
SPRAVATO. SPRAVATO® is intended for use only in a certified Healthcare Setting.

Outpatient Healthcare Settings are required to enroll patients prior to patient treatment and submit *Patient Mo*
each patient treatment to the SPRAVATO® REMS.

Outpatient Healthcare Setting Enrollment is intended only for outpatient medical offices and cl
Emergency departments within hospitals are certified through the Inpatient Healthcare Setting enr

How does my Outpatient Healthcare Setting become certified in the SPRAVATO® REMS?



Step 1: Designate an Authorized Representative to oversee
implementation and compliance with the REMS requirements.



Step 2: Review the following materials:

- *SPRAVATO® Prescribing Information*
- *SPRAVATO® REMS Program Overview*

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Pharmacies

SPRAVATO® REMS Pharmacy Enrollment - for Outpatient Dispensing

Pharmacies must be certified in the SPRAVATO® REMS to be able to receive and dispense SPRAVATO®.

If you are an Inpatient Pharmacy (support inpatient units, emergency department, etc.) and operate under the same physical location with your Inpatient Healthcare Setting, your pharmacy will be considered certified once the Inpatient Healthcare Setting Enrollment form is completed/submitted, and you do not require a separate pharmacy enrollment form. Enrollment is intended only for pharmacies that dispense to outpatient facilities.

How does my Pharmacy become certified in the SPRAVATO® REMS?

1

Step 1: Designate an Authorized Representative to oversee implementation and compliance of the SPRAVATO® REMS requirements.

2

Step 2: Review the following materials:

- *SPRAVATO® Prescribing Information*
- *SPRAVATO® REMS Program Overview*

3

Step 3: Complete and submit the *SPRAVATO® REMS Pharmacy Enrollment Form*.

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Patients

What is the SPRAVATO® REMS (Risk Evaluation and Mitigation Strategy)

Because of the risks associated with SPRAVATO®, the Food and Drug Administration (FDA) has required a special Evaluation and Mitigation Strategy (REMS). As part of the REMS, your healthcare provider will discuss the risks of sedation (feeling sleepy), dissociation (feeling disconnected from yourself, including thoughts, feelings, and things you see or hear) on SPRAVATO® with you. Both you and your healthcare provider must sign the *Patient Enrollment Form* for you to receive SPRAVATO® in an outpatient medical office or clinic, excluding emergency departments. Your healthcare provider will provide you with a copy of the form to the SPRAVATO® REMS.

How do I enroll in the SPRAVATO® REMS?

If your healthcare provider and you have both agreed that SPRAVATO® is the appropriate treatment for you, you will need to enroll in the SPRAVATO® REMS in order to receive treatment with SPRAVATO® in an outpatient medical office or clinic, excluding emergency departments.

These are the steps to take in partnership with your healthcare provider:



Step 1: Make sure you understand:

- A. How to enroll and take part in the SPRAVATO® REMS
- B. The benefits and risks of SPRAVATO®
- C. That each time you receive SPRAVATO®:

- You will need to use SPRAVATO® Nasal Spray yourself under direct observation of a healthcare provider in a healthcare setting, such as an outpatient medical office or clinic, excluding emergency departments.

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Contact Us

Contact the SPRAVATO® REMS



Phone: 1-855-382-6022



Fax: 1-877-778-0091

Hours of Operation: Monday — Friday 8:00 AM — 8:00 PM ET

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.



For SPRAVATO® REMS Program
information contact:

Phone: 1-855-382-6022

Fax: 1-877-778-0091

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Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

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Resources



Inpatient Healthcare Setting Resources for SPRAVATO® REMS

*SPRAVATO® REMS Inpatient Healthcare Setting
Enrollment Form*

SPRAVATO® Prescribing Information

SPRAVATO® REMS Program Overview



Outpatient Healthcare Setting Resources for SPRAVATO® REMS

*SPRAVATO® REMS Outpatient Healthcare Setting
Enrollment Form*

SPRAVATO® REMS Program Overview

SPRAVATO® REMS Patient Enrollment Form

SPRAVATO® Prescribing Information

SPRAVATO® REMS Patient Monitoring Form

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO®

*I am a

☐ Healthcare Setting ☐ Prescriber ☐ Pharm

If you have questions about the SPRAVATO® REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

nts or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN
online at www.fda.gov/medwatch.

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 1-855-382-6022.

[Forgot Username](#)

LOGIN

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO

*I am a



Healthcare Setting



Prescriber



Pharmacist

Healthcare Setting Authorized Representative

*First Name

*Last Name

*Telephone Number

*Fax Number

*Email Address

*Credentials



Physician



Physician Assistant



Nurse

1. If
er at

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO®

*I am a



Healthcare Setting



Prescriber



Pharm

Healthcare Setting Authorized R

*First Name

*Last Name

*Telephone Number

*Fax Number

*Email Address

*Credentials



Physician



Physician Assistant



Nurse

*Credentials Other

Account Submitted Successfully

Thank you for submitting your information to create your web account for the SPRAVATO[®] REMS.

A confirmation of this submission has been sent to the email address provided. You can expect to receive 2 emails, one contains your username and the second contains your temporary password. Please login with the username provided. You will then be prompted to update your password.

If you do not receive the emails within the next few hours, or would like to update your enrollment information at any time, please contact the SPRAVATO[®] REMS at 1-855-6022.

LOGIN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATorems.com

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO[®] to Janssen at 1-800-JANSSEN or online at www.fda.gov/medwatch.

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ter at

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO

*I am a

☐ Healthcare Setting

☐ Prescriber

☐ Phar

If you have questions about the SPRAVATO® REMS or need help enrolling,
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Monday – Friday, 8:00 AM – 8:00 PM ET

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online at www.fda.gov/medwatch.

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 1-855-382-6022.

User Name

[Forgot Username](#)

LOGIN

Login

Please enter your password

* Password:

CANCEL

NEXT

I am a

☐

Healthcare Setting

☐

Prescriber

☐

Pharmacist

If you have questions about the SPRAVATO® REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare providers should report all adverse events and product quality complaints associated with SPRAVATO® at 1-800-JANSSEN (1-800-526-7736).

Reference ID: 4649523

Change Password



Your password has expired and must be changed.

*New Password:



*Re-type new Password:

CANCEL

NEXT

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Login

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[Forgot Username](#)

LOG IN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare provider only

Update Profile



* Security Caption:

* Security Question

* Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

CANCEL

NEXT

certify



Register



Review
Materials



Online
Enrollment

as an Inpatient Healthcare Setting or an Outpatient Healthcare Setting.

ame designated authorized representative, you will be prompted to enroll another Inpatient

cy department, etc.), your Inpatient Pharmacy,
) license and physical location, will be
parate pharmacy enrollment is not required.

ARE SETTING

Outpatient Healthcare Settings

This form is intended only for Outpatient Medical Of
Emergency departments within hospitals are certifi

CERTIFY OUTPAT

nts or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSS
online at www.fda.gov/medwatch.



Register



Review
Materials



Online
Enrollment

review now by clicking on each link. Each document will open in a new

NEXT

ents or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSS
online at www.fda.gov/medwatch.

Enrollment Form



Registration



Review
Materials



Online
Enrollment

the *SPRAVATO® REMS Program Overview*

om, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

emergency department, etc.), your Inpatient Pharmacy, operating under the same Drug Enforcement Administration (DEA) registration, and the form must be completed/submitted. A separate pharmacy enrollment is not required.

etting address)

CONTINUE

SPRAVATO® REMS Inpatient Healthcare Setting Enrollment Form

✓
Registration

✓
Review
Materials

Instructions

1. Review the SPRAVATO® Prescribing Information and the SPRAVATO® REMS Program Overview
2. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS Program

As an Inpatient Healthcare Setting (with inpatient units, emergency department, etc.), your Inpatient Pharmacy, or location, will be considered certified once this form is completed/submitted. A separate pharmacy enrollment is not required.

*Indicates Required Field

Healthcare Setting Information

*DEA License Number (associated with the Healthcare Setting address)

12345

Name of DEA License Holder (if different from Healthcare Setting Name)

*DEA License Expiration Date (MM/DD/YYYY)

99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

*City

Blue Bell

*Healthcare Setting Telephone Number

555-555-1212

*Healthcare Setting Type (select all that apply)

- ☐ Hospital-Emergency Department ☐ Hospital-Inpatient ☐ Mental Health Facility
☐ Other

CO

Address 2

*State

PA

Healthcare Setting

SPRAVATO® REMS Inpatient Healthcare Setting Enrollment Form



Registration



Review
Materials

Instructions

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99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

Address Line 2

*City

Blue Bell

*State

PA

*Healthcare Setting Telephone Number

555 555-1212

Healthcare Setting Fax

*Healthcare Setting Type (select all that apply)

- ☐ Hospital-Emergency Department ☐ Hospital-Inpatient ☐ Mental Health Facility
☒ Other

Healthcare Setting Certification


Registration




Review
Materials




Online
Enrollment

Setting(s) in the SPRAVATO[®]

SPRAVATO[®] REMS Coordinating

ANOTHER INPATIENT HEALTHCARE SETTING

CERTIFY OUTPATIENT HEALTHCARE SETTING

ents or product quality complaints associated with SPRAVATO[®] to Janssen at 1-800-JANS

Healthcare Setting Certification

✓
Registration



✓
Review
Materials



✓
Online
Enrollment

SPRAVATO® REMS.

e]

TO ANOTHER INPATIENT HEALTHCARE SETTING

CERTIFY OUTPATIENT HEALTHCARE SETTING

events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN
or online at www.fda.gov/medwatch.



Register



Review
Materials



Online
Enrollment

review now by clicking on each link. Each document will open in a new

NEXT

ents or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSE
online at www.fda.gov/medwatch.

SPRAVATO[®] REMS Outpatient Healthcare Setting Enrollment Form



Instructions

1. Review the SPRAVATO[®] *Prescribing Information* and the SPRAVATO[®] *REMS Program Overview*
2. Complete this form online at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO[®] REMS at 1-877-778-0091

This form is intended only for Outpatient Medical Offices and Clinics.
Emergency departments within hospitals are certified through the Inpatient Healthcare Setting enrollment.

**Indicates Required Field*

Healthcare Setting Information

*DEA License Number (associated with the Healthcare Setting address)

CONTINUE

SPRAVATO® REMS

Outpatient Healthcare Setting Enrollment Form

 **Registration**

 **Review Materials**

Instructions

1. Review the SPRAVATO® *Prescribing Information* and the *SPRAVATO® REMS Program Overview*
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12345

CONTINUE

Name of DEA License Holder (if different from Healthcare Setting Name)

*DEA License Expiration Date (MM/DD/YYYY)

99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

Address Line 2

*City

Blue Bell

*State

PA

*Healthcare Setting Telephone Number

555 555-1212

Healthcare Setting Type

*Healthcare Setting Type (select all that apply)

- ☐ Mental Health Facility ☐ Outpatient Clinic ☐ Independent Practice ☐ Group Practice ☐ Other

SPRAVATO® REMS Outpatient Healthcare Setting Enrollment Form

 **Registration**

 **Review
Materials**

Instructions

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12345

CONTINUE

Name of DEA License Holder (if different from Healthcare Setting Name)

*DEA License Expiration Date (MM/DD/YYYY)

99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

Address Line 2

*City

Blue Bell

*State

PA

*Healthcare Setting Telephone Number

555-555-1212

Healthcare Setting Fax

*Healthcare Setting Type (select all that apply)

- ☐ Mental Health Facility ☒ Outpatient Clinic ☐ Independent Practice ☐ Group Practice
☒ Other

SPRAVATO[®] REMS Outpatient Healthcare Setting Enrollment Form



Registration



Review
Materials



Instructions

1. Review the SPRAVATO[®] Prescribing Information and the SPRAVATO[®] REMS Program Overview
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12345

CONFIRM

Name of DEA License Holder (if different from Healthcare Setting Name)

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99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

Address Line 2

*City

Blue Bell

*State

PA

*Healthcare Setting Telephone Number

555-555-1212

Healthcare Setting Email

*Healthcare Setting Type (select all that apply)

- ☐ Mental Health Facility ☒ Outpatient Clinic ☐ Independent Practice ☐ Group Practice
☒ Other

SPRAVATO® REMS Outpatient Healthcare Setting Enrollment Form

 **Registration**

 **Review
Materials**

Instructions

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99/99/9999



*Healthcare Setting Name

ABC HealthCare

*Healthcare Setting Address 1

123 Main Street

Address L

*City

Blue Bell

*State

PA

*Healthcare Setting Telephone Number

555 555-1212

Healthcar

*Healthcare Setting Type (select all that apply)

- ☐ Mental Health Facility ☒ Outpatient Clinic ☐ Independent Practice ☐ Group Practice
☒ Other

SPRAVATO[®] REMS Outpatient Healthcare Setting Certification


Registration




Review
Materials




Online
Enrollment

✓ Complete

Outpatient Healthcare Setting



The Outpatient Healthcare Setting is now certified in the SPRAVATO[®] REMS.

[Outpatient Healthcare Setting #1 Name]

Please check your email for additional requirements.

🕒 Pending

Outpatient Healthcare Setting



The certification of the following Outpatient Healthcare Setting(s) in the SPRAVATO[®] REMS is pending.

[Outpatient Healthcare Setting #2 Name]

If you have any questions, please contact the SPRAVATO[®] REMS Coordinating Center at 1-855-382-6022.

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO®

*I am a

☐ Healthcare Setting ☐ Prescriber ☐ Pharm

If you have questions about the SPRAVATO® REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

nts or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN
online at www.fda.gov/medwatch.

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 1-855-382-6022.

[Forgot Username](#)

LOGIN

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO

* I am a

☐

Healthcare Setting

☐

Prescriber

☒

Pharmacy Authorized Representative

Pharmacy Authorized Representative

* First Name

* Last Name

* Title

* Telephone Number

* Fax Number

* Email Address

Account Submitted Successfully

Thank you for submitting your information to create your web account for the SPRAVATO[®] REMS.

A confirmation of this submission has been sent to the email address provided. You can expect to receive 2 emails, one contains your username and the second contains your temporary password. Please login with the username provided. You will then be prompted to update your password.

If you do not receive the emails within the next few hours, or would like to update your enrollment information at any time, please contact the SPRAVATO[®] REMS at 1-855-6022.

LOGIN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATorems.com

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ter at

OR

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Register

To create your online account for the SPRAVATO

*I am a

☐ Healthcare Setting

☐ Prescriber

☐ Phar

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online at www.fda.gov/medwatch.

Login

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[Forgot Username](#)

LOGIN

Login

Please enter your password

* Password:

CANCEL

NEXT

I am a

☐

Healthcare Setting

☐

Prescriber

☐

Pharmacist

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call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare providers should report all adverse events and product quality complaints associated with SPRAVATO® at 1-800-JANSSEN (1-800-526-7736).

Reference ID: 4649523

Change Password



Your password has expired and must be changed.

*New Password:



*Re-type new Password:

CANCEL

NEXT

If you have questions about the SPRAVATO® REMS or need help enrolling,
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Monday – Friday, 8:00 AM – 8:00 PM ET

Users should report all adverse events and product quality complaints associated with SPRAVATO®
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Login

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[Forgot Username](#)

LOG IN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare provider only

Update Profile



* Security Caption:

* Security Question

* Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

CANCEL

NEXT



Register



Review
Materials



Online
Enrollment

review now by clicking on each link. Each document will open in a new

NEXT

nts or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANS
online at www.fda.gov/medwatch.



Register



Review
Materials



Online
Enrollment

the *SPRAVATO® REMS Program Overview*

om, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

, emergency department, etc.) and operate under the same DEA license and physical location
Healthcare Setting Enrollment form is completed/submitted, and you **do not require a separate**
is.

CONTINUE

SPRAVATO[®] REMS Pharmacy Enrollment Form


Register


Review
Materials

Instructions

1. Review the *SPRAVATO[®] Prescribing Information* and the *SPRAVATO[®] REMS Program Overview*
2. Complete this form online at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO[®] REMS Program

If you are an Inpatient Pharmacy (support inpatient units, emergency department, etc.) and operate under the same name as the pharmacy, your pharmacy will be considered certified once the Inpatient Healthcare Setting Enrollment form is completed/submitted. only for pharmacies that dispense to outpatient facilities.

* Indicates Required Field

Pharmacy Information

* DEA License Number (On file with distributor account)

2345

CONFIRM

* DEA Expiration Date (MM/DD/YYYY):

99/99/9999



* Name of Pharmacy

ABC Pharmacy

* Pharmacy Address 1

123 Main Street

Address Line 2

* City

Blue Bell

* State

PA

* ZIP

99999

* Pharmacy Type (select all that apply)

☐ Community/Retail ☐ Specialty ☐ Other

Your pharmacy information will be shared with Janssen's patient support and distribution partners, to allow you to receive support and resources.

Pharmacy Shipping Address, if different from above

SPRAVATO® REMS Pharmacy Enrollment Form



Instructions

1. Review the *SPRAVATO® Prescribing Information* and the *SPRAVATO® REMS Program Overview*
2. Complete this form online at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO REMS Program

If you are an Inpatient Pharmacy (support inpatient units, emergency department, etc.) and operate under the same pharmacy will be considered certified once the Inpatient Healthcare Setting Enrollment form is completed/submitted only for pharmacies that dispense to outpatient facilities.

* Indicates Required Field

Pharmacy Information

* DEA License Number (On file with distributor account)

2345

CONTINUE

* DEA Expiration Date (MM/DD/YYYY):

99/99/9999



* Name of Pharmacy

ABC Pharmacy

* Pharmacy Address 1

123 Main Street

Address Line 2

* City

Blue Bell

* State

PA

* ZIP

99999

* Pharmacy Type (select all that apply)

☐ Community/Retail ☐ Specialty ☒ Other

* Other Pharmacy Type

Other

Your pharmacy information will be shared with Janssen's patient support and distribution partners, to allow you to

Certification


Register




Review
Materials




Online
Enrollment

5.

CONTINUE

nts or product quality complaints associated with SPRAVATO[®] to Janssen at 1-800-JANS
online at www.fda.gov/medwatch.

Certification



SPRAVATO® REMS is pending.

SPRAVATO® REMS Coordinating Center at

CONTINUE

For adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN
online at www.fda.gov/medwatch.

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO®

*I am a

☐ Healthcare Setting ☐ Prescriber ☐ Pharm

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Monday – Friday, 8:00 AM – 8:00 PM ET

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online at www.fda.gov/medwatch.



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OR

Don't have an online account?

Register

To create your online account for the SPRAVATO

* I am a

☐ Healthcare Setting ☒ Prescriber ☐ Pha

Prescriber

Healthcare Setting Information

* Certified Healthcare Setting DEA License Num

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call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET



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OR

Don't have an online account?

Register

To create your online account for the SPRAVATO[®]

*I am a

☐

Healthcare Setting

☒

Prescriber

☐

Pharmacist

Prescriber

Healthcare Setting Information

*Certified Healthcare Setting DEA License Number

12345

Prescriber Information

*First Name

*Last Name

*Telephone Number

Fax Number

*Email Address

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 1-855-382-6022.

[Forgot Username](#)

LOGIN

OR

Don't have an account?

Register

To create an account, you must be a:

* I am a
☐ Healthcare Professional

Prescriber

[Healthcare Professional](#)

* Certified

Prescriber

* First Name

* Last Name

* Telephone

Fax Number

* Email Address

* Prescribing Institution

* Credentialing

☐ Physician

* Credentialing

Other

* Specialty

☐ Psychologist

Account Submitted Successfully

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OR

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☐ Prescriber

☐ Phar

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[Forgot Username](#)

LOGIN

Login

Please enter your password

* Password:

CANCEL

NEXT

I am a

☐

Healthcare Setting

☐

Prescriber

☐

Pharmacist

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*New Password:



*Re-type new Password:

CANCEL

NEXT

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[Forgot Username](#)

LOG IN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare provider only

Update Profile



* Security Caption:

* Security Question

* Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

CANCEL

NEXT

My Patients

Below is a list of your patients.

Enroll a Patient ▶

Patient Listing

-  Download the list to spreadsheet format by clicking the Excel icon just above the column headers.
-  Search/Filter the list by entering information in the textbox below any column header.
-  Sort the list by clicking on any column header.
-  Click on Patient REMS ID to view treatment history.

If you w
cannot t



Patient REMS ID	First Name	Last Name	Address	City	State	Zip	
111111	Robert	Smith	123 Main Street	Philadelphia	PA	19042	
22222	Mary	Connors	3 Broadway	Blue Bell	PA	19042	

SPRAVATO® REMS

Patient Monitoring Form - Outpatient Use Only

Instructions

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATorems.com or by fax (1-877-778-0091).

**Indicates Required Field*

Patient Information

First Name: Peggy

Middle Initial:

Birthdate (MM/DD/YYYY): 1/1/2000

Sex: Female

Concomitant Medications

Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?

*Benzodiazepines

☐ Yes ☐ No

*Non-benzodiazepine sedative hypnotics

☐ Yes ☐ No

*Psychostimulants

☐ Yes ☐ No

*Monoamine oxidase inhibitors (MAOIs)

☐ Yes ☐ No

Healthcare Provider Conducting Patient Monitoring

*First Name

John

*Last Name

Smith

*Telephone

555.555.1212

*Email

jsmith@abc

SPRAVATO[®] REMS

Patient Monitoring Form - Outpatient Use Only

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This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

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**Indicates Required Field*

Patient Information

First Name: Peggy

Birthdate (MM/DD/YYYY): 1/1/2000

Middle Initial:

Sex: Female

Concomitant Medications

Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?

*Benzodiazepines

☐ Yes ☐ No

*Non-benzodiazepine sedative hypnotics

☐ Yes ☐ No

*Psychostimulants

☐ Yes ☐ No

*Monoamine oxidase inhibitors (MAOIs)

☐ Yes ☐ No

Healthcare Provider Conducting Patient Monitoring

*First Name

John

*Last Name

Smith

*Telephone

555.555.1212

*Email

j.smith@oh

AGEMENT

orm for Patient ID 999999.

PRINT/DOWNLOAD

MY PATIENTS

s or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JA
online at www.fda.gov/medwatch.



1

/ 2



70%

**SPRAVATO® REMS****Patient Monitoring Form - Outpatient Use Only**For Healthcare Setting Use Only
Patient Label or Barcode Here**INSTRUCTIONS:**This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATOREMS.com or by fax (1-877-778-0091).

* Indicates Required Field

Patient Information (PRINT)			
First Name*	MI	Last Name*	Birthdate* (MM/DD/YYYY): Sex*: ☐ Male ☐ Female ☐ Other
Concomitant Medication			
Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?			
• Benzodiazepines*	☐ Yes	☐ No	
• Non-benzodiazepine sedative hypnotics*	☐ Yes	☐ No	
• Psychostimulants*	☐ Yes	☐ No	
• Monoamine oxidase inhibitors (MAOIs)*	☐ Yes	☐ No	
Healthcare Provider Conducting Patient Monitoring (PRINT)			
First Name*	Last Name*		
Telephone*	Email*		
Healthcare Setting Information (PRINT)			
Healthcare Setting Name*			
Healthcare Setting Address 1*		Healthcare Setting Address 2*	
City*	State*	ZIP*	
Patient Treatment Session Information (Administration and Monitoring)			
Treatment Date*	Date (MM/DD/YYYY):		
Dose Administered*	☐ 56 mg ☐ 84 mg ☐ Other: _____		
Treatment Duration*	Total time _____ minutes (from 1st device administration to completion of monitoring) Patient must be monitored for at least 2 hours		
REMS Evaluation Question*	If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring? _____ minutes from start of administration		
Monitoring of Vital Signs*	Vital signs were in acceptable range prior to: • administration? ☐ Yes ☐ No • treatment session completion? ☐ Yes ☐ No		
Monitoring of Blood Pressure*	Prior to administration _____ mmHg	40 mins post-administration _____ mmHg	Prior to treatment session completion _____ mmHg
Did the patient experience Sedation and/or Dissociation			
Sedation*: ☐ Yes ☐ No		Dissociation*: ☐ Yes ☐ No	
Onset of symptoms from start of administration*		Onset of symptoms from start of administration*	
☐ 1-20 mins ☐ 20-60 mins ☐ 60-90 mins ☐ 90-120 mins ☐ >120 mins		☐ 1-20 mins ☐ 20-60 mins ☐ 60-90 mins ☐ 90-120 mins ☐ >120 mins	

SPRAVATO[®] REMS

Patient Enrollment Form - Outpatient Use Only

Instructions

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments

1. Complete this form online at www.SPRAVATorems.com, or complete the paper form and fax to the SPRAVATO

**Indicates required field*

Healthcare Setting Information

Change Healthcare Setting ▶

Healthcare Setting DEA License Number (associated with the Healthcare Setting address): 12345

Healthcare Setting Name:

Address 1: 100 Main Street

City: Malvern

Phone: 555 555-1212

Address 2:

State: PA

Fax: 555 555-1212

Prescriber Information

*First Name

Marc

*Last Name

Jones

*Credentials

☒ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other

*Specialty

☐ Psychiatry

*Prescriber DEA License Number

12345

*Email

mjones@ab

*Phone

555 555-1212

Fax

555 555-34

Referring Healthcare Provider - if different from Prescriber

☐ Referring Healthcare Provider- Same as Prescriber

MY PATIENTS

CERTIFIED PHARMACIES

DELEGATE M

SPRAVATO[®] REMS Patient Enrollment Form - Out

Instructions

This form is intended only for use by outpatient medica

1. Complete this form online at www.SPRAVATOREMS.com.

**Indicates required field*

Healthcare Setting Information

Change Healthcare Setting ▶

Healthcare Setting DEA License Number (associated with the Healthcare Setting address): 12345

Healthcare Setting Name:

Address 1: 100 Main Street

City: Malvern

Phone: 555.555-1212

Address 2:

State: PA

Fax: 555.555-3434

Change Healthcare Setting



Please click on the Healthcare Setting name to select, then click "Continue".

DEA License Number	HCS Name	City	State
11111	Healthcare Facility Name1	Philadelphia	PA
22222	Healthcare Facility Name2	NY	NY

CANCEL

CONTINUE

SPRAVATO[®] REMS Patient Enrollment Form - Outpatient Use Only

Instructions

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1. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO

**Indicates required field*

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Healthcare Setting DEA License Number (associated with the Healthcare Setting address): 12345

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Address 1: 100 Main Street

City: Malvern

Phone: 555 555-1212

Address 2:

State: PA

Fax: 555 5

Prescriber Information

*First Name

Marc

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Jones

*Credentials

☒ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other

*Specialty

☐ Psychi

*Prescriber DEA License Number

12345

*Email

mjones@ab

*Phone

555 555-1212

Fax

555 555-34

Referring Healthcare Provider - if different from Prescriber

☒ Referring Healthcare Provider- Same as Prescriber

Welcome

Agree to Terms

Sign

Done



2

3

4

A new document from SPRAVATO[®] REMS is available for you to sign.

You will be given the opportunity to:

- Preview the document.
- Send feedback or questions to SPRAVATO[®] REMS.
- Decline signing and send feedback to SPRAVATO[®] REMS.
- Sign the document electronically using AssureSign.



Continue

Powered by AssureSign

[Terms of Use](#) [Privacy Policy](#)

Welcome



Agree to Terms



Sign

3

Done

4

Review the terms and conditions below and check the checkbox indicating your agreement to receive and sign this document electronically. Click **Start Signing** when you are ready to sign.

By checking the box below, I agree that the electronic digitized signatures I apply on the following document are representations of my signature and are legally valid and binding as if I had signed the document with ink on paper in accordance with the Uniform Electronic Transactions Act (UETA) and the Electronic Signatures in Global and National Commerce Act (E-SIGN) of 2000.



AssureSign complies with requirements and standards of the Electronic Signatures In Global and National Commerce Act (E-SIGN Act) effective October 1, 2000, the Uniform Electronic Transaction Act (UETA), and the Government Paperwork Elimination Act (GPEA)

☐ I have read and agree to the terms and conditions

Preview Document



Start Signing

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[Terms of Use](#) [Privacy Policy](#)

Reference ID: 4649523



Please sign with your mobile device with a pen on paper.



Back

Adopt a Signature

Provide your name by drawing with touch, mouse, or stylus.

Signature

By clicking "Adopt Signature", I agree that the signature and initials above will be the electronic representation of my signature and initials for all purposes when I use them to sign documents. Applying them to a document is legally equivalent to signing with a pen on paper.

Adopt Signature



Sex: ☐ M ☐ F ☐ Other

99999

...will be provided to the REMS.
...my changes in my vital signs.

...the provider determines I am ready

...facts resolve, I may feel:

...e of all patients who receive

...support administration of

...th information for the purpose of
...nsing of SPRAVATO, and
...as otherwise required by law.

Sex:

[Terms of Use](#) [Privacy Policy](#)

Welcome

Agree to Terms

Sign

Done

All Information Entered

You have entered all requested information and signatures.

When ready, click Finish to complete this step of the document signing process.

Back

Finish

1 of 2



Patient Enrollment Form - Outpatient Use Only



INSTRUCTIONS:

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments

1. Complete this form online at www.SPRAVATOREMS.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

This section is to be completed by the Prescriber

* Indicates required field

Healthcare Setting Information		
Healthcare Setting Name*: Professional Testing Facility		
Healthcare Setting DEA License Number* (associated with the Healthcare Setting address): 99999		
Address 1*: 999 Broadway		Address 2:
City*: Philadelphia	State*: PA	ZIP*: 99999
Phone*: 555-555-1212	Fax*: 555-555-3434	
Prescriber Information		
First Name*: John		Last Name*: Smith
Credentials*: ☒ Physician ☐ Physician Assistant ☐ Nurse ☐ Pharmacist ☐ Other _____		Prescriber DEA License Number*: 444444
Specialty*: ☒ Psychiatry ☐ Internal Medicine ☐ Family Practice ☐ Other _____		
Phone*: 555-555-7777	Fax: 555-555-8888	Email*: jsmith@xyz.com
Prescriber Signature*: 		Date*:
Referring Healthcare Provider – if different from Prescriber		
First Name:		Last Name:

Welcome

Agree to Terms

Sign

Done



2

3

4

A new document from SPRAVATO® REMS is available for you to sign.

You will be given the opportunity to:

- Preview the document.
- Send feedback or questions to SPRAVATO® REMS.
- Decline signing and send feedback to SPRAVATO® REMS.
- Sign the document electronically using AssureSign.

UserName: abc@abc.com

Note - Please check your email for the password.

Password*



Continue

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Reference ID: 4649523

Welcome

Agree to Terms

Sign

Done



Review the terms and conditions below and check the checkbox indicating your agreement to receive and sign this document electronically. Click **Start Signing** when you are ready to sign.

By checking the box below, I agree that the electronic digitized signatures I apply on the following document are representations of my signature and are legally valid and binding as if I had signed the document with ink on paper in accordance with the Uniform Electronic Transactions Act (UETA) and the Electronic Signatures in Global and National Commerce Act (E-SIGN) of 2000.



AssureSign complies with requirements and standards of the Electronic Signatures In Global and National Commerce Act (E-SIGN Act) effective October 1, 2000, the Uniform Electronic Transaction Act (UETA), and the Government Paperwork Elimination Act (GPEA)

☐ I have read and agree to the terms and conditions

Preview Document



Start Signing

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Reference ID: 4649523

Welcome

Agree to Terms

Sign

Done



Please sign with your mobile device
with a pen on paper.

X _ _ _ _ _

Back

Adopt a Signature

Provide your name by drawing with touch, mouse, or stylus.

Signature

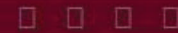
X _ _ _ _ _



By clicking "Adopt Signature", I agree that the signature and initials above will be the electronic representation of my signature and initials for all purposes when I use them to sign documents. Applying them to a document is legally equivalent to signing with a pen on paper.

Adopt Signature

4



See: ☐ M ☒ P ☐ Other

99999

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Welcome

Agree to Terms

Sign

Done

All Information Entered

You have entered all requested information and signatures.

When ready, click Finish to complete this step of the document signing process.

Back

Finish

1 of 2

Patient Information

First Name*: Mary	MI: M	Last Name*: Smith	Birthdate*: (MM/DD/YYYY): 1/1/2000	Sex*: ☐ Male ☒ Female ☐ Other
Email*: (Email is required for online enrollment only) abc@abc.com			Phone Number*: 555-555-1212	
Address 1*: 100 Main St			Address 2:	
City*: Philadelphia			State*: PA	ZIP*: 99999

Patient Agreement

By signing this form, I understand and acknowledge that:

Before my treatment begins, I will:

- Enroll in the SPRAVATO® REMS by completing this Patient Enrollment Form with my healthcare provider. Enrollment information will be submitted to the SPRAVATO® REMS.
- Receive counseling on safety risks and the need for monitoring to observe for resolution of sedation and dissociation, and for any changes in vital signs.

During treatment and after administration I will:

- Use the SPRAVATO® nasal spray myself under the direct observation of a healthcare provider.
- Be observed at the healthcare setting where I receive SPRAVATO® for at least 2 hours after each treatment until the healthcare provider determines I am ready to leave the healthcare setting.

I understand:

- Sedation and dissociation can result from treatment with SPRAVATO® and I must stay after each treatment. Until these effects resolve, I may experience:
 - sleepy and/or
 - disconnected from myself, my thoughts, feelings and things around me.
- I should make arrangements to safely get home.
- I should not drive or use heavy machinery for the rest of the day on which I receive SPRAVATO®.
- I should contact my doctor or inform him/her at my next visit if I believe I have a side effect or reaction from SPRAVATO®.
- In order to receive SPRAVATO® as an outpatient, I am required to be enrolled in the REMS, and my information will be stored in a database of all outpatients who receive SPRAVATO® in the United States.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may contact me or my prescriber via phone, mail, fax, or email to support administration of the REMS.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may use, disclose, and share my personal health information for the purpose of the operations of the REMS, including enrolling me into the REMS and administering the REMS, coordinating the dispensing of SPRAVATO®, and releasing and disclosing my personal health information to the Food and Drug Administration (FDA), as necessary, and as otherwise required by law.

Patient Name (please print): Mary Smith

Patient Signature*: 

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ANAGEMENT

Date of Birth: 1/1/2000

REMS Status: Enrolled

Most Recent Status Date: 5/23/2018

tment Dosage: 10mg

HCS Location: ABC Location

tment Dosage: 10mg

HCS Location: XYZ Location

Certified Pharmacy Listing

Below is a listing of pharmacies that are REMS-certified and can purchase SPRAVATO®.

 Search/Filter the list by entering information in the textbox below any column header.

 Sort the list by clicking on any column header.

Pharmacy Name 	Address 1 	Address 2 	City 	State 	Zip 
				-- Please Select --	
ABC Pharmacy	100 Main Street	Suite 41	Spicewood	TX	123
XYZ Pharmacy	999 Broadway		Philadelphia	PA	123

Phone: 1-855-382-6022

Fax: 1-877-778-0091

www.SPRAVATorems.com

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN or online at www.fda.gov/medwatch.

ed. If
ter at

OR

Don't have an online account?

Register

To create your online account for the SPRAVATO

*I am a

☐ Healthcare Setting ☐ Prescriber ☐ Phar

If you have questions about the SPRAVATO® REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

ents or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSS
online at www.fda.gov/medwatch.

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 855-382-6022.

[Forgot Username](#)

LOGIN

Login

Please enter your password

* Password:

CANCEL

NEXT

I am a

☐

Healthcare Setting

☐

Prescriber

☐

Pharmacist

If you have questions about the SPRAVATO[®] REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATorems.com

Healthcare providers should report all adverse events and product quality complaints associated with SPRAVATO[®] at 1-800-JANSSEN (1-800-526-7736).

Reference ID: 4649523

Change Password



Your password has expired and must be changed.

*New Password:



*Re-type new Password:

CANCEL

NEXT

If you have questions about the SPRAVATO® REMS or need help enrolling,
call 1-855-382-6022
Monday – Friday, 8:00 AM – 8:00 PM ET

Users should report all adverse events and product quality complaints associated with SPRAVATO®
at 1-800-JANSSEN (1-800-526-7736).

Login

Your username was supplied to you via email when you registered. If you need assistance, please contact the REMS Coordinating Center at 855-382-6022.

[Forgot Username](#)

LOG IN

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOREMS.com

Healthcare provider only

Update Profile



* Security Caption:

* Security Question

* Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

-- Please Select --

▼ Answer

CANCEL

NEXT

My Patients

Below is a list of your patients.

Patient Listing

-  Download the list to spreadsheet format by clicking the Excel icon just above the column headers.
-  Search/Filter the list by entering information in the textbox below any column header.
-  Sort the list by clicking on any column header.
-  Click on Patient REMS ID to view treatment history.

If you w
cannot t





Patient REMS ID	First Name	Last Name	Address	City	State	Zip	
							
111111	Robert	Smith	123 Main Street	Philadelphia	PA	19042	
22222	Mary	Connors	3 Broadway	Blue Bell	PA	19042	

SPRAVATO® REMS

Patient Monitoring Form - Outpatient Use Only

Instructions

This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATOrems.com or by fax (1-877-778-0091).

**Indicates Required Field*

Patient Information

First Name: Peggy

Birthdate (MM/DD/YYYY): 1/1/2000

Middle Initial:

Sex: Female

Concomitant Medications

Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?

*Benzodiazepines

☐ Yes ☐ No

*Non-benzodiazepine sedative hypnotics

☐ Yes ☐ No

*Psychostimulants

☐ Yes ☐ No

*Monoamine oxidase inhibitors (MAOIs)

☐ Yes ☐ No

Healthcare Provider Conducting Patient Monitoring

*First Name

John

*Last Name

Smith

*Telephone

555.555.1212

*Email

jsmith@abc.com

SPRAVATO® REMS

Patient Monitoring Form - Outpatient Use Only

Instructions

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1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATOREMS.com or by fax (1-877-778-0091).

**Indicates Required Field*

Patient Information

First Name: Peggy

Birthdate (MM/DD/YYYY): 1/1/2000

Middle Initial:

Sex: Female

Concomitant Medications

Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?

*Benzodiazepines

☐ Yes ☐ No

*Non-benzodiazepine sedative hypnotics

☐ Yes ☐ No

*Psychostimulants

☐ Yes ☐ No

*Monoamine oxidase inhibitors (MAOIs)

☐ Yes ☐ No

Healthcare Provider Conducting Patient Monitoring

*First Name

John

*Last Name

Smith

*Telephone

555.555.4343

*Email

j.smith@abc.com

Patient Monitoring Form

Thank you for submitting a Patient Monitoring Form for Patient ID 999999.

PRINT/DOWNLOAD

MY PATIENTS

Phone: 1-855-382-6022
Fax: 1-877-778-0091
www.SPRAVATOrms.com

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1

/ 2



70%

**SPRAVATO® REMS****Patient Monitoring Form - Outpatient Use Only**For Healthcare Setting Use Only
Patient Label or Barcode Here**INSTRUCTIONS:**This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.

1. Complete all required fields on this form after every treatment session for all outpatients enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within 7 days, online at www.SPRAVATOREMS.com or by fax (1-877-778-0091).

* Indicates Required Field

Patient Information (PRINT)			
First Name*	MI	Last Name*	Birthdate* (MM/DD/YYYY): Sex*: ☐ Male ☐ Female ☐ Other
Concomitant Medication			
Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?			
• Benzodiazepines*	☐ Yes ☐ No		
• Non-benzodiazepine sedative hypnotics*	☐ Yes ☐ No		
• Psychostimulants*	☐ Yes ☐ No		
• Monoamine oxidase inhibitors (MAOIs)*	☐ Yes ☐ No		
Healthcare Provider Conducting Patient Monitoring (PRINT)			
First Name*		Last Name*	
Telephone*		Email*	
Healthcare Setting Information (PRINT)			
Healthcare Setting Name*			
Healthcare Setting Address 1*		Healthcare Setting Address 2*	
City*		State*	ZIP*
Patient Treatment Session Information (Administration and Monitoring)			
Treatment Date*	Date (MM/DD/YYYY):		
Dose Administered*	☐ 56 mg ☐ 84 mg ☐ Other: _____		
Treatment Duration*	Total time _____ minutes (from 1st device administration to completion of monitoring) Patient must be monitored for at least 2 hours		
REMS Evaluation Question*	If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring? _____ minutes from start of administration		
Monitoring of Vital Signs*	Vital signs were in acceptable range prior to: • administration? ☐ Yes ☐ No • treatment session completion? ☐ Yes ☐ No		
Monitoring of Blood Pressure*	Prior to administration _____ mmHg	40 mins post-administration _____ mmHg	Prior to treatment session completion _____ mmHg
Did the patient experience Sedation and/or Dissociation			
Sedation*: ☐ Yes ☐ No		Dissociation*: ☐ Yes ☐ No	
Onset of symptoms from start of administration*		Onset of symptoms from start of administration*	
☐ 1-20 mins ☐ 20-60 mins ☐ 60-90 mins ☐ 90-120 mins ☐ >120 mins		☐ 1-20 mins ☐ 20-60 mins ☐ 60-90 mins ☐ 90-120 mins ☐ >120 mins	

Patient Profile



REMS ID: 111111

Robert Smith

123 Main Street

Philadelphia, PA 19042

rsmith@abc.com

Date of Birth: 1/1/2000

REMS Status: Enrolled

Most Recent Status Date: 5/23/2018

Patient Monitoring Forms

Treatment Date: 5/23/2018

Treatment Dosage: 10mg

HCS Location: ABC Location

Treatment Date: 3/23/2018

Treatment Dosage: 10mg

HCS Location: XYZ Location

Phone: 1-855-382-6022

Fax: 1-877-778-0091

www.SPRAVATOrems.com

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSS online at www.fda.gov/medwatch.

and can purchase SPRAVATO®.

ow any column header.

Address 2	City	State	Zip
		-- Please Select --	
Suite 41	Spicewood	TX	1234
	Philadelphia	PA	1234

ents or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSS
online at www.fda.gov/medwatch.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s004

MULTI-DISCIPLINE REVIEW

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Product Quality Review

NDA/BLA Multi-disciplinary Review and Evaluation

NDA 211243 S004

Spravato (esketamine) nasal spray

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	211243 s4
Priority or Standard	Standard
Submit Date(s)	October 2, 2019
Received Date(s)	October 2, 2019
PDUFA Goal Date	August 2, 2020
Division/Office	Division of Psychiatry
Review Completion Date	
Established/Proper Name	Esketamine
(Proposed) Trade Name	Spravato
Pharmacologic Class	antidepressant
Code name	JNJ-54135419
Applicant	Janssen Pharmaceuticals, Inc.
Dosage form	Intranasal solution
Applicant proposed Dosing Regimen	84 mg twice per week for 4 weeks
Applicant Proposed Indication(s)/Population(s)	MDD with Active Suicidal Ideation and Intent
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	SPRAVATO is indicated, in conjunction with an oral antidepressant, for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	84 mg twice per week for 4 weeks (may be reduced to 56 mg twice per week for 4 weeks based on tolerability)

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OPQ=Office of Pharmaceutical Quality
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OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Signatures

See electronic signatures.

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Glossary

AC	advisory committee
AD	antidepressant
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
APA	American Psychiatric Association
AR	adverse reaction
BHS	Beck Hopelessness Scale
BLA	biologics license application
BMI	Body Mass Index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
BPRS	Brief Psychiatric Rating Scale
BRF	Benefit Risk Framework
BSS	Beck Scale for Suicidal Ideation
CADSS	Clinician-Administered Dissociative States Scale
CBER	Center for Biologics Evaluation and Research
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CGI-SR-I	Clinical Global Impression of Suicide Risk – Imminent
CGI-SR-LT	Clinical Global Impression of Suicide Risk – Long-Term
CGI-SS-R	Clinical Global Impression of Severity of Suicidality – Revised
CGJ-SR	Clinical Global Judgment of Suicide Risk
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
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
DBP	diastolic blood pressure
DHOT	Division of Hematology Oncology Toxicology
DRC	Data Review Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram

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ECT	electroconvulsive therapy
eCRF	electronic case report form
eCTD	electronic common technical document
EQ-5D-5L	European Quality of Life Group, 5-Dimension, 5-Level
ER	emergency room
ESK	esketamine
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
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IN	intranasal
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IWRS	interactive web response system
LSD	lysergic acid diethylamide
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MDMA	3,4-methylenedioxy-methamphetamine
MDSI	major depressive disorder, without psychotic features, assessed to be at imminent risk for suicide (i.e., with suicidal ideation and intent)
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
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
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
PCP	phencyclidine
PD	pharmacodynamics
PI	prescribing information

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PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRN	as-needed
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
QLDS	Quality of Life in Depression Scale
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SI	suicidal ideation
SIBAT	Suicidal Ideation and Behavior Assessment Tool
SOC	standard of care
TCA	tricyclic antidepressant
TEAE	treatment emergent adverse event
TRD	treatment-resistant depression
TSQM-9	Treatment Satisfaction Questionnaire for Medication

1 Executive Summary

1.1. Product Introduction

SPRAVATO is an esketamine drug-device combination designed for intranasal administration. Esketamine is the S-enantiomer of ketamine, an N-methyl-D-aspartate glutamate (NMDA) receptor blocker that enhances glutamine release in the brain. 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 in a 28-mg unit-dose nasal spray device. SPRAVATO was approved in March 2019 for the treatment of treatment resistant depression (TRD) in adults.

With this supplemental new drug application (NDA), the Applicant proposes SPRAVATO for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior (MDSI). The proposed dosing for this indication is 84 mg twice weekly for 4 weeks; the dosage may be reduced to 56 mg twice weekly based on tolerability. As with the TRD indication, SPRAVATO for MDSI is used in conjunction with oral antidepressant treatment. Additionally, the patients studied for this indication—all of whom presented with acute suicidal ideation—were admitted for inpatient treatment for several days when SPRAVATO was initiated. SPRAVATO cannot substitute for inpatient treatment.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The studies submitted in support of SPRAVATO for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior were adequate and well-controlled. Studies 54135419SUI3001 and 54135419SUI3002 (hereafter, 3001 and 3002, respectively) were nearly identical randomized, double-blind, placebo-controlled, parallel-group trials of esketamine 84 mg intranasally twice weekly for 4 weeks added to standard of care. Standard of care included optimized oral antidepressant treatment (which could include augmenting medications in addition to traditional antidepressants) and a 5-day inpatient hospital stay. The primary endpoint for these studies was the change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours post-first esketamine dose. Study ESKETINSUI2001 (hereafter, 2001) was a similarly designed proof-of-concept study with the primary endpoint of MADRS change-from-baseline at 4 hours post-first esketamine dose. The MADRS is a scale frequently used to measure symptoms of depression in clinical trials and recognized in the FDA Clinical Outcome Assessment Compendium.

In Studies 3001 and 3002, the Applicant included a measure of suicidal ideation (SI), 24 hours post-first esketamine dose as a prespecified secondary endpoint with control for type I error. The SI measure, developed with Agency input and acceptable to the Division, was the Clinical Global Impression of Severity of Suicidality – Revised (CGI-SS-R).

The study population included adults with acute SI with intent (within the previous 24 hours) and a physician's opinion that acute psychiatric hospitalization was clinically warranted due to the subject's imminent risk of suicide.

In Studies 3001 and 3002, the mean MADRS baseline score of approximately 40 decreased by approximately 12 to 13 in the placebo group and 16 to 17 in the esketamine group at 24 hours. The differences between MADRS scores in the placebo and esketamine groups were both statistically significant and clinically meaningful. In Study 2001, the change in MADRS total score from baseline to 4 hours post-dose was approximately 9 in the placebo group and 13 in the esketamine group.

Neither Study 3001 nor 3002 demonstrated a difference between the placebo and esketamine groups in the CGI-SS-R change-from-baseline at 24 hours. Both placebo and esketamine groups showed a clinically meaningful decrease in SI. Therefore, there was no evidence presented in this application that esketamine decreases suicidal ideation or behavior beyond standard of care.

Based on Agency review, this application has met the evidenciary standard for safety and effectiveness. Accordingly, SPRAVATO is recommended for approval for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

The studies submitted for the approval of intranasal esketamine for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior (MDSI) met the evidentiary standard by providing substantial evidence of effectiveness from at least two adequate and well-controlled studies (3001 and 3002). There is also supportive evidence of esketamine's efficacy for the depressive symptoms in this patient population from the proof-of-concept study (2001). In all three studies, the placebo-subtracted mean MADRS score reductions in the esketamine arms are consistent with the improvement seen in other FDA-approved antidepressants. It is also clinically relevant that these reductions were seen hours after starting esketamine whereas traditional oral antidepressants take weeks to produce a meaningful change in depressive symptoms.

Although esketamine did not reduce suicidal ideation (SI) beyond the reduction observed with standard clinical care, the fact that a population with SI was studied is clinically important. Almost all antidepressant development programs have historically excluded patients with acute SI. It is often assumed that antidepressants are as effective for depression in this population as for people with MDD and no SI—however, there is little data to support this assumption. This application provides evidence that, in the case of esketamine, the depressive symptoms of people with MDSI respond.

The safety profile of esketamine was characterized with the initial SPRAVATO approval and this supplement contains no data that alters this initial assessment. Acute risks (such as dissociation, sedation, increased blood pressure, and potential for abuse and diversion) are currently mediated by the SPRAVATO REMS. Chronic dosing concerns (such as bladder toxicity, cognitive changes, and neurotoxicity) have not shown unexpected, severe, or irreversible safety signals in the long-term esketamine safety studies thus far. Ongoing open-label and postmarketing safety studies and pharmacovigilance and surveillance (including REMS reporting) will provide data and continuing attention to these safety concerns.

There is substantial evidence of effectiveness for intranasal esketamine, in combination with oral antidepressant treatment, for the treatment of depressive symptoms in people with MDSI. The risks do not outweigh the benefits of treatment for this population. Accordingly, the Agency review team for NDA 211243, supplement 004, recommends approval of intranasal esketamine for this indication in adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	MDD with acute suicidal ideation or behavior (MDSI) is a serious and life-threatening condition with high rates of individual and society-level morbidity. MDD is a chronic disease and suicidal ideation and behavior are often recurrent. Patients with MDSI usually require inpatient treatment and are unable to work, have difficulty maintaining relationships, and may commit suicide.	MDSI is a high-risk condition in serious need of approved treatments.
Current Treatment Options	- It has been assumed that treatment with available oral antidepressants can improve depressive symptoms in patients who are acutely suicidal. However, people with MDD and acute SI are usually excluded from drug registration studies. Therefore, data on response to treatment for this particular group of patients (whether a unique subpopulation of patients or people in a particular phase of their illness) are lacking. - Oral antidepressants, when effective for MDD, usually take several weeks to demonstrate their effects. For people who are acutely suicidal, urgent treatment of their mood symptoms is important. - Treatments cleared by the Agency’s Center for Devices and Radiological Health (CDRH) for MDD are electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and (in severe cases) vagus nerve stimulator (VNS) implantation. All have significant adverse reactions to consider, including the 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 other MDD treatments.	Existing pharmacological treatments for MDD have little direct data to support their efficacy in people who are also acutely suicidal. Additionally, oral antidepressants exert their effects over weeks and there are scant data to support their utility with regard to acute relief of mood symptoms in people who are acutely suicidal. Device-related MDD treatments either have serious associated risks or lack compelling data regarding comparative efficacy with antidepressants.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- Evidence: Studies 3001 and 3002 demonstrated statistically significant and clinically meaningful changes in their primary endpoints: A rating scale of depression symptoms administered 24 hours after the first esketamine dose. Additional support comes from the proof-of-concept study (2001) in which there was a statistically significant and clinically meaningful decrease in depressive symptoms 4 hours after the first esketamine administration. The esketamine course was 4 weeks, but subjects were followed through Day 90. Although not formally statistically examined, the mean severity of depression symptoms did not return to baseline levels after the course of esketamine was finished. - Uncertainties: Esketamine showed no improvement beyond standard-of-care on SI as measured in 3001 and 3002. All patients enrolled in Studies 2001, 3001, and 3002 were started on oral antidepressant treatment and admitted for at least 5 days of inpatient care. Although the esketamine group did not show relapse to baseline depression levels after discontinuing study drug, there did not appear to be a meaningful difference at Day 90 between the group that had received esketamine and the group that had received placebo.	These studies provide substantial evidence of effectiveness for intranasal esketamine for the treatment of the depressive symptoms of MDSI—a population often excluded from MDD trials. It is also worth noting that people with MDD and SI require urgent treatment and esketamine appears to offer more rapid treatment of depressive symptoms than the approved oral antidepressants. It appears that the 4-week course of esketamine twice per week is adequate for treatment of MDSI (in the context of continued oral antidepressant treatment). However, based on the analysis of submitted data, it cannot be determined why patients who received esketamine did not return to their baseline depression severity after completing their 4-week course. Because the placebo group also improved—and was not different from the esketamine group by Day 90—it is not likely a durability effect of the esketamine treatment; it may be the effects of the oral antidepressant treatment. Therefore, the label should reflect that the use of esketamine for MDSI is intended for 4 weeks, but there are no

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		definitive data on dosing recommendations beyond this initial course. Esketamine did not demonstrate improvement of SI beyond that offered by oral medication and inpatient hospitalization. Esketamine is NOT a replacement for inpatient treatment and patients presenting with SI and who are appropriate for hospitalization should be hospitalized regardless of whether esketamine is started.
Risk and Risk Management	- Acute Safety: As with the initial application for TRD, the major effects of concern identified in this submission were sedation (29% versus 12% in placebo), dissociation (48% versus 13%), and elevated blood pressure (15% versus 6%). No cases of acute hepatotoxicity or clinically meaningful liver function test trends were noted. - Subacute/Chronic Safety: The major effects of concern with chronic esketamine use are possible bladder toxicity, cognitive impairment, and neurotoxicity (based on nonclinical studies of NMDA receptor blockers). - Abuse Potential: Esketamine has similar drug-liking characteristics (i.e., euphoria and dissociation) to ketamine, a known drug of abuse.	SPRAVATO was approved for TRD with a Risk Evaluation Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) to mitigate the risks of sedation, dissociation, and elevated blood pressure. With an MDSI indication, the administration of the REMS should be amended to account for inpatient and outpatient use as well as the potential start of esketamine in an urgent setting (e.g., emergency rooms). However, there was nothing in this supplement that would require amending the content of the REMS. Although esketamine for MDSI is intended as a time-limited course of treatment, patients with MDSI who also meet the criteria for TRD may be

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		continued on esketamine indefinitely. Existing labeling addresses most chronic use concerns. Additionally, a long-term esketamine follow-up study is underway to provide more information on concerns related to chronic esketamine use. Esketamine’s abuse potential has been addressed by categorizing it as a Schedule III controlled substance. The REMS requirements (esketamine is only used in a physician’s office) also minimize this risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	8.1, 8.2, 8.3, 8.4
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	8.1, 8.2, 8.3, 8.4
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. An estimated 17.3 million adults in the United States had at least one major depressive episode in 2017, with an estimated incidence of approximately 242 million people worldwide (SAMHSA 2018; GBD 2018). 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 is associated with increased mortality rates (at a median rate of 10 years of life lost; Walker et al. 2015). Table 1 lists the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for a major depressive episode (American Psychiatric Association 2013).

Table 1. Diagnostic Criteria for a Major Depressive Episode¹

A	Five (or more) of the following symptoms present during the same 2-week period and represent a change from previous functioning; at least one of which is either (1) or (2): 1. Depressed mood most of the day, nearly every day² 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day² 3. Significant weight loss (when not dieting) or gain, or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6. Fatigue or loss of energy nearly every day 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day² 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B	Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C	The episode is not attributable to the physiological effects of a substance or another medical condition
D	The episode is not better explained by a psychotic illness
E	There has never been a manic or hypomanic episode

¹ Reviewer-adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association 2013)

² As indicated by either subjective report or observation made by others

The Applicant studied adult patients with MDD with active suicidal ideation (i.e., with a plan) with intent. In adults with MDD, the reported prevalence of suicidal ideation ranges as high as 60%, with a lifetime incidence of attempted suicide between 10% and 20%, and an estimated lifetime risk of completed suicide of 3.4% (Hasin et al. 2018; Holma et al. 2010; Blair-West et al. 1999). Studies have indicated that, among patients with MDD, patients with suicidal ideation or behavior have more severe depressive symptoms, greater psychiatric comorbidity including alcohol dependence/abuse, worse functioning and quality of life, and more prior suicide attempts (Sokero et al. 2003; Zisook et al. 2011). Studies also indicate that most patients with MDD who attempt or complete suicide have suicidal ideation prior to the event, and patients with more severe ideation (i.e., including intent or intent with a plan) are at a greater risk of attempt or completion (Brown et al. 2000; Sokero et al. 2003).

In summary, MDD is a chronic, serious condition with a high rate of morbidity and increased mortality, including the potential for suicide. Patients with MDD with suicidal ideation or behavior appear to have a more severe presentation, and those with active suicidal ideation with intent appear to be at greater risk of suicide attempt or completion.

2.2. Analysis of Current Treatment Options

First-line treatments for MDD include oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, and others) and psychotherapy. Antidepressants have demonstrated efficacy in the treatment of MDD, including in patients who are severely depressed (Fournier et al. 2010; Gartlehner et al. 2008; Williams et al. 2000). However, about 30 to 40% of patients with MDD fail to respond to first-line treatments (Rush et al. 2006). If first-line treatments fail, treatment options include switching to a different antidepressant (either in the same or a different class), adding augmentation treatment to an ongoing antidepressant (typically a drug with a different mechanism of action, including antidepressants, certain approved-for-augmentation or off-label second-generation antipsychotics, and off-label lithium or thyroid hormone), adding or switching psychotherapy, or referral for a procedure such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS; APA 2010; Brunoni et al. 2017). ECT is approved for the treatment of severe major depressive episodes (unipolar or bipolar) or catatonia in individuals aged 13 or over who are either treatment-resistant or require a rapid response. TMS is approved to treat the symptoms of MDD (without inducing seizure) in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.

For almost all of these first- or second-line treatments (except ECT), the onset to response—even when effective—often takes at least 2 to 4 weeks, with continued suffering and risk of adverse sequelae, including suicide. No other approved pharmacological treatment rapidly reduces depressive symptoms in patients with MDD (with or without suicidal ideation and behavior) and no MDD treatment has been proven to reduce the severity of suicidal ideation or behavior in patients with MDD (clozapine is approved for reducing suicidal behavior in patients

with schizophrenia or schizoaffective disorder). Importantly, almost all of the pivotal studies leading to the approval of oral antidepressants have excluded patients with active suicidal ideation. Although clinical treatment often assumes that antidepressants will improve mood in this subgroup of MDD patients, their actual effect is unknown.

With ECT treatment of MDD, response typically begins to occur after two to four treatments (with treatments given typically three times per week), with a median time to first response of 1 week in one study of 253 patients (Hussain et al. 2004). The American Psychiatric Association (APA) practice guideline for the treatment of MDD recommends ECT as a treatment of choice for patients with severe MDD who, among other reasons (e.g., associated psychotic or catatonic features), have an urgent need for response (e.g., suicidal ideation; APA 2010; Kellner et al. 2010). However, the use of ECT is limited by associated significant adverse reactions and interventional concerns (such as use of general anesthesia, seizure induction, and memory loss).

Spravato (intranasal esketamine) was approved in March 2019, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. As noted in its Prescribing Information, in a randomized, double-blind, placebo-controlled, 4-week, phase 3 study, most of Spravato's treatment difference on the primary efficacy measure (change from baseline in the MADRS total score at 4 weeks) was observed at 24 hours.

Several small studies in the published literature have examined the off-label use of ketamine for the rapid reduction of depressive symptoms and a reduction in suicidal ideation or behavior, in subjects with MDD or TRD, with some apparent positive effect (Chen 2018; Grunebaum 2018; Lapidus 2014; Nugent et al. 2019; Price 2014; Wilkinson 2018). However, there are no adequate studies examining the safety of off-label ketamine use and there are indications from nonclinical studies that ketamine may be neurotoxic in some populations (Olney 1989). Lithium has been studied off-label for the reduction of suicide in patients with mood disorders. In the 280-patient subgroup of patients with unipolar depressive disorders (involving three of four trials in a meta-analysis, while the fourth involved bipolar disorder), the number of suicides was lower with lithium treatment than placebo (i.e., five suicides occurred in patients treated with placebo versus none with lithium: OR 0.13, 95% CI 0.02 to 0.76; Cipriani et al. 2013).

In summary, with the exception of ECT, current approved treatments for MDD often take at least 2 to 4 weeks for the onset of benefit, with continued suffering and risk. No other approved pharmacological treatment is associated with the rapid reduction of depressive symptoms in patients with MDD (with or without suicidal ideation and behavior). Use of ECT, which is approved for treatment of MDD when a rapid response is required (and has shown some benefit in the reduction of suicidal ideation and behavior) is limited by adverse reactions and interventional concerns. Although several small studies suggest benefit with the off-label use of ketamine for the rapid reduction of depressive symptoms in subjects with MDD or TRD, ketamine's use for these indications remains unapproved.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Esketamine is the S-enantiomer of ketamine, an anesthetic agent approved in 1970 under the brand name Ketalar (NDA 016812). On September 4, 2018, the Applicant submitted an NDA for the treatment of TRD, which was approved on March 5, 2019.

Under IND 114345, for esketamine for TRD, a Type C meeting was held on October 22, 2013, during which the Division agree (b) (4)

(b) (4) was a potentially acceptable target for drug development. The Division agreed that there is an unmet clinical need for the reduction of symptoms of MDD within 24 hours, including suicidal ideation (b) (4)

(b) (4) A second Type C meeting was held on December 14, 2015, to discuss the Suicidal Ideation and Behavior Assessment Tool (SIBAT) developed by the Sponsor. The Division also noted that the term (b) (4) was not appropriate for labelin (b) (4)

(b) (4) and requested that the the new item, the Clinical Global Impression – Severity of Suicidality (CGI-SS) be used as the secondary endpoint instead.

A face-to-face Pre-IND meeting was held on July 7, 2016, to discuss the preliminary results from Trial SUI2001, explore the possibility of an expedited NDA submission, obtain guidance on the elements of the proposed phase 3 program and a proposal to revise the CGI-SS, and raise a question about deletin (b) (4)

(b) (4) The Division did not object to the use of the MADRS in the MDSI population and agreed with the CGI-SS-revised (CGI-SS-R) as the secondary efficacy endpoint in the phase 3 trial design, pending further SIBAT validation work (clarified in post-meeting communication).

An application for IND 129516 was submitted on June 16, 2016, for the treatment of MDSI. The initial clinical study proposed was a phase 1 study ESKETINTRD1018 entitled, “An Open-Label, Single-Ascending Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine in Elderly (≥65 years of age) Japanese, and Healthy Younger Adult Japanese Subjects (20 to 55 Years of Age, Inclusive).” A may-proceed communication was conveyed via email on July 15, 2016, and letter issued on July 26, 2016.

A request for breakthrough therapy designation for MDSI was included with the IND application, which was granted on August 9, 2016. The decision to grant was based on the results of Trial SUI2001, in which esketamine plus standard of care demonstrated a statistically significant treatment difference from placebo plus standard of care on the primary efficacy endpoint, change from baseline to 4 hours post-dose on the MADRS total score, and on the

secondary endpoint, change from baseline to 24 hours (Day 2) on the MADRS total score.

A face-to-face End-of-Phase 2 meeting was held on October 19, 2016, to obtain the Division's input and agreement on the adequacy of the proposed phase 3 adult program to assess the safety and efficacy of esketamine in MDSI, the overall development program to support an NDA for use in adults, and the planned pediatric program in MDSI. The Division agreed that the overall design of phase 3 protocols for the adult program appeared acceptable, and clarified that the revised CGI-SS-R was acceptable as the key secondary endpoint for the MDSI phase 3 studies. The Division agreed that a planned 30% U.S. enrollment appeared acceptable; however, positive results driven by a non-U.S. cohort would present a review issue and may affect approvability. (This number was later revised to 20 to 25% in June 2018 communication with the Division; the Division agreed it was generally acceptable provided the efficacy between U.S. and non-U.S. subgroups was consistent.) The Division agreed to the Applicant's proposal for capturing and categorizing suicide-related adverse events (AEs) in the phase 3 studies (i.e., to count the initial episode of suicidality as an AE only if there is a worsening of baseline severity, and to report the initial per-protocol hospitalization as a serious AE only if the duration of admission is extended because of a subject's clinical worsening). For labeling purposes, the Division did not agree with use of the terminology (b) (4) in the target indication as it was not specific; agreement was reached on "suicidal ideation."

For the pediatric development program, the Division reiterated the importance of conducting neurotoxicity assessment in juvenile animals in order to cover for exposure in children ages 9 to 12 years. Agreement was reached for the use of the SIBAT in patients 12 to 17 years-old and use of the clinician reported components of the SIBAT along with the clinician interview for patients 9 to <12 years-old.

An agreed Pediatric Study Plan (PSP) was issued on January 13, 2017 for:

A partial waiver for conducting pediatric studies with intranasal esketamine in neonates, infants and children (aged 0 to <9) for the treatment of MDD in subject (b) (4). This partial waiver request is based upon the statutory grounds as stated in 21 CFR 314.55(c)(3): "Necessary studies are impossible or highly impracticable because, for example, the number of such patients is so small or geographically dispersed."

A deferral for intranasal esketamine as a treatment for MDD in children and adolescent subjects 9 to < 18 years of age (b) (4). The statutory basis for this deferral request and as outlined in 21 CFR 314.55(b), is that "the drug is ready for approval in adults before studies in pediatric patients are complete."

A Pediatric Written Request (PWR) was issued on August 2, 2017, amended January 8, 2018, under IND 129516 for the following required studies:

(b) (4)



Guidance Written Response Only minutes were issued on November 30, 2018, to obtain agreement that the SIBAT is a valid instrument for use in clinical trials to assess the efficacy and safety of esketamine for the rapid reduction of the symptoms of major depressive disorder (MDD), including suicidal ideation 

Pre-NDA Written Responses Only minutes were issued on May 20, 2019, wherein the Division agreed with the proposed content and format of a supplemental NDA (sNDA) with cross-references to pertinent sections of the TRD NDA, proposed cut-off dates for safety reporting of ongoing studies for the sNDA and the 4-month safety update, and the scope of the published literature search and review. The Division agreed with waiver of an integrated summary of efficacy and the pooling safety strategy.

A face-to-face pre-NDA meeting was scheduled for August 7, 2019, to discuss the efficacy and safety results from the completed phase 3 adult studies and confirm acceptability of these data to support the planned sNDA. On July 31, 2019, Sponsor requested cancellation of the meeting after reviewing the preliminary comments issued on July 30, 2019. In preliminary comments, the Division suggested the addition of a Limitation of Use statement to avoid creating the impression that patients would no longer merit hospitalization should they experience immediate post-treatment improvement. The Division also referred the Applicant to the guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2018).

On October 2, 2019, the Applicant submitted this efficacy supplement to extend the indicated use of SPRAVATO to the reduction of symptoms of depression in adult patients with MDD who have active suicidal ideation with intent (MDSI). A Priority review was requested by the

Applicant based on their breakthrough therapy designation. However, given the lack of effect on suicidal ideation compared to placebo (the basis for their breakthrough therapy designation), the Division determined the review classification would be Standard. The Agency conveyed this in the No-filing-review-issues-identified Letter dated November 27, 2019.

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

None.

3.3. Office of Scientific Investigations (OSI)

The clinical investigator sites of Drs. Barker, Litman, Kruger, Quarantini, and Yadalam were inspected in support of this submission. Based on the results of these inspections, the conduct of the above studies was adequate, and the clinical data generated from Drs. Barker, Litman, Kruger, Quarantini, and Yadalam sites appear to be reliable in support of this sNDA (see separate OSI review).

3.4. Product Quality

No changes are proposed with respect to Drug Product Quality and to the CMC information in the proposed package insert. The applicant's claim for an exclusion from an EA (environmental assessment) is acceptable based on the FDA EA Team Review Recommendation. Based on the product quality review dated 2/7/2020 by Lin Qi/David Lewis, this supplement is recommended for APPROVAL from the standpoint of CMC.

3.5. Clinical Microbiology

No issues (see separate product quality review).

3.6. Devices and Companion Diagnostic Issues

No issues.

4 Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

SPRAVATO (esketamine HCl) was approved on March 5, 2019, for TRD. Since approval, the drug label has been updated with negative *in vitro* and *in vivo* genotoxicity study findings (Labeling Supplement 3 received on August 14, 2019). There were no nonclinical studies submitted in the current supplement to support the indication of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. The Sponsor is relying on nonclinical data submitted previously in support of the TRD indication, which is a chronic indication. Considering the acute/chronic intermittent use for the current indication—and the population for whom it is indicated (i.e., adults)—there are no nonclinical concerns that would impact the drug approval. Therefore, this supplement is recommended for APPROVAL from a Pharmacology/Toxicology perspective.

4.2. Referenced NDAs, BLAs, DMFs

Not applicable for this submission.

4.3. Pharmacology

Not applicable for this submission.

4.4. ADME/PK

Not applicable for this submission.

4.5. Toxicology

4.5.1. General Toxicology

Not applicable for this submission.

4.5.2. Genetic Toxicology

Not applicable for this submission.

4.5.3. Carcinogenicity

Not applicable for this submission.

4.5.4. Reproductive and Developmental Toxicology

Not applicable for this submission.

5 Clinical Pharmacology

5.1. Executive Summary

There were no clinical pharmacology studies submitted in this efficacy supplement and there is no change in the labeling language in sections relevant to clinical pharmacology for SPRAVATO (esketamine HCl) label. The clinical pharmacology information for SPRAVATO was reviewed in detail when the original NDA211243 was submitted.

5.1.1. Pharmacology and Clinical Pharmacokinetics

Not applicable for this submission.

5.1.2. General Dosing and Therapeutic Individualization

General Dosing

Not applicable for this submission.

Therapeutic Individualization

Not applicable for this submission.

Outstanding Issues

Not applicable for this submission.

5.2. Comprehensive Clinical Pharmacology Review

5.2.1. General Pharmacology and Pharmacokinetic Characteristics

Not applicable for this submission.

5.2.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable for this submission.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Not applicable for this submission.

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Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable for this submission.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable for this submission.

Question on clinically relevant specifications (TBD)?

Not applicable for this submission.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Sources of clinical data consisted chiefly of two phase 3 trials (SUI3001 (ASPIRE I) and SUI3002 (ASPIRE II)) and one phase 2 trial (ESKETINSUI2001). See Table 2 for a listing of all adult trial sources of data. See Table 3 for a listing of all pediatric trial sources of data.

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Table 2. Listing of Adult Clinical Trials Relevant to NDA 211243-s004

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Countries (No. of Sites)
<i>Controlled Studies to Support Efficacy and Safety</i>								
54135419 SUI3001 (ASPIRE I)	03039192	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	IN ESK 84 mg (could be reduced after first dose to 56 mg for tolerability) or IN PBO twice weekly, plus SOC ^a	Primary: CFB on MADRS total score at 24 hours post-first-dose Key secondary: CGI-SS-R CFB 24 h post-first-dose	25-day treatment phase; 65-day follow-up phase	226 enrolled: 225 treated (113 on ESK + SOC, 112 on PBO + SOC)	Ages 18 to 64 with MDSI, initially inpatient	United States (13), Bulgaria (5), Estonia (2), Germany (3), Hungary (5), Malaysia (3), South Africa (2), Republic of Korea (5), Spain (7), Taiwan (4)
54135419 SUI3002 (ASPIRE II)	03097133	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	IN ESK fixed 84 mg (may be reduced at any time after first dose to 56 mg for tolerability for all subsequent doses) or IN PBO twice weekly, plus SOC ^a	Primary: CFB on MADRS total score at 24 hours post-first-dose Key secondary: CFB on CGI-SS-R at 24 hours post-first-dose	25-day treatment phase; 65-day follow-up phase	230 enrolled, 227 treated (114 on ESK + SOC, 113 on PBO + SOC)	Ages 18 to 64 with MDSI, initially inpatient	United States (13), Argentina (4), Austria (2), Belgium (2), Brazil (5), Canada (1), Czech Republic (2), France (5), Lithuania (2), Poland (4), Spain (3), Turkey (4)

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ESKETIN SUI2001	02133001	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	IN ESK fixed 84 mg (may be reduced at any time after first dose to 56 mg for tolerability for all subsequent doses) or IN PBO twice weekly, plus SOC ^a	Primary: CFB on MADRS total score at 4 hours post-first-dose	25-day treatment phase; 56-day follow-up phase	68 enrolled, 66 treated (35 on ESK + SOC, 31 on PBO + SOC)	Ages 18 to 64 with MDSI, initially inpatient	United States (10)
Studies to Support Safety								
54135419 TRD2005	02918318	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	IN ESK fixed 28, 56, or 84 mg or IN PBO twice weekly, plus AD monotherapy	Primary: CFB on MADRS total score at Day 28	28-day treatment phase and 168-day follow-up phase	183 planned, ongoing	Ages 20 to 64 with TRD	Japan
ESKETIN TRD3006	03434041	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	IN ESK flexible 56 or 84 mg or IN PBO twice weekly, plus newly-initiated AD monotherapy	Primary: CFB on MADRS total score at Day 28	28-day treatment phase plus follow-up phase	234 planned (210 Chinese and 24 U.S.), ongoing	Ages 18 to 64 with TRD	United States, China

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54135419 TRD3008 (SUSTAIN 3)	02782104	Open-label, multicenter, long-term extension study	IN ESK open-label, flexible 28 (elderly only), 56, or 84 mg twice weekly during 4-week open-label induction phase for direct entry (other responders-only transferred after induction phase from other phase 3 studies), then weekly for first 4 weeks, then weekly or every other weekly during maintenance phase	Safety and tolerability, with special attention to cognitive function, adverse events, post-dose effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation, and suicidal ideation/behavior	4-week induction phase followed by maintenance phase long-term (estimated up to 3 years)	1140 as of December 2018, ongoing	Ages 18 and older with TRD	222 sites at 27 countries worldwide including United States
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Source: Clinical Reviewer-created from Tabular Listing of All Clinical Studies – MDSI, Trials SUI3001, 3002, and 2001 clinical study reports, and clinicaltrials.gov, accessed January 8, 2020

AD = antidepressant, CFB = change from baseline, CGI-SS-R = Clinical Global Impression of Severity of Suicidality – Revised, ESK = esketamine, IN = intranasal, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, MDSI = major depressive disorder, without psychotic features, with active suicidal ideation and intent, NCT = National Clinical Trial, No = number, PBO = placebo, SOC = standard of care, TRD = treatment-resistant depression

*Standard of care included an oral antidepressant either as monotherapy or augmented with an adjunctive agent.

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Table 3. Listing of Pediatric Clinical Trials Relevant to NDA 211243-s004

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Countries (No. of Sites)
<i>Studies to Support Safety</i>								
ESKETIN SUI2002	03185819	Randomized, double-blind, double-dummy, active, controlled, multicenter, parallel-group study	IN ESK fixed 28, 56, or 84 mg or active control (oral midazolam) twice weekly, with intranasal or oral dummy, plus fluoxetine, escitalopram, or sertraline monotherapy	Primary: change from baseline on Children's Depression Rating Scale-Revised total score at 24 hours post-first-dose	25-day treatment phase and 56-day follow-up phase	145 planned, currently recruiting	Ages 12 to 17 with MDD, without psychotic features, with active suicidal ideation with intent, initially inpatient	United States (16), Brazil (4), France (5), Hungary (2), Poland (2), Spain (7)

Source: Clinical Reviewer-created from Tabular Listing of All Clinical Studies – MDSI and clinicaltrials.gov, accessed January 6, 2020
Abbreviations: NCT = National Clinical Trial; No = number

6.2. **Review Strategy**

The efficacy review will focus on the two phase 3 trials, SUI3001 (ASPIRE I) and SUI3002 (ASPIRE II; nearly-identical randomized, double-blind, parallel-group trials) and the similarly designed phase 2 trial SUI2001. The studies are described in more detail in Sections 7.1, 7.2, and 7.3, respectively. Andrew Potter, PhD, the statistical reviewer, replicated the Applicant's analyses; Dr. Potter also conducted additional analyses described in sections below.

The safety review will examine the aforementioned trials, as well as any pertinent information from treatment-resistant depression (TRD) studies, including interim data from TRD3008 (SUSTAIN 3, an open-label, long-term, multi-year safety study). The Applicant's Integrated Summary of Safety (ISS) includes pooled data from SUI3001 and SUI3002, and data from SUI2001. Additional supporting data were presented from ongoing TRD studies (TRD3008, TRD3006, and TRD2005) and SUI2002. The safety review will also examine the 120-day safety update for the supplement submitted on January 30, 2020, as well as the Periodic Adverse Drug Experience Reports (PADERs) submitted on March 31, 2020; January 3, 2020; September 27, 2019; and July 2, 2019, and any relevant information from the 12-month REMS assessment submitted on March 5, 2020.

7 Statistical and Clinical Review of Relevant Individual Efficacy Trials, Integrated Review of Effectiveness, and Review of Safety

7.1. Trial SUI3001 (ASPIRE I)

7.1.1. Study Design

Overview and Objective

Trial SUI3001 was titled, “A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide.” The trial’s primary objective was to evaluate efficacy of intranasal esketamine 84 mg in addition to comprehensive standard of care in reducing the symptoms of MDD including suicidal ideation in patients who are assessed to be at imminent risk of suicide. Esketamine’s efficacy was compared to placebo plus comprehensive standard of care. Standard of care included oral antidepressant monotherapy or oral antidepressant plus augmentation therapy.

Trial Design

Basic Study Design: Trial SUI3001 was a phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in adult subjects (ages 18 to 64) with major depressive disorder (MDD), without psychotic features, assessed to be at imminent risk for suicide (i.e., with suicidal ideation (SI) and intent (overall abbreviation MDSI)). See Figure 1 for the Applicant’s study design schematic.

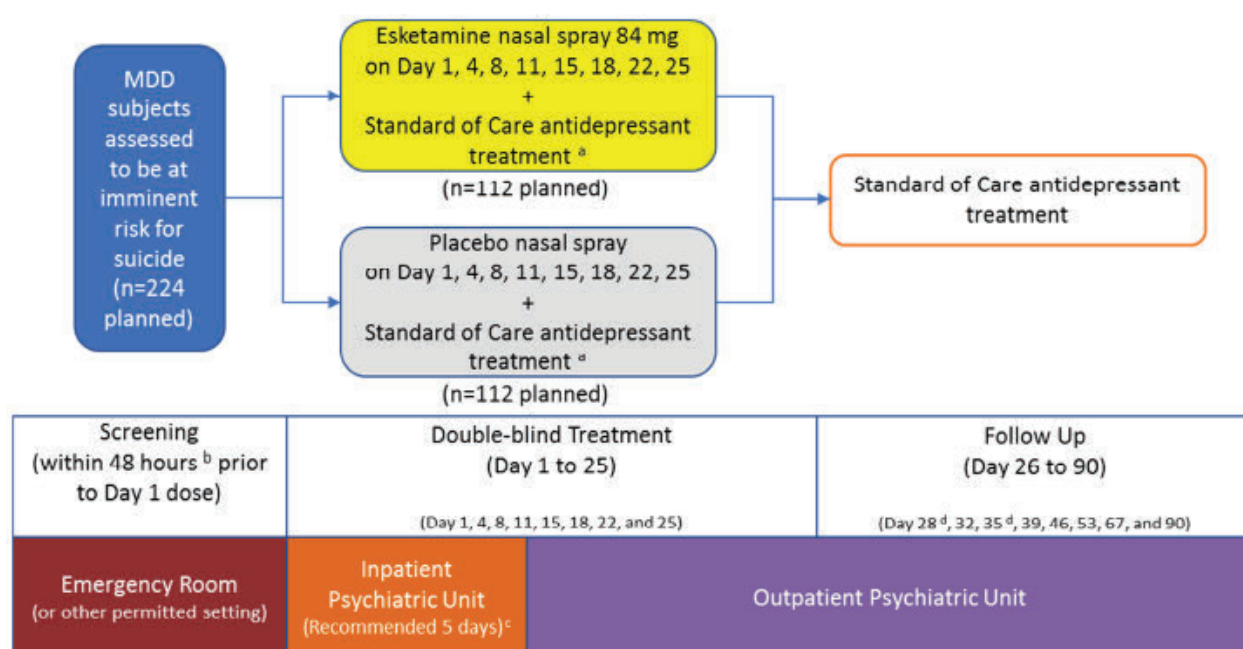
The trial had three phases:

- Screening Phase: Screening evaluation was performed within 48 (if possible, 24) hours before the Day 1 intranasal (IN) dose of study agent, to prospectively assess each subject’s eligibility for trial entry and determination of appropriate standard of care (SOC) antidepressant (AD) treatment (i.e., initiation or optimization of AD monotherapy or an AD plus augmentation therapy). Screening was performed in the emergency room (ER) or other permitted setting (e.g., subjects who had recently attempted suicide and were hospitalized for medical stabilization, or subjects admitted directly to the inpatient psychiatric unit).
- Treatment Phase: Subjects were randomized 1:1 to receive twice-weekly IN doses of esketamine 84 mg or placebo for 4 weeks. Subjects were to remain on the inpatient psychiatric unit for a recommended duration of 5 days, with shorter or longer stays

permitted if clinically warranted per local standard of care. Following discharge, subsequent visits for the treatment phase were conducted twice weekly at an outpatient facility through Day 25. SOC AD treatment was adjusted during the first 2 weeks.

- Follow-Up Phase: Subjects were to be monitored twice weekly for the first 2 weeks, then weekly for the next 2 weeks, then every 2 weeks for the remainder of the follow-up period through Day 90. SOC AD treatment was to be managed based on clinician judgment.

Figure 1. Trial SUI3001 Study Design Schematic



Source: Trial SUI3001 clinical study report Figure 1, p. 27

Abbreviations: MDD = major depressive disorder

^a Standard of care antidepressant treatment was initiated or optimized on Day 1

^b If possible, screening was performed within 24 hours before the Day 1 intranasal dose

^c Discharge before 5 days was discussed and approved by the Applicant's medical monitor

^d Remote contact

***Clinical Reviewer's Comment:** The basic study design was reasonable. A strength of the design is its SOC reflection of real-world clinical practice, in which a patient with SI with intent would likely be hospitalized and begin AD initiation, optimization, or augmentation therapy.*

Trial Location: The study was conducted at a total of 49 sites in 10 countries: 13 sites in the United States; 7 sites in Spain; 5 sites each in Bulgaria, Hungary, and the Republic of Korea; 4

sites in Taiwan; 3 sites each in Germany and Malaysia; and 2 sites each in Estonia and South Africa.

Clinical Reviewer's Comment: The Division agreed in pre-NDA communication with a proposal for 20 to 25% of the study population to be U.S.-based, given similar results across subgroups.

Choice of control group: The study used a placebo control group. Subjects receiving placebo received the same SOC AD treatment and inpatient hospitalization.

Clinical Reviewer's Comment: The TRD studies also used placebo with concurrent AD treatment.

Diagnostic Criteria: Subjects needed to meet the Diagnostic and Statistical Manual for Mental Disorders (5th edition; DSM-5) criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI).

Key Eligibility Criteria:

Key inclusion criteria other than diagnosis were:

- Male and female adults ages 18 to 64, inclusive
- Current SI with intent, confirmed by a “Yes” response to MINI Question B3 (“Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (i.e., about killing yourself?”), referring to the present; AND a “Yes” response to MINI Question B10 (“Intend to act on thoughts of killing yourself?”), referring to the past 24 hours. If the screening period was >24 hours, assessment of B3 and B10 of the MINI must have been repeated to confirm eligibility
- In the physician’s opinion, acute psychiatric hospitalization was clinically warranted due to the subject’s imminent risk of suicide
- Had a MADRS total score of >28 pre-dose on Day 1
- As part of SOC treatment, subjects agreed to be hospitalized voluntarily for a recommended period of 5 days after randomization (shorter or longer if clinically warranted)
- If recovering from a recent suicide attempt, were eligible if medically stable

Key exclusion criteria were:

- Current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder; current clinical diagnosis of autism, dementia, or intellectual disability; current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features
- Met DSM-5 criteria for borderline personality disorder; subjects not meeting full DSM-5 criteria but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors were also excluded
- Met DSM-5 criteria for moderate or severe substance or alcohol use disorder (except for nicotine or caffeine) within the 6 months before screening; a lifetime history of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3,4-methylenedioxymethamphetamine (MDMA) hallucinogen-related use disorder was also exclusionary
- Positive urine test result(s) for PCP, cocaine, or amphetamines (inclusive of amphetamine, methamphetamine, and MDMA) at screening (except if due to permitted prescribed psychostimulants); positive result(s) for opiates, benzodiazepines, or barbiturates may have been eligible (whether due to prescribed use, non-prescribed use, or overdose attempt, per clinician judgment (and in consultation with the Applicant's medical monitor for the latter two scenarios); heroin use was exclusionary
- Other clinically significant medical disease, including a history or current signs and symptoms of liver or renal insufficiency, current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae, unstable coronary artery disease, congestive heart failure, tachyarrhythmias, recent myocardial infarction, uncontrolled hyperthyroidism, severe dehydration/hypovolemia
- Uncontrolled hypertension (systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg) despite diet, exercise, or a stable dose of anti-hypertensive treatment for at least 2 weeks at screening; any past history of hypertensive crisis; or any condition in which the elevation of blood pressure could be a serious risk

Clinical Reviewer's Comment: The eligibility criteria are acceptable. The MADRS severity criterion was similar to that used in the TRD trials (i.e., ≥ 28). The exclusion criteria are reasonable in terms of reducing confounding factors or safety risks, though they may be less representative of real-world clinical practice patients.

Dose Selection: The Applicant selected 84 mg, with the option, any time after the first dose, for a one-time reduction to 56 mg for tolerability, maintained for all subsequent doses. The Applicant noted that available nonclinical studies supported up to 84 mg per day, and that this dose (and lack of titration) was selected given the benefit-risk assessment of treatment for a

life-threatening condition that is a psychiatric emergency (i.e., MDSI), to provide the greatest opportunity for rapid onset of efficacy and longer durability of activity, with acceptable tolerability. The Applicant reported that results from the phase 2 Trial SUI2001 provided evidence of efficacy of the 84 mg dose. The Applicant noted a significant dose-response relationship had been observed in Trial TRD2003 between 28, 56, and 84 mg doses of esketamine. Regarding treatment duration, the Applicant noted that patients with MDD with SI are at risk for increased suicidal ideation and behavior both in the first several days after initiating treatment with a standard AD, and post-hospitalization; therefore, 4 weeks was selected to be consistent with the timeframe that standard ADs take to exert their action. Regarding treatment frequency, the Applicant noted that the mean duration of response to ketamine after a single dose is approximately 5 days, so twice-weekly dosing was selected for the phase 2 Trial SUI2001 and the TRD2001 study, which supported this dosing regimen.

Clinical Reviewer's Comment: The rationale for starting with the potentially most effective dose, and the treatment duration, appears reasonable.

Study Treatments: The two study treatments were 84 mg (or adjusted to 56 mg as described above) of esketamine or placebo, self-administered IN under the direct supervision of the investigator or designee, twice weekly for 4 weeks. The IN treatments were administered via three IN devices, administered at time 0, 5 minutes, and 10 minutes, each with two sprays (one per nostril).

Regarding SOC AD monotherapy or AD plus augmentation therapy, the Applicant noted that AD SOC treatment would be “determined by the treating physician(s) based on clinical judgment and practice guidelines.” No specific ADs or augmentation agents were prescribed for use; only monoamine oxidase inhibitors (MAOIs) were prohibited. Regarding tricyclic antidepressants (TCAs), the Applicant noted that given the target population (MDSI) and TCAs’ known risk of lethality in overdose, caution was advised if prescribed. The Applicant noted that “lithium use for another [other than bipolar disorder] indication (e.g., augmentation treatment for TRD) is permitted” and that “use of antipsychotics (except clozapine) for treatment of depression is not excluded.” Thyroid hormone supplement was allowed for “subjects needing supplements” who “must be on a stable thyroid supplement dose for at least 4 weeks” before Day 1.

Clinical Reviewer's Comment: Regarding AD choices, the primary trials submitted in support of Spravato's original application (i.e., TRD3001, TRD3002, TRD3003, and TRD3005) allowed the choice of four specific ADs, so this design was a change. At a Type C IND meeting in October 2013 and in non-hold comments for the review of the protocol for the similarly-designed phase 2 study SUI2001, the Division requested that the Applicant review MDD treatment guidelines and derive an AD SOC treatment algorithm (or similar) for future protocols; it doesn't appear that this was done prior to the phase 3 trials. If one accepts the idea that no AD appears superior for the treatment of MDD (i.e., in terms of effect sizes), and without any specific drug-drug interactions to avoid with

esketamine (other than blood pressure with MAOIs, which were excluded), this design doesn't appear to pose a confounding issue in terms of AD choice. A more recent meta-analysis of ADs suggested varying response rates (as a measure of efficacy) and acceptability (Cipriani et al. 2018), which, if true, could indicate confounding by choice of AD, if there was a noticeable imbalance in concomitant ADs between groups.

Augmentation therapy does not appear to have been explicitly defined. The American Psychiatric Association (APA) MDD practice guideline describes augmentation "with another non-MAOI AD generally from a different pharmacological class" (bupropion and mirtazapine are common choices); or with "a non-AD medication such as lithium, thyroid hormone, or a second-generation antipsychotic (APA 2010, 18-19)." Lithium and antipsychotics were specifically noted as allowed, but it appears thyroid hormone was prohibited as a newly initiated therapy (i.e., only allowed for pre-existing thyroid supplementation use). FDA-approved MDD augmentation treatments include aripiprazole, quetiapine fumarate, and brexpiprazole. It is possible, but probably unlikely, that an investigator could have considered an additional AD as combination therapy, rather than augmentation, and avoided their use. It is unclear what effect any lack of clarity around or lack of prescribed options for augmentation treatment may have. See study results below for an analysis of concomitant medication usage.

Assignment to Treatment: Subjects were randomized via a central computer-generated schedule in a 1:1 ratio between the two treatment groups. The randomization was balanced using randomly permuted blocks and was stratified by study center and by the physician's assessment of the appropriate SOC AD treatment (i.e., AD monotherapy or AD plus augmentation therapy). SOC was determined prior to randomization on Day 1. An interactive web response system (IWRS) assigned a unique treatment code providing the treatment assignment and matching medication kits for each subject.

Clinical Reviewer's Comment: *Given that the range of AD choices was much larger than the TRD studies as mentioned above, and that augmentation choices were also undefined, the benefits of stratification by general SOC option (i.e., AD monotherapy or AD plus augmentation therapy) may be multiple. If the augmentation therapies are largely antipsychotics, the stratification may be useful for adverse effects comparison, or any possible esketamine-antipsychotic class interaction not previously noted. It is possible that these general options may capture two phenotypes of subjects (e.g., subjects who have tried multiple monotherapy ADs and therefore get augmentation therapy may indicate a more TRD population), but that may be largely dependent upon investigator practice patterns.*

Blinding: Randomization codes were maintained within the IWRS, which had the functionality to allow the investigator to break the blind for an individual subject (only if specific emergency treatment/course of action would be dictated by knowing the treatment status of an individual,

and recommended to do so after discussion with the Applicant). Data that could unblind the treatment assignment (e.g., plasma concentrations, treatment allocation) were handled with special care to maintain blinding. Different raters performed efficacy and safety assessments, and efficacy raters were not involved in clinical care. Any unblinding events were to be documented with date, time, and reason for unblinding, and the Applicant was to be informed as soon as possible.

The placebo IN solution was designed to appear identical to esketamine IN. A bittering agent (denatonium benzoate) was added to simulate the taste of the IN solution with the active drug, in a matching nasal spray pump device.

Clinical Reviewer's Comment: An active control, such as the midazolam being used in pediatric Trial SUI2002 (see Table 3), may have been preferable, to at least somewhat mimic the immediate psychoactive effects of esketamine. However, it would also have the potential to complicate interpretation of both efficacy and safety data. The Applicant divided efficacy and safety assessments among raters to address personnel unblinding, but not for the subject.

Dose Modification and Discontinuation: After the first dose of 84 mg (i.e., starting with the Day 4 dose or later), if required because of tolerability issues, a one-time dose reduction to 56 mg was allowed for all subsequent doses; no further adjustment was allowed during the double-blind phase.

As above, the Applicant noted that AD SOC treatment would be “determined by the treating physician(s) based on clinical judgment and practice guidelines.” AD monotherapy or AD plus augmentation therapy was to be initiated or optimized at the time of randomization on Day 1. If a subject had started an AD within the past 2 weeks, they could continue the AD at the current or optimized dose. Dose titration/adjustments of SOC AD treatment should have occurred during the first 2 weeks of double-blind treatment, with doses remaining stable for the remainder of the double-blind phase. During the double-blind phase, the investigator was to consult with the Applicant’s medical monitor in advance if additional changes were clinically indicated. During the follow-up phase, AD treatment was managed based on the clinician’s judgment.

Clinical Reviewer's Comment: The possibility of dose reduction appears appropriate. Prohibition of attempted re-challenge at 84 mg may have limited the possibility of dropouts from intolerance.

Similar to the abovementioned lack of specifics regarding AD or augmentation therapy choices, SOC AD treatment based on investigator “clinical judgment” could feasibly involve different approaches (e.g., rapidity of titration of oral antidepressant or

management of side effects). It is not clear how this flexibility may have impacted findings.

Administrative Structure: An Independent Data Monitoring Committee (IDMC) monitored the data to ensure ongoing safety of subjects, meeting every 6 months. Contract research organizations (CROs) were involved with investigator recruitment (IQVIA), medical monitoring (IQVIA), recordkeeping (b) (4) IQVIA), and database design, set-up, management, cleaning, coding, serious adverse event reconciliation, and identification and documentation of protocol deviations (TATA).

Procedures and Schedule: See Figure 1 for a study design schematic. See Table 4 for the schedule of events and assessments for Trial SUI3001, and see Table 5 for the Suicidal Ideation and Behavior Assessment Tool (SIBAT) schedule of events and assessments.

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Table 4. Trial SUI3001 Schedule of Events and Assessments

Phase	Screening	Double-blind Treatment															Follow Up											
Visit Number	1	2						3	4 ^b	5 ^b	6 ^b	7 ^b	8 ^b	9 ^b	10 ^b	-	-	-	11 ^b	12 ^b	13 ^b	14 ^a	15 ^a	16 ^a	17 ^a	18 ^a	-	
Week		1						2			3			4						4	5	5	6	7	8	10	13	
Day	1 ^c	1						2 ^{ff}	4	8	11	15	18	22	25	D/C ^a	DB ET ^d	DB RC ^d	28 RC ⁱⁱ	32	35 RC ⁱⁱ	39	46	53	67	90/ FU ET ^{dd}	90 RC ^{dd}	
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr ^{ee}																					
Study Procedures																												
Setting																												
Emergency Room (ER) or other permitted setting ^e	X	X	X	X	X	X	X ^f																					
Inpatient psychiatric unit ^g								X	X																			
Outpatient psychiatric unit										X	X	X	X	X	X	-	-			X		X	X	X	X	X		
Screening/Administrative																												
Informed consent	X																											
Informed consent for optional genetic research samples	X																											
Inclusion/exclusion criteria	X	X																										
Medical history, psychiatric history, and demographics	X																											
Standard of care antidepressants assignment ^{hh}	X	X																										
Urine pregnancy test for women of childbearing potential ⁱ	X													X		X												
Urine drug screen ^j	X													X		X												
Mini International Psychiatric Interview (MINI) ^j	X																											
Question B3 and B10 from MINI (current status) ^{j, k}	X																											
Study Drug Administration																												
Practice session for use of intranasal device		X																										
Randomization			X																									
Study Drug Administration ^m (intranasal esketamine or placebo)			X						X	X	X	X	X	X														
Safety Assessments																												
Physical examination	X													X		X										X		
Nasal examination	X													X ^h		X												

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Phase	Screening	Double-blind Treatment												Follow Up											
Visit Number	1	2				3	4 ^b	5 ^b	6 ^b	7 ^b	8 ^b	9 ^b	10 ^b	-	-	-	11 ^b	12 ^b	13 ^b	14 ^a	15 ^a	16 ^a	17 ^a	18 ^a	-
Week		1				2				3				4				4	5	5	6	7	8	10	13
Day	- ^c	1				2 ^{ff}	4	8	11	15	18	22	25	D/C ^a	DB ET ^d	DB RC ^d	28 RC ⁱⁱ	32	35 RC ⁱⁱ	39	46	53	67	90/ FU ET ^{dd}	90 RC ^{dd}
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr ^{ee}																		
Vital signs ⁿ	X	X ^o		X ^o	X ^o	X ^o		X ^o	X ^o	X ^o	X ^o	X ^o	X ^o		X									X	
12-lead ECG	X ^p			X ^q				X ^q					X ^q		X										
Pulse oximetry ^r		X (every 15 min)						X	X	X	X	X	X												
Body weight	X												X ^h		X									X	
Height	X																								
Modified Observer's Assessment of Alertness/Sedation (MOAA/S) ^{j, t}		X (every 15 min)						X	X	X	X	X	X												
Clinician Administered Dissociation States Scale (CADSS) ^{j, s}		X		X		X		X	X	X	X	X	X												
Efficacy Assessments																									
Suicide Ideation and Behavior Assessment Tool (SIBAT) ^w		X					X	X	X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X	X			X		X	X	X	X	X
Montgomery Asberg Depression Rating Scale (MADRS) (Recall: 7 days) ^j		X																			X	X	X	X	X
MADRS (Recall: since last assessment) ^j								X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X	X	X	X	X	X						
MADRS (Recall: 4 hours) ^{j, ee}						X ^{v, z}							X ^{v, z}												
MADRS (Recall: 24 hours) ^j							X																		
Beck Hopelessness Scale (BHS) (Recall: Last 7 days) ^l		X						X ^h					X ^h		X						X			X	
Quality of Life in Depression Scale (QLDS) ^l		X						X		X ^h			X ^h		X						X			X	
EQ-5D-5L ^l		X						X		X ^h			X ^h		X						X			X	
Treatment Satisfaction Questionnaire for Medication (TSQM-9) ^l										X ^h			X ^h		X						X			X	
Clinical Laboratory Assessments																									
Hematology, Chemistry	X ^x												X ^h		X										
Urinalysis	X ^x												X ^h		X										

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Phase	Screening	Double-blind Treatment													Follow Up									
Visit Number	1	2			3	4 ^b	5 ^b	6 ^b	7 ^b	8 ^b	9 ^b	10 ^b	-	-	-	11 ^b	12 ^b	13 ^b	14 ^a	15 ^a	16 ^a	17 ^a	18 ^a	-
Week		1			2			3			4					4	5	5	6	7	8	10	13	
Day	- ^c	1			2 ^{ff}	4	8	11	15	18	22	25	D/C ^u	DB ET ^d	DB RC ^d	28 RC ⁱⁱ	32	35 RC ⁱⁱ	39	46	53	67	90/ FU ET ^{dd}	90 RC ^{dd}
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr ^{ee}																	
Medical Resource Utilization																								
Health Resource Use Questionnaire (HRUQ) ^j												X	X	X							X		X	
Biomarkers																								
Blood sample collection (serum and plasma biomarkers) ^{aa}		X ^y					X					X ^{h,y}		X										
Blood sample collection (RNA biomarkers) ^{az}		X					X					X ^h		X										
Pharmacogenomics (DNA/epigenetics) – Optional																								
Blood sample collection ^{bb}		X					X					X ^h		X										
Pharmacokinetics																								
Blood sample collection ^{cc}				X			X																	
Ongoing Subject Review																								
Prior and concomitant therapy		Continuous															X		Continuous					
Adverse events		Continuous													X	X	X	X	Continuous					X

Abbreviations: BHS, Beck Hopelessness Scale; CADSS, Clinician Administered Dissociative States Scale; DB, double-blind; D/C, discharge; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 dimension- 5-level; ER, emergency room; ET, early termination; FU, follow-up; HRUQ, Health Resource Use Questionnaire; ICF, informed consent form; MADRS, Montgomery-Asberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; QLDS, Quality of Life in Depression Scale; RC, remote contact; RNA, ribonucleic acid; SIBAT, Suicide Ideation and Behavior Assessment Tool; SpO₂, oxygen saturation; TSQM-9, Treatment Satisfaction Questionnaire for Medication

Footnotes:

- ^a Visit can be performed ±3 days.
- ^b Visit can be performed ±1 day. Intranasal treatment sessions should not be given on consecutive days.
- ^c The subject should be screened (ie, starting with the signing of the informed consent form) within 48 hours prior to intranasal dosing on Day 1 (if possible, the subject should be screened within 24 hours prior to the Day 1 intranasal dose).
- ^d Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit will have an Early Termination (DB ET) visit conducted at the time of discontinuation. For subjects who discontinue from double-blind treatment with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 days after the last dose of intranasal study medication (if the date of the DB ET visit is less than 3 days after the last dose of intranasal study medication) and on Day 25 for MADRS assessment and adverse event collection. The investigator must ensure the subject is appropriately transitioned/monitored for any additional care required.
- ^e Not applicable for subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or for medical stabilization (following recent suicide attempt). These subjects will receive their first dose of study medication in the inpatient psychiatric unit. Other permitted setting is a non-ER setting that has appropriate staffing to manage acutely suicidal patients.

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- ^f For subjects dosed in the ER or other permitted setting, it is recommended that subjects not be transferred from the ER to the inpatient psychiatric unit until after the 4 hour postdose assessments are completed.
- ^g Subjects can be admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or for medical stabilization (following recent suicide attempt). These subjects will receive their first dose of study medication in the inpatient psychiatric unit. The recommended duration of inpatient hospitalization is 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care by the investigator's opinion. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor.
- ^h Performed predose.
- ⁱ In addition to the scheduled time points, additional pregnancy and drug screening can be performed at the investigator's discretion during the study.
- ^j Clinician-administered assessment.
- ^k Subjects will be asked to respond to Questions B3 and B10 of the MINI relative to their current state. The response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of Questions B3 and B10 of the MINI must be repeated prior to randomization to confirm eligibility.
- ^l Subject-completed assessment.
- ^m On each dosing day, subjects will self-administer 1 spray into each nostril (ie, 2 sprays per intranasal device) at each of the following 3 time points: t = 0, 5 minutes and 10 minutes, where time = 0 is defined as the time of the first 100- μ L spray. After Day 1, a one-time decrease to intranasal esketamine 56 mg or intranasal placebo, in a blinded manner, will be permitted if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. In this case, the subject would receive the decreased dose on all remaining dosing days. Please see details about study drug administration in Section 6.2.
- ⁿ Blood pressure, heart rate, respiratory rate, and temperature (tympenic recommended).
- ^o Blood pressure, heart rate, and respiratory rate at predose and at t = 40 minutes, 1 hour, and 1.5 hours postdose on each dosing day. Temperature at predose only on each dosing day.
- ^p At screening, the ECG tracing will be sent to the central ECG laboratory but the investigator or sub-investigator is also required to review the ECG locally to determine subject eligibility.
- ^q Performed 1 hour postdose.
- ^r On each dosing day, pulse oximetry (SpO₂) will be performed every 15 minutes from predose to 1.5 hour postdose (see Section 9.7 for further guidance on timing of pulse oximetry assessments).
- ^s CADSS will be performed on dosing days predose and at 40 minutes and 1.5 hours postdose. If any CADSS items are scored zero at 40 minutes, these items will not be repeated at 1.5 hours postdose.
- ^t MOAA/S will be performed every 15 minutes on dosing days from predose to 1.5 hour postdose, or longer, if necessary (see Section 9.7 for further guidance on MOAA/S assessments).
- ^u Discharge (D/C) visit is performed on the actual day of discharge from initial hospitalization required at study entry. If the actual day of discharge coincides with another scheduled study visit, all study procedures for the scheduled visit should be completed and duplicate assessments are not required.
- ^v MADRS performed at 4 hours postdose.
- ^w The SIBAT has both clinician-administered and subject-reported modules; not all modules are completed at every visit. Refer to the SIBAT Time and Events Schedule for an outline of which module(s) will be performed at each scheduled time point.
- ^x Samples will be collected for analysis by local laboratory (for eligibility) and central laboratory. If standard of care clinical laboratory tests are performed within 24 hours prior to the screening visit (ie, prior to signing of the ICF) the results for laboratory tests required per protocol at screening can be used for determination of subject eligibility. In this case, after the subject signs the ICF, a sample(s) for the local laboratory is not required, but samples for the central laboratory are still required.
- ^y Menstrual cycle information will be collected on these visits.
- ^z The sleep item will not be assessed at the 4-hour postdose time point on Day 1 and Day 25. The MADRS scores for the sleep item recorded predose on the same day will be carried forward.
- ^{aa} Approximately 20 mL serum and 10 mL plasma samples will be collected at each time point.
- ^{bb} A 6 mL whole blood sample will be collected at each time point.
- ^{cc} A 2 mL whole blood sample will be collected at each of the following postdose times: 30-50 minutes, 1.5 hour to 2.5 hours, and 4 hours to 12 hours.
- ^{dd} Subjects, who discontinue from the follow-up phase prior to completion of the Day 90 visit, will have an Early Termination (FU ET) visit conducted at the time of discontinuation. For subjects who discontinue with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented on Day 90 for MADRS assessment and adverse event collection. Subjects who discontinue during the double-blind treatment phase prior to Day 25 will also have a Remote Contact on Day 90 for MADRS assessment and adverse event collection.
- ^{ee} The 4-hour assessments at the Day 1 and Day 25 visit should be performed within $\pm$ 30 minutes of the 4-hour postdose time point.

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- ff The 24-hour assessments at the Day 2 visit should be performed within ± 2 hours of the 24-hour postdose time point.
- gg A 2.5mL whole blood sample will be collected at each time point.
- hh The standard of care antidepressant treatment (antidepressant monotherapy or antidepressant plus augmentation therapy) will be determined by the treating physician(s) based on clinical judgment and practice guidelines prior to randomization, and the treatment will be initiated on Day 1. See Section 6.2 for further details.
- ii Remote contact will be implemented for MADRS assessment and adverse event collection.

Source: Trial SUI3001 protocol Time and Events Schedule (including Applicant footnotes), p. 29

Table 5. Trial SUI3001 Suicidal Ideation and Behavior Assessment Tool Schedule of Events and Assessments

Phase	Screening	Double-blind Treatment															Follow Up									
Visit Number	1	2					3	4 ^b	5 ^b	6 ^b	7 ^b	8 ^b	9 ^b	10 ^b	-	-	-	11 ^b	12 ^b	13 ^b	14 ^a	15 ^a	16 ^a	17 ^a	18 ^a	-
Week		1					2			3		4					4	5	5	6	7	8	10	13		
Day	-	1					2 ^j	4 ^c	8 ^c	11 ^c	15 ^c	18 ^c	22 ^c	25 ^c	D/C ^d	DB ET ^f	DB RC ^f	28 RC ^g	32	35 RC ^g	39	46	53	67	90/ FU ET ^h	90 RC ^h
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr ⁱ																			
SIBAT																										
Subject Completed Modules																										
Module 1 About me		X																								
Module 2 My Risk/ Protective Factors		X							X		X		X	X	X										X	
Module 3 My Current Thinking		X					X	X	X	X	X	X	X	X	X			X		X	X	X	X	X		
Module 4 My Actions									X	X	X	X	X	X	X			X		X	X	X	X	X		
Module 5 My Risk		X					X	X	X	X	X	X	X	X	X			X		X	X	X	X	X		
Clinician Completed Modules																										
Module 6. Clinician Semi-Structured Interview		X					X	X	X	X	X	X	X	X	X			X		X	X	X	X	X		
Module 7. Clinical Global Impressions ^e		X					X	X	X	X	X	X	X	X	X			X		X	X	X	X	X		
Module 8. Clinical Judgment of optimal Suicide Management		X					X		X		X		X	X	X			X			X		X	X		

Abbreviations: CGI-SR-I, Clinical Global Impression of Imminent Suicide Risk; CGI-SR-LT, Clinical Global Impression of Long-term Suicide Risk; CGI-SS-R, Clinical Global Impression of Severity of Suicidality – Revised; DB, double-blind; D/C, discharge; ET, early termination; FoST, frequency of suicidal thinking; FU, follow-up; RC, remote contact; SIBAT, Suicide Ideation and Behavior Assessment Tool

Footnotes:

^a Visit can be performed +/- 3 days.

^b Visit can be performed +/- 1 day. Intranasal treatment sessions should not be given on consecutive days.

^c The SIBAT modules will be performed predose.

^d Discharge (D/C) visit is performed at on the actual day of discharge from inpatient hospitalization. If the actual day of discharge coincides with another scheduled study visit, the SIBAT modules will be performed according to the procedures under D/C column and duplicate assessments are not required.

^e Module 7 includes the Clinical Global Impression of Severity of Suicidality – Revised (CGI-SS-R), Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), Clinical Global Impression of Long-term Suicide Risk (CGI-SR-LT), and assessment of frequency of suicidal thinking (FoST).

^f Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit will have an Early Termination (DB ET) visit conducted at the time of discontinuation. For subjects who discontinue from double-blind treatment with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 days after the last dose of intranasal study medication (if the date of the DB ET visit is less than 3 days after the last dose of intranasal study medication) and on Day 25 for MADRS assessment and adverse event collection. The investigator must ensure the subject is appropriately transitioned/followed for any additional care required.

^g Remote contact will be implemented for MADRS assessment and adverse event collection.

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- ^h Subjects, who discontinue from the follow-up phase prior to completion of the Day 90 visit, will have an Early Termination (FU ET) visit conducted at the time of discontinuation. For subjects who discontinue with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented on Day 90 for MADRS assessment and adverse event collection. Subjects who discontinue during the double-blind treatment phase prior to Day 25 will also have a Remote Contact on Day 90 for MADRS assessment and adverse event collection.
- ⁱ The 4-hour assessments at the Day 1 visit should be performed within ± 30 minutes of the 4-hour postdose time point.
- ^j The 24-hour assessments at the Day 2 visit should be performed within ± 2 hours of the 24-hour postdose time point.

Source: Trial SUI3001 protocol Suicidal Ideation and Behavior Assessment Tool Time and Events Schedule (including Applicant footnotes), p. 34

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Dietary Restrictions/Instructions: Food was restricted for at least 2 hours before each study drug administration, and drinking of fluids was restricted at least 30 minutes before the first nasal spray on each dosing day. During the outpatient double-blind phase, subjects should have refrained from using alcohol within 24 hours before and after each intranasal treatment session; if a subject appeared intoxicated, dosing was delayed per the permitted visit time window (see Table 4 schedule of events).

Clinical Reviewer's Comment: Similar to the TRD studies, the food restriction appears reasonable to reduce the chance of aspiration with any nausea or vomiting. The alcohol restriction appears appropriate for safety purposes with esketamine administration.

Concurrent Medications: Prohibited medications included: amantadine, anorexians, anticonvulsants (unless allowed for non-seizure indications on a case-by-case basis), MAOIs (during study and within 2 weeks prior to Day 1), chloral hydrate, dextromethorphan, ketanserin, methyldopa, metyrosine, non-vitamin K antagonist oral anticoagulation agents, reserpine, scopolamine, St. John's Wort, and warfarin.

Oral, intravenous or intramuscular corticosteroids and diphenhydramine were allowed on an as-needed (PRN) basis only (continuous oral corticosteroid use was allowed on a case-by-case basis; diphenhydramine was prohibited within 8 hours of IN study drug administration). Caution was advised with any TCA use given the target population and risk of lethality. Trazodone was allowed as a PRN AD but not within 8 hours before IN study drug administration. Antipsychotic use was allowed for depression treatment, and PRN for sleep (except clozapine) but not within 8 hours before IN study drug administration. Lithium was allowed for continuous use for non-bipolar indications such as TRD. Subjects needing thyroid hormone supplementation needed to be on a stable dose for at least 4 weeks before Day 1.

Benzodiazepines were permitted at dosages ≤ 6 mg lorazepam-equivalents, but not within 8 hours before IN study drug administration, within 4 hours after the first administration on Day 1, or within 8 hours of Day 2 assessments. Clonidine and non-benzodiazepine hypnotic use was prohibited within 8 hours before IN study drug administration. Prescription opioids could be continued, per clinician's judgment. Amphetamines could be continued, but not within 12 hours before IN study drug administration, or 2 hours following.

Electroconvulsive therapy (ECT) was prohibited during the study.

Clinical Reviewer's Comment: Concurrent medication restrictions appear reasonable for the purposes of limiting confounding of safety and efficacy assessments. (Allowing opioid use was a change from the TRD studies, but up to clinician's judgment.) The Applicant did not address psychotherapy or other somatic therapies such as transcranial magnetic stimulation (TMS), but it seems unlikely somatic therapies would have been arranged in the 3 weeks of outpatient double-blind phase to any meaningful extent. (It is

possible that different inpatient units may have incorporated varying levels of supportive or crisis-intervention-type therapy.)

Treatment Compliance: All doses of study medication were self-administered under direct supervision of investigators or designees, and a log was maintained of all study drug dispensed and returned.

Clinical Reviewer's Comment: The Applicant did not address SOC AD compliance during the outpatient double-blind phase. The Treatment Satisfaction Questionnaire for Medication (TSQM-9) was administered. Per the Applicant, it is a patient-reported outcome (PRO) measure to assess patients' satisfaction with medication; it does not appear to address compliance. The protocol did not clarify whether this would apply to IN study drug and SOC AD treatment, or only one or the other. In the TRD studies, oral AD compliance was assessed by pill counts and drug accountability.

Rescue Medication: The Applicant did not appear to prespecify rescue medications.

Clinical Reviewer's Comment: In the TRD studies, the Applicant had prespecified midazolam or short-acting benzodiazepine for agitation/anxiety, as well as specific PRNs for nausea. The Applicant noted use of medications of interest (e.g., benzodiazepines); see Section 7.1.2 for details.

Subject Completion, Discontinuation, or Withdrawal: A subject was considered to have completed treatment if s/he completed assessments up to and including Day 25 of the double-blind treatment phase. Subjects who prematurely discontinued study treatment for any reason before completion of the double-blind phase were not considered treatment completers. A subject was considered to have completed the study if s/he completed assessments up to and including Day 90.

Subjects were not automatically withdrawn from the study if they had to discontinue treatment before the end of the double-blind treatment phase. A subject's treatment was discontinued for the following reasons: lost to follow-up, withdrawal of consent, death, lack of efficacy in investigator's judgment, in best interest of subject to discontinue for safety or tolerability reasons in investigator's judgment, pregnancy during the double-blind phase, blind is broken, violation of protocol procedures per investigator's judgment and consultation with Applicant, and change in inpatient status from voluntary to involuntary as a result of judicial or other legal administrative order.

If a subject discontinued treatment for any reason other than lost to follow-up, death, or withdrawal of consent before the end of the double-blind treatment phase, an Early Termination visit was conducted, and the subject was contacted 3 days after the last IN dose, on Day 25, and Day 90 for MADRS assessment and adverse event (AE) collection. In addition,

the investigator was to ensure the subject was appropriately transitioned or followed for any additional care required.

A subject was withdrawn from the study during the follow-up phase for the following reasons: lost to follow-up, withdrawal of consent, death, and violation of protocol procedures per investigator's judgment and in consultation with the Applicant. Similar to above procedures, subjects were contacted on Day 90 for assessment, and transition/follow-up provided.

Every reasonable effort was to be made by study site personnel to contact the subject and determine the reason for discontinuation/withdrawal, including at least three attempts via telephone, certified letters, emails, etc. All reasons for withdrawal were to be documented in the electronic case report form (eCRF). Subjects who withdrew were not replaced.

Study Endpoints

Primary Endpoint: MADRS total score change from baseline (Day 1, pre-dose) to 24 hours post-first-dose.

The MADRS is a commonly utilized, clinician-rated scale designed to be used in subjects with MDD to measure depression severity and detect changes due to AD treatment. The test consists of 10 items, each scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts; it does not target so-called "reverse neurovegetative" symptoms (i.e., increased sleep or appetite/weight). The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days. In this study, the MADRS was administered using a since-last-assessment recall, a 4-hour recall on Day 1 and Day 25 post-dose, and a 24-hour recall on Day 2. For the MADRS performed at 4 hours post-dose on Days 1 and 25, the MADRS scores for the sleep item recorded pre-dose on the same day were carried forward.

At a Type C IND meeting in October 2013, the Division agreed that there was "an unmet clinical need for th (b) (4)

(b) (4) as long as that effect can be maintained (emphasis added)." At a Type B end-of-phase-2 meeting in October 2016, the Division agreed with the primary endpoint for the phase 3 studies. See Section 3.1 for presubmission regulatory discussion.

Clinical Reviewer's Comment: The MADRS is included in the Clinical Outcome Assessment (COA) Compendium (August 2019). The clinical meaningfulness of an improvement within 24 hours is dependent upon whether the effect can be maintained, as the Division noted at the October 2013 meeting.

Key Secondary Endpoint: Clinical Global Impression of Severity of Suicidality-Revised version (CGI-SS-R) change from baseline (Day 1, pre-dose) to 24 hours post-first-dose.

The Sponsor incorporated the CGI-SS-R as one of the modules of the SIBAT, which was created for this development program and is described further below. The CGI-SS-R is a revised version of the CGI-SS that was used for the InterSePT study, which the Agency used to support labeling of clozapine for reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder (Meltzer et al. 2003). The CGI-SS-R is a clinician-rated, one-item assessment that asks raters to consider their total clinical experience with suicidal patients and all information now available to them, and assess how suicidal the patient is at this time. It is rated on a seven-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients), with details as per Table 6. Scoring is based on the totality of the information available to the clinician, including information from the SIBAT.

Table 6. Clinical Global Impression – Severity of Suicidality – Revised

“Considering your total clinical experience with suicidal patients and all information available to you, how suicidal is the patient at this time?”	
Rating	Guide to Rating
0 – Normal, not at all suicidal	Not suicidal
1 – Questionably suicidal	Minimal ideations; little if any impulsivity for suicide; few risk factors; many protective factors and no impact on function.
2 – Mildly suicidal	Occasional ideations; little if any impulsivity for suicide; few risk factors; adequate protective factors and no or minimal impact on function.
3 – Moderately suicidal	Intermittent ideations; with possible impulsivity for suicide; may or may not have plan or recent attempt*; several risk factors; protective factors may outweigh risk factors and some impact on function.
4 – Markedly suicidal	Regular ideations with intent or potential for impulsive actions for suicide; may or may not have plan or recent attempt*; multiple risk factors outweigh protective factors; and marked impact on function.
5 – Severely suicidal	Frequent ideations with intent; well-worked-out suicide plan; may or may not have recent attempt*; multiple risk factors outweigh protective factors; and major impact on function.
6 – Among the most extremely suicidal patients	Nearly constant suicidal ideations and intent; well-worked-out plan and preparation underway or recent attempt*; and severe impact on function.

Source: Applicant’s Assessing the Measurement Properties of the Suicidal Ideation and Behavior Assessment Tool (SIBAT) Final Report, Appendix A, p. 161

* Consider seriousness/lethality of any plan or suicide attempt in the overall rating

The SIBAT is a novel, computerized, multi-module assessment tool that captures both patient-reported and clinician-rated information relevant to suicidal ideation, behavior, and risk. The patient-rated section has modules of demographics and suicide history, risk/protective factors, suicidal thinking, suicide behavior, and suicide risk. The information generated in this section is summarized and used to support the clinical decision-making of the second section. The clinician-rated section has modules for a semi-structured interview; for the CGI-SS-R, the

Clinical Global Impression for Suicide Risk – Imminent (CGI-SR-I), the Clinical Global Impression for Suicide Risk – Long-Term (CGI-SR-LT), and the Frequency of Suicidal Thinking; and for the Clinical Judgment of Optimal Suicide Management.

The Sponsor conducted a validation program for the SIBAT. At a Type C IND meeting in December 2015, the Sponsor asked if concerns around the use of the CGI-SR-I as a key endpoint should persist, would the Division consider the CGI-SS as an alternate measure given the regulatory precedent for its use in clozapine. The Division advised it remained open to both as key secondary endpoints, and requested that the CGI-SS be administered to align and anchor the Sponsor's findings with clozapine. At a Type B meeting in July 2016, the Sponsor advised the Division of their conclusion that the CGI-SS was not well-suited to measure rapid change or address the Division's concerns regarding measurement of suicide risk, and proposed a revision wherein the clinician would be asked to assess (b) (4).

Although the Division did not agree with the Sponsor's wording in the background package questions, in follow-up email communication, the Division clarified agreement with CGI-SS-R use as key secondary pending further validation work. At a Type B end-of-phase-2 meeting in October 2016, the Division agreed with the key secondary endpoint for the phase 3 studies. See Section 3.1 for presubmission regulatory discussion.

Clinical Reviewer's Comment: The Division agreed with the CGI-SS-R as a key secondary endpoint after several discussions at meetings and updating by the Applicant.

Other Secondary Endpoints:

- MADRS remission rate (MADRS ≤ 12) at 4 hours and 24 hours post-first-dose, and through the end of the double-blind treatment phase (Day 25).
- MADRS total score change from baseline at 4 hours post-first-dose and through Day 25.
- CGI-SS-R change from baseline at 4 hours post-first-dose and through Day 25.
- Proportion of subjects achieving resolution of suicidality (CGI-SS-R score of 0 or 1) at 4 hours and 24 hours post-first-dose, and through Day 25.
- CGI-SR-I change from baseline at 4 hours and 24 hours post-first-dose, and through Day 25. As part of the SIBAT described above, the CGI-SR-I is a clinician-rated, one-item assessment that asks the rater to consider all aspects of the patient's suicidal thinking, behavior, and related contributory/protective factors, and make their best clinical judgment of the patient's imminent risk for suicide within the next 7 days. It is rated on a seven-point scale from 0 (no imminent suicide risk: no evidence of risk noted) to 6 (extreme imminent suicide risk: highly likely to attempt suicide in the next 7 days).

- Beck Hopelessness Scale (BHS) change from baseline through Day 25. The BHS is a self-report measure of pessimism. Twenty true-false items are rated 0 or 1 within the domains of future, motivation, expectations. Higher scores indicate greater hopelessness and scores greater than 8 have been predictive of suicide.
- European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L) change from baseline through Day 25. The EQ-5D-5L measures five dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression) each of which has five potential levels of responses (no problems, slight problems, moderate problems, severe problems, extreme problems).
- Quality of Life in Depression Scale (QLDS) change from baseline through Day 25. The QLDS is a disease-specific patient-reported outcome measure designed to assess health-related quality of life in patients with MDD. The 34-item instrument has a recall period of “at the moment” and is rated yes/no or true/not true. The score ranges from 0 (good quality of life) to 34 (very poor quality of life).
- TSQM-9 scores through Day 25. The TSQM-9 is a 9-item generic patient-reported outcome measure designed to assess patients’ satisfaction with medication. It is derived from the longer TSQM Version 1.4 and covers domains of effectiveness, convenience, and global satisfaction. The recall period is “the last 2 to 3 weeks,” and scores range from 0 to 100, with lower scores indicating lower satisfaction.
- SIBAT change from baseline in Module 5 My Risk, Question 3 (subject-reported frequency of suicidal thinking), through the end of Day 25. As part of the SIBAT described above, Question 3 from Module 5 asks patients to describe their thinking about suicide right now. There are five response options ranging from “I have no suicidal thoughts” to “I have suicidal thoughts all of the time.”
- Pharmacokinetics (PK): plasma esketamine and noresketamine concentrations will be summarized; plasma concentrations of esketamine (and noresketamine concentrations, if warranted) will be included in a population analysis

Safety Endpoints:

- AE monitoring.
- Clinical laboratory tests (standard hematology, chemistry, and urinalysis).
- Physical examination (including nasal).
- Electrocardiogram (ECG).

- Vital signs.
- SIBAT.
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S) on dosing days. The MOAA/S is a clinician-rated instrument used to track sedation based on the American Society of Anesthesiologists continuum. Scores range from 0 (no response to painful stimulus) to 5 (readily responds to name spoken in normal tone).
- Clinician-Administered Dissociative States Scale (CADSS) on dosing days. The CADSS is a 23-item instrument for the measurement of present-state dissociative symptoms, divided into three components: depersonalization, derealization, and amnesia. Subjects' responses are coded on a 5-point scale from 0 (not at all) to 4 (extremely).
- Pulse oximetry on dosing days.

Clinical Reviewer's Comment: Other secondary endpoints are not intended for inclusion in labeling. Safety endpoints are acceptable. The MOAA/S and CADSS were used in the TRD studies. The SIBAT was used in place of the C-SSRS and contains items for Columbia Classification Algorithm of Suicide Assessment (C-CASA) mapping. Of note, the four-item Brief Psychiatric Rating Scale (BPRS) and the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) were not utilized, as they had been for the phase 2 proof-of-concept Trial SUI2001 and the TRD studies.

Exploratory Endpoints:

- Change from baseline in MADRS, CGI-SS-R, CGI-SR-I, BHS, QLDS, and EQ-5D-5L through the end of the follow-up phase (Day 90)
- TSQM-9 scores, medical resource utilization, and biomarkers through Day 90
- SIBAT change from baseline in Module 3 My Current Thinking through Day 25 and Day 90

Statistical Analysis Plan

- The primary estimand is defined by the following 4 components:
 - Population: subjects with MDD who are at imminent risk of suicide
 - Endpoint: change from baseline to 24 hours post first dose (Day 2) in the MADRS total score
 - Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind phase.
 - Summary Measure: the difference in variable least squares means.

Statistical Reviewer's Comment: The Applicant's estimand only contains four components instead of the current five components as the SAP was written in 2018 before ICH E9(R1) was finalized in Fall 2019. This estimand is acceptable from a statistics prospective.

- All efficacy analyses were conducted using the Full Analysis Set (FAS). The FAS population consisted of all randomized subjects who received at least one dose of esketamine and at least one post-dose MADRS evaluation.
- For the primary endpoint of change in MADRS score from baseline to Day 2 (Δ MADRS), the primary analysis was an ANCOVA analysis. The model included fixed effect terms for treatment arm, baseline MADRS score, center, and standard-of-care antidepressant treatment (i.e., antidepressant monotherapy or an antidepressant plus augmentation therapy). The esketamine treatment effect was estimated using the least squares (LS) mean difference at Day 2 from this ANCOVA model.
- For the secondary endpoint of change in CGI-SS-R score from baseline to Day 2 (Δ CGI-SS-R), the primary analysis was an ANCOVA analysis on the ranked change from baseline to Day 2. To calculate the ranks, the Applicant first calculated Δ CGI-SS-R for each patient. Then, the Δ CGI-SS-R scores were ranked ignoring treatment arm. The model included fixed-effect terms for treatment arm, baseline CGI-SS-R score (unranked), center, and standard-of-care antidepressant treatment (i.e., antidepressant monotherapy or an antidepressant plus augmentation therapy). The esketamine treatment effect was estimated by the Hodges-Lehmann (HL) estimator of the median differences. This HL estimator was not stratified by center or standard-of-care antidepressant treatment. In addition, this HL estimate was not adjusted for baseline CGI-SS-R.

Statistical Reviewer's Comment: Although the proposed ranked ANCOVA and HL estimator may address potential issues in ANCOVA related to violations of the normality assumption, these methods are sensitive to a large numbers of ties. For a 7 category variable such as CGI-SS-R, the observed Δ CGI-SS-R could primarily land in a small number of categories (e.g., -3, -2, -1, 0, 1). In this situation, these rank based methods may not follow the asymptotic results for size of the test along with coverage of confidence intervals. In addition, HL-estimator only provides interpretable estimates of a shift parameter for comparing two continuous distributions. CGI-SS-R has a categorical distribution. Therefore, the HL-estimator may not provide interpretable estimates.

- **Bayesian Ordinal Item Response Theory (BIRT)** (exploratory, pre-specified on the individual trials) assumes that a latent trait underlies categorical endpoint. This latent trait captures a patient's underlying suicidality. The BIRT model assumes that the CGI-SS-R follows a categorical distribution. In this model, a treatment improves CGI-SS-R if the odds ratio for decreasing one category on the CGI-SS-R is greater than 1.
- The Applicant imputed missing data using last observation carried forward (LOCF).

Statistical Reviewer's Comment: The Applicant's LOCF, single imputation method may be acceptable for the Day 2 endpoint if a small number of patients do not have a Day 2 measurement. However, this approach may yield biased estimates and underestimate the standard error of the treatment effect if a sufficient number of patients dropped out. LOCF is not a reasonable missing data method for exploring the long-term (Day 25 and Day 90) esketamine efficacy.

Protocol Amendments

There were three amendments to the original protocol, with noteworthy changes highlighted below:

Amendment 1 (April 7, 2017):

- Duration of hospitalization was amended to clarify that shorter or longer hospitalizations were permitted if clinically warranted per local standard of care.
- A remote contact was added at Day 35 to ensure twice weekly monitoring for the first 2 weeks after study treatment.
- Exclusion criteria were revised to explicitly specify a detailed list of important medical conditions which were exclusionary (as noted above), including conditions in which the elevation of blood pressure could be a serious risk.

Amendment 2 (April 20, 2017):

- Reasons for discontinuation of study treatment updated to include a change in hospitalization status from voluntary to involuntary, or worsening of underlying condition.
- Updated study procedures to clarify that subjects should refrain from alcohol use within 24 hours before and after intranasal treatment sessions, and that if a subject appears intoxicated, dosing should not occur (delayed per the permitted time window).
- The Applicant clarified how the treatment effect size in the sample size determination was determined and that the CGI-SS-R treatment effect would be estimated with a Hodges-Lehmann estimator.

Amendment 3 (February 8, 2018):

- The interim analysis was removed to ensure that the study has sufficient numbers of subjects from key global regions/countries needed to support global health authority registration.
- Module 3 SIBAT My Current Thinking assessment was changed from a secondary to an exploratory objective as it was not designed as a stand-alone endpoint.
- Exclusion criterion regarding positive test result for psychostimulants modified to clarify that subjects taking prescribed psychostimulants per Appendix 1 were permitted to enroll.

Clinical Reviewer's Comment: The first subject in this study signed informed consent on June 29, 2017, and the last observation for the last subject recorded as part of the database was December 18, 2018. Therefore, Amendment 3 could theoretically impact study results, but the specific revisions appear unlikely to do so. Safety assessment could consider the impact of any subjects taking concomitant prescribed psychostimulants with subgroup analysis; although upon prior and concomitant medication dataset review, it appears one subject in each group was taking methylphenidate, and one subject in each group was taking lisdexamfetamine, so the numbers are unlikely to have an impact.

7.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study protocol, amendments, informed consent form, and other

appropriate study-related information were reviewed by an independent ethics committee or institutional review board before the start of the study. The Applicant attests that the study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

See Appendix 17.2 for details.

Patient Disposition

See Table 7 for trial analysis sets and Table 8 for subject disposition, including reasons for discontinuation during the double-blind treatment phase (through Day 25). See Figure 2 for the Applicant's diagram of subject flow that includes reasons for discontinuation during follow-up (through Day 90). Esketamine and placebo will refer to esketamine plus SOC, or placebo plus SOC:

- Of 270 subjects screened, 44 subjects were screen failures.
- Of the 226 subjects randomized, one subject in the esketamine group discontinued during the double-blind treatment phase (for other reason) before receiving the first dose of study drug, but was included in the safety analysis set.
- The Applicant did not include another esketamine subject in the full efficacy analysis set who discontinued because of an AE after the first dose of study drug, and did not provide efficacy data after baseline (Day 1, pre-dose).
- In terms of treatment completion (i.e., through Day 25 double-blind treatment), more subjects completed treatment in the esketamine group (89.5%) than the placebo group (83.0%).
- For the follow-up analysis set (i.e., subjects who entered the follow-up phase or provided AE data post-treatment-phase), more subjects were included in the esketamine group (88.6%) than the placebo group (81.3%).
- In terms of follow-up completion (i.e., through Day 90), slightly more subjects completed follow-up in the esketamine group (73.7%) than the placebo group (71.4%), though more subjects discontinued during the follow-up phase in the esketamine group (17) than placebo (11), including more withdrawal by subjects (9 versus 5) and for AEs (2 versus 0). There was one death in the esketamine group during the follow-up phase, discussed in Section 7.5.4 Safety Results.

Table 7. Trial SUI3001 Analysis Sets

	Placebo + SOC	Esk 84 mg + SOC	Overall
Randomized	112	114	226
Safety Analysis Set	112 (100.0%)	113 (99.1%)	225 (99.6%)
Full Analysis Set	112 (100.0%)	111 (97.4%)	223 (98.7%)
Follow-up Analysis Set	91 (81.3%)	101 (88.6%)	192 (85.0%)

Source: Statistical Reviewer, Trial SUI3001 clinical study report Table 5, p. 68.

Abbreviations: Esk = esketamine, SOC = standard of care

Table 8. Trial SUI3001 Subject Disposition

	Placebo + SOC	Esk 84 mg + SOC	Total
Analysis set: All Randomized	112	114	226
Completed study treatment	93 (83.0%)	102 (89.5%)	195 (86.3%)
Discontinued study treatment	19 (17.0%)	12 (10.5%)	31 (13.7%)
Reason for discontinuation			
Adverse event	5 (4.5%)	5 (4.4%)	10 (4.4%)
Withdrawal by subject	6 (5.4%)	2 (1.8%)	8 (3.5%)
Lack of efficacy	6 (5.4%)	1 (0.9%)	7 (3.1%)
Other	1 (0.9%)	3 (2.6%)	4 (1.8%)
Change from voluntary to involuntary hospitalization	0	1 (0.9%)	1 (0.4%)
Lost to follow-up	1 (0.9%)	0	1 (0.4%)

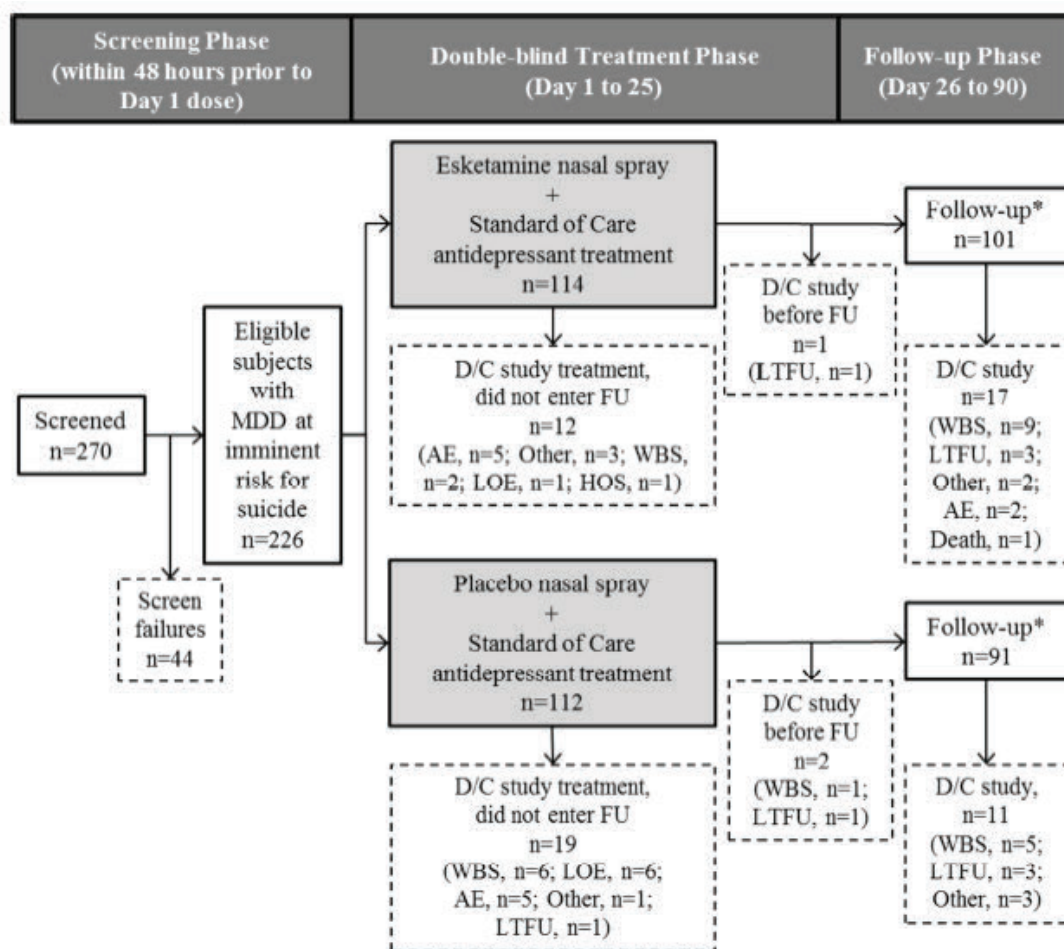
Note: 1 subject in Esk 84 mg + SOC who was randomized but did not receive any study medication is included in this summary.

[TSIDS01A.RTF] [JNJ-54135419\SUI3001\DR_FINAL\RE_CSR\PROD\TSIDS01A.SAS] 07MAY2019, 12:02

Source: Trial SUI3001 clinical study report Table 6, p. 69

Abbreviations: Esk = esketamine, SOC = standard of care

Statistical Reviewer's Comment: Table 7 differs from the Applicant's Table because one patient in the esketamine arm who did not have a valid baseline MADRS score recorded due to technical issues in recording the MADRS item scores in the electronic case report form. The statistical Reviewer excluded this patient from efficacy analyses.

Figure 2. Trial SUI3001 Subject Flow Diagram

* Subjects entered the follow-up phase or provided adverse event data after the double-blind treatment phase. AE = adverse event; D/C = discontinued FU = follow-up phase; HOS = change from voluntary to involuntary hospitalization; LOE = lack of efficacy; LTFU = Lost to follow-up; MDD = major depressive disorder; n = number; WBS = withdrawal by subject

Source: Trial SUI3001 clinical study report Figure 2 (including Applicant footnotes), p. 70

Clinical Reviewer's Comment: Nearly equal numbers of subjects between treatment groups completed the first treatment and Day 2 assessment for the full efficacy analysis set, and a similar percentage between groups completed Day 90 assessments. Of note, equal numbers of subjects withdrew for AEs during the double-blind phase, but more subjects in the placebo group withdrew for lack of efficacy. It is possible that if subjects were unintentionally unblinded given the lack of an active control (versus an inert placebo), they may have been more inclined to drop out of the study, including during the follow-up phase.

Protocol Violations/Deviations

See Table 9 for major protocol deviations for Trial SUI3001, reported in 12.8% of subjects across both treatment arms. Overall, roughly similar numbers of subjects with major protocol deviations occurred in both treatment groups. No subjects appear to have been withdrawn for protocol violations (see Table 8).

Table 9. Trial SUI3001 Major Protocol Deviations

	Placebo + SOC 112	Esk 84 mg + SOC 114	Total 226
Analysis set: All Randomized			
Subjects with major protocol deviations	16 (14.3%)	13 (11.4%)	29 (12.8%)
Entered but did not satisfy criteria	1 (0.9%)	2 (1.8%)	3 (1.3%)
Developed withdrawal criteria but not withdrawn	0	1 (0.9%)	1 (0.4%)
Received wrong treatment or incorrect dose	0	1 (0.9%)	1 (0.4%)
Other	15 (13.4%)	10 (8.8%)	25 (11.1%)

Note: Subjects may appear in more than one category.

[TSIDEV01.RTF] [JNJ-54135419\SUI3001\DBR_FINAL\RE_CSR\PROD\TSIDEV01.SAS] 03MAY2019, 14:57

Source: Trial SUI3001 clinical study report Table 9, p. 78

Abbreviations: Esk = esketamine, SOC = standard of care

Regarding subjects who entered the study, but did not satisfy enrollment criteria:

- One subject in the esketamine group had a screening period longer than 24 hours but assessment of MINI Question B3 and B10 Current Status was not repeated.
- One subject in the esketamine group did not have a baseline MADRS score because the Day 1 data was not saved on the electronic tablet device.
- One subject in the placebo group had uncontrolled hypertension (diastolic blood pressure (DBP) 92 mmHg) on Day 1 (on inspection of the dataset, it appears all subsequent measurements were lower).

Regarding subjects who developed withdrawal criteria but were not withdrawn, one subject in the esketamine group should have been withdrawn for blood pressure (BP) measurements, but continued to receive study agent. On inspection of the dataset, it appears Subject (b) (6) had a Day 1 baseline (pre-dose) BP of 131/80 mmHg with a double-blind phase high measurement of 188/127 mmHg on Day 1 at 40 minutes post-dose, which lowered to 138/108 by 1 hour 30 minutes post-dose. Subsequent treatment day measurements were not as high; the next highest reading was 140/103 mmHg at 40 minutes post-dose on Day 8 (from a Day 8 pre-dose baseline of 118/80).

Regarding subjects who received the wrong treatment or incorrect dose, one subject in the esketamine group received an incorrect dose on Day 1, as the second and third nasal sprays assigned to this subject were noted as “partially administered.”

Regarding “other” major protocol deviations, there were 25 subjects with 27 deviations. Of note:

- The stratification factor for SOC (AD monotherapy versus AD plus augmentation therapy) was entered incorrectly for 18 subjects from 13 study centers (seven in the esketamine group and 11 in the placebo group). Data review noted the majority of errors were by site staff entry mistake, one from miscommunication, and one from a subject entered as AD monotherapy who was cross-titrating on two ADs on Day 1.
- Safety assessments from two subjects (one in each group) were reviewed by efficacy raters (an ECG in the placebo group, and unspecified safety records in the esketamine group).
- One subject in the placebo group was not administered a Day 2 MADRS.
- One subject in the placebo group received psychotherapy only instead of SOC AD treatment throughout the double-blind phase.
- One subject in the esketamine group was not started on SOC AD treatment at randomization.
- One subject in the placebo group did not have an ECG performed as scheduled.

Clinical Reviewer’s Comment: The incidence of protocol deviations across all treatment arms (range 11.4 to 14.3%) does not appear excessive for a trial of this nature and does not raise significant concerns about study conduct. Although some deviations may impact efficacy findings for individual subjects, most appear unlikely to significantly affect the study conclusions because they occurred at a relatively low rate compared to the overall study population and were relatively balanced between groups. However, the only deviation that occurred in a larger number of subjects was incorrect SOC stratification (6.1% in the esketamine group and 9.8% in the placebo group). The Applicant did not clarify what actions were taken, if any, to manage the deviations. If the stratification errors were not corrected, it seems possible that subgroup analysis could be affected.

Table of Demographic Characteristics

See Table 10 for a summary of full efficacy set demographic and baseline characteristics for

Trial SUI3001. Overall, subjects were 61.6% female and 38.4% male, although the esketamine group included a higher percentage of males than placebo (42.0 versus 34.8%). Overall, the mean age was similar between groups (37.9 ± 12.54 standard deviation (SD) versus 40.8 ± 13.17 SD years), although a higher percentage of subjects in the esketamine group were in the 55 to 64 age range (21.4 versus 10.7%), with fewer subjects in the 35 to 54 age range (39.3 versus 47.3%; the 18 to 34 age distribution was similar between groups). Approximately two-thirds of subjects were white, and one-quarter were Asian. One-quarter of subjects were enrolled in the United States, 19.6% overall were enrolled in Spain, and <10% were enrolled in each of the remaining countries. Subjects were generally enrolled equally across groups in each country. Weight and body mass index (BMI) were comparable across groups, with an overall mean BMI of 26.5 ± 6.70 SD kg/m².

More subjects were treated with AD monotherapy than AD plus augmentation therapy. The distribution of AD SOC by treatment received was similar between groups. A number of subjects received both AD monotherapy and AD plus augmentation therapy (9.0% in the placebo group, and 3.6% in the esketamine group).

Table 10. Trial SUI3001 Full Efficacy Analysis Set Demographic and Baseline Characteristics

Demographic Parameters	Placebo + SOC (N=112)* n (%)	Esk + SOC (N=112) n (%)	Total (N=224)^ n (%)
Sex			
Female	73 (65.2%)	65 (58.0%)	138 (61.6%)
Male	39 (34.8%)	47 (42.0%)	86 (38.4%)
Age (years)			
Mean (SD)	37.9 (12.54)	40.8 (13.17)	39.3 (12.91)
Median	38.0	39.0	39.0
Min, max	18, 64	19, 62	18, 64
18 to 34	47 (42.0%)	44 (39.3%)	91 (40.6%)
35 to 54	53 (47.3%)	44 (39.3%)	97 (43.3%)
55 to 64	12 (10.7%)	24 (21.4%)	36 (16.1%)
Race			
White	74 (66.1%)	77 (68.8%)	151 (67.4%)
Asian	28 (25.0%)	28 (25.0%)	56 (25.0%)
Black or African American	7 (6.3%)	4 (3.6%)	11 (4.9%)
Other	2 (1.8%)	1 (0.9%)	3 (1.3%)
Multiple	1 (0.9%)	1 (0.9%)	2 (0.9%)
Native Hawaiian or Other Pacific Islander	0	1 (0.9%)	1 (0.4%)
Ethnicity			
Not Hispanic or Latino	104 (93.7%)*	102 (91.1%)	206 (92.4%)^
Hispanic or Latino	7 (6.3%)*	10 (8.9%)	17 (7.6%)^

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Country			
United States	28 (25.0%)	28 (25.0%)	56 (25.0%)
Spain	20 (17.9%)	24 (21.4%)	44 (19.6%)
Republic of Korea	10 (8.9%)	10 (8.9%)	20 (8.9%)
Bulgaria	10 (8.9%)	9 (8.0%)	19 (8.5%)
Germany	10 (8.9%)	8 (7.1%)	18 (8.0%)
Taiwan	8 (7.1%)	9 (8.0%)	17 (7.6%)
Malaysia	9 (8.0%)	7 (6.3%)	16 (7.1%)
Hungary	8 (7.1%)	7 (6.3%)	15 (6.7%)
South Africa	8 (7.1%)	7 (6.3%)	15 (6.7%)
Estonia	1 (0.9%)	3 (2.7%)	4 (1.8%)
Weight (kg)			
Mean (SD)	74.5 (20.66)*	76.3 (22.82)	75.4 (21.74)^
Median	69.9*	75.0	72.0^
Range	41, 143	47, 207	41, 207
Body Mass Index (kg/m ²)			
Mean (SD)	26.4 (7.13)*	26.7 (6.28)	26.5 (6.70)^
Median	24.8*	25.8	25.1^
Range	17, 61	18, 56	17, 61^
Underweight (<18.5)	4 (3.6%)*	1 (0.9%)	5 (2.2%)^
Normal (18.5 to <25)	55 (49.5%)*	49 (43.8%)	104 (46.6%)^
Overweight (25 to <30)	27 (24.3%)*	34 (30.4%)	61 (27.4%)^
Obese (30 to <40)	20 (18.0%)*	26 (23.2%)	46 (20.6%)^
Severe Obesity (≥40)	5 (4.5%)*	2 (1.8%)	7 (3.1%)^
SOC AD Treatment as Randomized			
AD Monotherapy	65 (58.0%)	59 (52.7%)	124 (55.4%)
AD Plus Augmentation Therapy	47 (42.0%)	53 (47.3%)	100 (44.6%)
SOC AD Treatment as Received			
AD Monotherapy	51 (45.9%)*	52 (46.4%)	103 (46.2%)^
AD Plus Augmentation Therapy	50 (45.0%)*	56 (50.0%)	106 (47.5%)^
AD Monotherapy / AD Plus Augmentation Therapy+	10 (9.0%)*	4 (3.6%)	14 (6.3%)^

Source: Adapted from Trial SUI3001 clinical study report Table 7, p. 72, and ADVS dataset

Abbreviations: AD = antidepressant; Esk = esketamine, SD = standard deviation, SOC = standard of care

* Placebo N=111 for these parameters

^ Total N=223 for these parameters

+ Subjects received both AD monotherapy and AD plus augmentation therapy

Clinical Reviewer's Comment: Overall, sex and age parameters were generally representative of U.S. patient populations, and the differences between treatment groups appears unlikely to impact study results. Race and ethnicity parameters were not representative of the U.S. population, with Asians notably overrepresented (25% in the study versus 5.9% in the U.S. population, per the U.S. Census Bureau). This was likely a result of enrollment in Malaysia, the Republic of Korea, and Taiwan (accounting for 23.7% of enrolled subjects overall); the Division did agree (see Section 3.1 Summary of

Presubmission/Submission Regulatory Activity) to the 25% U.S. enrollment achieved by the Applicant. African Americans and Hispanic or Latino populations were underrepresented (4.9% in the study versus 13.4% in the U.S. population, and 7.6% in the study versus 18.3% in the U.S. population, per the U.S. Census Bureau, respectively).

The Applicant presented SOC AD treatment as assigned before randomization, and as received. It is unclear if this is a function of the incorrect stratification as described above in protocol violations, or if investigators changed treatment plans during the study. It would appear the latter was true for the subjects noted to have received both AD monotherapy and AD plus augmentation therapy. This may muddy the subgroup analysis, though the numbers of subjects who received both were small overall (6.3%); however, this was larger in the placebo group (9.0 versus 3.6%).

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

See Table 11 for baseline psychiatric history characteristics. Overall, these were similar between treatment groups. Of note, the mean MADRS total score was 41.1 ± 6.07 SD, indicating a severely depressed population (range 29 to 58). The mean duration of the current depressive episode was 34.9 ± 51.92 SD months, with a median of 13.7 and a range of 1 to 339 months. The mean number of hospitalizations for depression or suicidality in the past 12 months was 0.5 ± 1.05 SD, with a range of 0 to 8; most subjects (67.9%) had none in the past 12 months, with one hospitalization for 21.4%. Based on the MINI, the largest group (64.3%) had a history of two to five lifetime depressive episodes, and 60.7% had a suicide attempt history. Based on the SIBAT, 28.1% had a suicide attempt in the past month. MADRS, CGI, MINI, and SIBAT suicidal parameters were similar between groups. Based on the CGI-SS-R, the largest group (35.9%) was markedly suicidal, with similar numbers (~25%) moderately or severely suicidal.

Table 11. Trial SUI3001 Full Efficacy Analysis Set Baseline Psychiatric History Characteristics

	Placebo + SOC 112	Esk 84 mg + SOC 112	Total 224
Analysis set: Full Efficacy			
MADRS Total Score			
N	112	111	223
Mean (SD)	41.0 (6.29)	41.3 (5.87)	41.1 (6.07)
Median	42.0	41.0	42.0
Range	(29; 58)	(29; 56)	(29; 58)
MADRS Item 10 - Suicidal Thoughts			
N	112	111	223
0	0	0	0
1	0	0	0
2	1 (0.9%)	0	1 (0.4%)
3	8 (7.1%)	4 (3.6%)	12 (5.4%)
4	27 (24.1%)	31 (27.9%)	58 (26.0%)
5	43 (38.4%)	49 (44.1%)	92 (41.3%)
6	33 (29.5%)	27 (24.3%)	60 (26.9%)
Duration of Current Depressive Episode, months			
N	106	99	205
Mean (SD)	33.8 (54.43)	36.1 (49.34)	34.9 (51.92)
Median	13.3	15.9	13.7
Range	(2; 339)	(1; 249)	(1; 339)
BHS Total Score			
N	112	112	224
Mean (SD)	15.9 (4.60)	15.3 (4.27)	15.6 (4.44)
Median	18.0	17.0	17.0
Range	(1; 20)	(1; 20)	(1; 20)
CGI-SS-R			
N	112	111	223
Normal, not at all suicidal	0	0	0
Questionably suicidal	3 (2.7%)	5 (4.5%)	8 (3.6%)
Mildly suicidal	11 (9.8%)	6 (5.4%)	17 (7.6%)
Moderately suicidal	28 (25.0%)	29 (26.1%)	57 (25.6%)
Markedly suicidal	42 (37.5%)	38 (34.2%)	80 (35.9%)
Severely suicidal	27 (24.1%)	29 (26.1%)	56 (25.1%)
Among the most extremely suicidal patients	1 (0.9%)	4 (3.6%)	5 (2.2%)
CGI-SR-I			
N	112	111	223
No imminent suicide risk	2 (1.8%)	3 (2.7%)	5 (2.2%)
Minimal imminent suicide risk	7 (6.3%)	5 (4.5%)	12 (5.4%)
Mild imminent suicide risk	8 (7.1%)	9 (8.1%)	17 (7.6%)
Moderate imminent suicide risk	31 (27.7%)	26 (23.4%)	57 (25.6%)
Marked imminent suicide risk	37 (33.0%)	38 (34.2%)	75 (33.6%)
Severely imminent suicide risk	26 (23.2%)	27 (24.3%)	53 (23.8%)
Extreme imminent suicide risk	1 (0.9%)	3 (2.7%)	4 (1.8%)
MINI Current Status: Think about suicide - Frequency			
N	112	112	224
Occasionally	14 (12.5%)	17 (15.2%)	31 (13.8%)
Often	54 (48.2%)	49 (43.8%)	103 (46.0%)
Very Often	44 (39.3%)	46 (41.1%)	90 (40.2%)

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MINI Current Status: Think about suicide - Intensity			
N	112	112	224
Mild	8 (7.1%)	8 (7.1%)	16 (7.1%)
Moderate	43 (38.4%)	41 (36.6%)	84 (37.5%)
Severe	61 (54.5%)	63 (56.3%)	124 (55.4%)
MINI Current Status: Intend to act on thoughts of killing yourself			
N	112	112	224
Yes	112 (100.0%)	112 (100.0%)	224 (100.0%)
No	0	0	0
MINI: Lifetime Suicide Attempt			
N	112	112	224
Yes	67 (59.8%)	69 (61.6%)	136 (60.7%)
No	45 (40.2%)	43 (38.4%)	88 (39.3%)
MINI: Number of Episodes of Depression in Life Time			
N	112	112	224
1	22 (19.6%)	23 (20.5%)	45 (20.1%)
2-5	74 (66.1%)	70 (62.5%)	144 (64.3%)
6-10	12 (10.7%)	13 (11.6%)	25 (11.2%)
>10	4 (3.6%)	6 (5.4%)	10 (4.5%)
Number of Hospitalization due to Depression or Suicidality in the Past 12 Months			
N	112	112	224
Mean (SD)	0.5 (1.07)	0.6 (1.04)	0.5 (1.05)
Median	0.0	0.0	0.0
Range	(0; 8)	(0; 7)	(0; 8)
0	81 (72.3%)	71 (63.4%)	152 (67.9%)
1	21 (18.8%)	27 (24.1%)	48 (21.4%)
2	4 (3.6%)	10 (8.9%)	14 (6.3%)
3	4 (3.6%)	1 (0.9%)	5 (2.2%)
4	1 (0.9%)	2 (1.8%)	3 (1.3%)
5	0	0	0
>5	1 (0.9%)	1 (0.9%)	2 (0.9%)
Time from the Last Hospitalization Discharge due to Depression or Suicidality in the Past 12 Months, months			
N	31	41	72
Mean (SD)	4.2 (3.59)	4.5 (4.03)	4.4 (3.82)
Median	2.7	4.7	3.4
Range	(0; 11)	(0; 12)	(0; 12)
0 - <2	14 (45.2%)	17 (41.5%)	31 (43.1%)
2 - <4	3 (9.7%)	3 (7.3%)	6 (8.3%)
4 - <7	5 (16.1%)	10 (24.4%)	15 (20.8%)
7 - 12	9 (29.0%)	11 (26.8%)	20 (27.8%)
SIBAT: Patient Reported Frequency of Suicidal Thinking			
N	112	111	223
I have no suicidal thoughts	4 (3.6%)	8 (7.2%)	12 (5.4%)
I have suicidal thoughts a little of the time	15 (13.4%)	12 (10.8%)	27 (12.1%)
I have suicidal thoughts some of the time	34 (30.4%)	35 (31.5%)	69 (30.9%)
I have suicidal thoughts most of the time	41 (36.6%)	43 (38.7%)	84 (37.7%)
I have suicidal thoughts all of the time	18 (16.1%)	13 (11.7%)	31 (13.9%)
SIBAT: Prior Suicide Attempt			
N	112	111	223
Yes	68 (60.7%)	66 (59.5%)	134 (60.1%)
No	44 (39.3%)	45 (40.5%)	89 (39.9%)

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	Placebo + SOC	Esk 84 mg + SOC	Total
Suicide attempt within the last month			
N	112	112	224
Yes	31 (27.7%)	32 (28.6%)	63 (28.1%)
No	81 (72.3%)	80 (71.4%)	161 (71.9%)

Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.

MADRS item 10 - suicide score ranges from 0 to 6; a higher score indicates a more severe condition.

Duration of current depressive episode is derived from MADRS euthymic baseline.

BHS total score ranges from 0 to 20; a higher score indicates a more severe condition.

CGI-SS-R (score ranges from 0-6; a higher score indicates a more severe condition): "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"

CGI-SR-I (score ranges from 0-6; a higher score indicates a more severe condition): "Considering all aspects of this patient's suicidal thinking, behavior and related contributory/protective factors, what is your best clinical judgment of this patient's imminent risk for suicide within the next 7 days?"

Time from last hospitalization discharge is missing for subjects without hospitalization due to depression or suicidality in the past 12 months.

SIBAT Prior Suicide Attempt from Module 1: "I have made one or more attempts to end my life"

SIBAT Patient Reported Frequency of Suicidal Thinking from Module 5, Question 3: "Which of the following ratings best describes your thinking about suicide right now?"

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Source: Trial SUI3001 clinical study report Table 8 (including Applicant footnotes), p. 74

Abbreviations: BHS = Beck Hopelessness Scale, CGI-SR-I = Clinical Global Impression for Suicide Risk – Imminent, CGI-SS-R = Clinical Global Impression for Severity of Suicidality – Revised, Esk = esketamine, MADRS = Montgomery-Åsberg Depression Rating Scale, MINI = Mini International Neuropsychiatric Interview, SD = standard deviation, SIBAT = Suicidal Ideation and Behavior Assessment Tool, SOC = standard of care

Clinical Reviewer's Comment: Baseline psychiatric history characteristics, including severity of depression, hospitalization history, suicide attempt history, and suicidality parameters (e.g., frequency or severity of thinking or CGI scoring) appear balanced between treatment groups. Of note, subjects in this study had a higher mean baseline MADRS total score (41.1 ± 6.07 SD) compared to subjects in study TRD3001 (37.6 ± 5.51 SD), which may result from higher scores on Item 10 regarding suicidal thoughts. On a minor note, it appears three subjects did not answer the same way regarding suicide attempt history on the MINI versus the SIBAT. And although subjects had to answer the MINI item B3 (Current Status: Think about suicide) affirmatively for inclusion, 5.4% of subjects answered "I have no suicidal thoughts" on the SIBAT; the small number is unlikely to impact study results significantly.

See Table 12 for safety analysis set prior medications of special interest, including ADs; second generation antipsychotics; mood stabilizers and antiepileptics; benzodiazepines; and non-benzodiazepine hypnotics and anxiolytics. Ninety-two percent of subjects were taking an AD; one-third were taking an antipsychotic; and two-thirds were taking a benzodiazepine. Overall, the classes were similar between treatment groups, with some individual medication exceptions. More subjects were taking venlafaxine in the esketamine group than placebo (23.0% versus 14.3%), more subjects were taking aripiprazole in the esketamine group than placebo (15.0% versus 3.6%), and more subjects were taking lorazepam in the placebo group than esketamine (38.4% versus 22.1%).

Table 12. Trial SUI3001 Safety Analysis Set Prior Medications of Special Interest

Medication Class Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC (N=112) n (%)	Esk + SOC (N=113) n (%)	Total (N=225) n (%)
Antidepressants	101 (90.2%)	105 (92.9%)	206 (91.6%)
Escitalopram	21 (18.8%)	28 (24.8%)	49 (21.8%)
Venlafaxine	16 (14.3%)	26 (23.0%)	42 (18.7%)
Mirtazapine	15 (13.4%)	21 (18.6%)	36 (16.0%)
Duloxetine	13 (11.6%)	15 (13.3%)	28 (12.4%)
Trazodone	13 (11.6%)	14 (12.4%)	27 (12.0%)
Bupropion	13 (11.6%)	11 (9.7%)	24 (10.7%)
Sertraline	12 (10.7%)	12 (10.6%)	24 (10.7%)
Antipsychotics (Second Generation)	40 (35.7%)	43 (38.1%)	83 (36.9%)
Quetiapine	22 (19.6%)	21 (18.6%)	43 (19.1%)
Aripiprazole	4 (3.6%)	17 (15.0%)	21 (9.3%)
Olanzapine	6 (5.4%)	6 (5.3%)	12 (5.3%)
Antipsychotics (First Generation)	5 (4.5%)	2 (1.8%)	7 (3.1%)
Mood Stabilizers and Antiepileptics	16 (14.3%)	19 (16.8%)	35 (15.6%)
Lamotrigine	7 (6.3%)	4 (3.5%)	11 (4.9%)
Gabapentin	3 (2.7%)	6 (5.3%)	9 (4.0%)
Lithium	3 (2.7%)	5 (4.4%)	8 (3.6%)
Benzodiazepines	77 (68.8%)	74 (65.5%)	151 (67.1%)
Lorazepam	43 (38.4%)	25 (22.1%)	68 (30.2%)
Clonazepam	30 (26.8%)	37 (32.7%)	67 (29.8%)
Alprazolam	17 (15.2%)	15 (13.3%)	32 (14.2%)
Non-benzodiazepine Hypnotics/Anxiolytics	24 (21.4%)	24 (21.2%)	48 (21.3%)
Zolpidem	10 (8.9%)	10 (8.8%)	20 (8.9%)
Zopiclone	6 (5.4%)	3 (2.7%)	9 (4.0%)
Pregabalin	4 (3.6%)	4 (3.5%)	8 (3.6%)

Source: Adapted from Trial SUI3001 clinical study report Attachment TSICM03

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: Overall, prior medication classes of interest appear to be balanced between treatment groups, and the few individual medication exceptions are unlikely to impact study results. As might be expected with subjects of this illness severity, one-third were already taking an antipsychotic (presumably either for augmentation purposes or, as it appears the doses were low or as-needed (PRN) for a number of subjects on quetiapine, likely off-label for insomnia).

Concomitant or Rescue Medication Use and Treatment Compliance

See Table 13 for safety analysis set treatment phase concomitant medications (including those used as SOC treatment) of special interest, including ADs; second generation antipsychotics;

mood stabilizers and antiepileptics; benzodiazepines; and non-benzodiazepine hypnotics and anxiolytics. The Applicant presented separate data for concomitant medications versus SOC received; where these numbers were different, the medication is presented additionally as SOC. (This appears to have made the most difference for trazodone, quetiapine, and gabapentin.)

The Applicant did not specify particular rescue medications, but noted that benzodiazepines and non-benzodiazepine hypnotics and anxiolytics would be of interest. Overall, medication use was similar between treatment groups, with some individual medication exceptions. As with prior medications, more subjects took aripiprazole in the esketamine group than placebo (15.0% versus 4.5%), and more subjects took lorazepam in the placebo group than esketamine (43.8% versus 32.7%). However, more subjects took clonazepam in the esketamine group than placebo (35.4% versus 25.9%).

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Table 13. Trial SUI3001 Safety Analysis Set Treatment Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC (N=112)	Esk + SOC (N=113)	Total (N=225)
Medication as SOC if different usage	n (%)	n (%)	n (%)
Antidepressants			
Venlafaxine	26 (23.2%)	32 (28.3%)	58 (25.8%)
Venlafaxine as SOC	25 (22.3%)	31 (27.4%)	56 (24.9%)
Mirtazapine	18 (16.1%)	20 (17.7%)	38 (16.9%)
Mirtazapine as SOC	15 (13.4%)	20 (17.7%)	35 (15.6%)
Duloxetine	19 (17.0%)	17 (15.0%)	36 (16.0%)
Duloxetine as SOC	19 (17.0%)	16 (14.2%)	35 (15.6%)
Escitalopram (/as SOC)	18 (16.1%)	18 (15.9%)	36 (16.0%)
Trazodone	15 (13.4%)	15 (13.3%)	30 (13.3%)
Trazodone as SOC	6 (5.4%)	4 (3.5%)	10 (4.4%)
Bupropion (/as SOC)	13 (11.6%)	11 (9.7%)	24 (10.7%)
Antipsychotics (Second Generation)			
Quetiapine	31 (27.7%)	27 (23.9%)	58 (25.8%)
Quetiapine as SOC	15 (13.4%)	17 (15.0%)	32 (14.2%)
Aripiprazole (/as SOC)	5 (4.5%)	17 (15.0%)	22 (9.8%)
Olanzapine	5 (4.5%)	5 (4.4%)	10 (4.4%)
Olanzapine as SOC	4 (3.6%)	5 (4.4%)	9 (4.0%)
Mood Stabilizers and Antiepileptics			
Lithium (/as SOC)	4 (3.6%)	6 (5.3%)	10 (4.4%)
Lamotrigine (/as SOC)	6 (5.4%)	2 (1.8%)	8 (3.6%)
Gabapentin	1 (0.9%)	5 (4.4%)	6 (2.7%)
Gabapentin as SOC	1 (0.9%)	0	1 (0.4%)
Valproic Acid (/as SOC)	2 (1.8%)	2 (1.8%)	4 (1.8%)
Benzodiazepines			
Lorazepam	80 (71.4%)	84 (74.3%)	164 (72.9%)
Clonazepam	49 (43.8%)	37 (32.7%)	86 (38.2%)
Alprazolam	29 (25.9%)	40 (35.4%)	69 (30.7%)
Alprazolam	15 (13.4%)	15 (13.3%)	30 (13.3%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Zolpidem	35 (31.3%)	26 (23.0%)	61 (27.1%)
Zopiclone	15 (13.4%)	13 (11.5%)	28 (12.4%)
Pregabalin	6 (5.4%)	5 (4.4%)	11 (4.9%)
Pregabalin as SOC	5 (4.5%)	4 (3.5%)	9 (4.0%)
Pregabalin as SOC	1 (0.9%)	1 (0.9%)	2 (0.9%)

Source: Adapted from Trial SUI3001 clinical study report Attachments TSICM01A, TSICM02A, and TSICM04A

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: The differences between concomitant use versus use as SOC for trazodone, quetiapine, and gabapentin likely stem from their off-label uses as

PRNs for insomnia (or also anxiety for gabapentin). Benzodiazepine and non-benzodiazepine hypnotic/anxiolytic use was already of note pre-treatment, and the numbers increased somewhat on-treatment (from 67.1 to 72.9% overall, and 21.3 to 27.1% overall, respectively). There was a larger increase in benzodiazepine use for the esketamine group (an 8.8% increase) than placebo (a 2.6% increase), and a larger increase in non-benzodiazepine hypnotic/anxiolytic use for the placebo group (a 9.9% increase) than esketamine (a 1.8% increase). One could speculate multiple reasons for these differences, but it may not be significant if some portion of the benzodiazepine use was for insomnia rather than anxiety or agitation. Overall, concomitant medication use during the double-blind phase (including as SOC) appears relatively balanced between treatment groups and unlikely to impact study results.

See Table 14 for follow-up analysis set follow-up phase concomitant medications (including those used as SOC treatment) of special interest, presented in the same manner as for the double-blind phase. Overall, medication use was similar between treatment groups, with some exceptions. More subjects took venlafaxine in the esketamine group than placebo (31.7% versus 20.9%). More subjects took benzodiazepines in the esketamine group than placebo (71.3% versus 61.5%). Of note during the follow-up phase, one subject in the esketamine group received esketamine (b) (6) two subjects in the esketamine group received ketamine (b) (6) and two subjects in the placebo group received ketamine (b) (6)

Table 14. Trial SUI3001 Follow-Up Analysis Set Follow-Up Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC	Esk + SOC	Total
- Medication as SOC if different than overall usage	(N=91)	(N=101)	(N=192)
	n (%)	n (%)	n (%)
Antidepressants			
Venlafaxine	19 (20.9%)	32 (31.7%)	51 (26.6%)
Venlafaxine as SOC	19 (20.9%)	31 (30.7%)	50 (26.0%)
Mirtazapine	17 (18.7%)	18 (17.8%)	35 (18.2%)
Mirtazapine as SOC	14 (15.4%)	18 (17.8%)	32 (16.7%)
Duloxetine	16 (17.6%)	16 (15.8%)	32 (16.7%)
Duloxetine as SOC	16 (17.6%)	15 (14.9%)	31 (16.1%)
Escitalopram (/as SOC)	15 (16.5%)	17 (16.8%)	32 (16.7%)
Trazodone	10 (11.0%)	14 (13.9%)	24 (12.5%)
Trazodone as SOC	6 (6.6%)	3 (3.0%)	9 (4.7%)
Bupropion (/as SOC)	12 (13.2%)	11 (10.9%)	23 (12.0%)
Antipsychotics (Second Generation)			
Quetiapine	22 (24.2%)	25 (24.8%)	47 (24.5%)
Quetiapine as SOC	13 (14.3%)	14 (13.9%)	27 (14.1%)
Aripiprazole (/as SOC)	8 (8.8%)	15 (14.9%)	23 (12.0%)
Olanzapine	4 (4.4%)	6 (5.9%)	10 (5.2%)
Olanzapine as SOC	3 (3.3%)	4 (4.0%)	7 (3.6%)
Mood Stabilizers and Antiepileptics			
Lithium (/as SOC)	3 (3.3%)	10 (9.9%)	13 (6.8%)
Lamotrigine (/as SOC)	6 (6.6%)	2 (2.0%)	8 (4.2%)
Gabapentin	2 (2.2%)	5 (5.0%)	7 (3.6%)
Gabapentin as SOC	1 (1.1%)	0	1 (0.5%)
Valproic Acid (/as SOC)	1 (1.1%)	2 (2.0%)	3 (1.6%)
Benzodiazepines			
Clonazepam	25 (27.5%)	34 (33.7%)	59 (30.7%)
Lorazepam	27 (29.7%)	30 (29.7%)	57 (29.7%)
Alprazolam	10 (11.0%)	14 (13.9%)	24 (12.5%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Zolpidem	12 (13.2%)	11 (10.9%)	23 (12.0%)
Pregabalin	4 (4.4%)	4 (4.0%)	8 (4.2%)
Pregabalin as SOC	0	2 (2.0%)	2 (1.0%)
Zopiclone	3 (3.3%)	4 (4.0%)	7 (3.6%)

Source: Adapted from Trial SUI3001 clinical study report Attachments TSICM01B, TSICM02B, and TSICM04B

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: As during the double-blind phase, the differences between concomitant use versus use as SOC for trazodone, quetiapine, and gabapentin in the

follow-up phase likely stem from their off-label uses as PRNs for insomnia (or also anxiety for gabapentin). It is difficult to know what to make of any differences between treatment groups, for example with benzodiazepine use, as enrollment decreased more for the placebo group than esketamine; it is possible that more symptomatic subjects left the placebo group. Overall, concomitant medication use during the follow-up phase (including as SOC) appears relatively balanced between treatment groups and unlikely to impact study results.

Regarding treatment compliance, the Applicant reported that doses of IN study agent were self-administered by subjects at the study site under the direct supervision of the investigator or designee. The Applicant did not comment upon any observation (or pill counting) of SOC AD treatment during the double-blind inpatient phase, or the double-blind outpatient and follow-up phases.

In terms of exposure, most subjects in both treatment groups received study agent on all 8 dosing days during the double-blind phase (86.7% in the esketamine group and 81.3% in the placebo group). As noted previously, equal numbers of subjects discontinued for AEs, and more subjects withdrew for lack of efficacy in the placebo group (see Table 8). See Table 15 for a summary of exposure to study agent by number of days exposed.

Table 15. Trial SUI3001 Safety Analysis Set Summary of Exposure to Study Agent

Number of Days Dosed	Placebo + SOC (N=112)	Esketamine + SOC (N=113)
	n (%)	n (%)
1	3 (2.7%)	5 (4.4%)
2	1 (0.9%)	0
3	5 (4.5%)	2 (1.8%)
4	5 (4.5%)	0
5	2 (1.8%)	1 (0.9%)
6	2 (1.8%)	2 (1.8%)
7	3 (2.7%)	5 (4.4%)
8	91 (81.3%)	98 (86.7%)

Source: Adapted from Trial SUI3001 clinical study report Table 10, p. 81

Abbreviations: SOC = standard of care

During the double-blind phase, one subject in the placebo group required dose reduction due to an AE, and one subject in the placebo group received a partial dose on 1 day because of an accidental spray in the air. Twenty-four of 113 (21.2%) of subjects in the esketamine group received less than 84 mg of esketamine on at least 1 dosing day:

- Twenty-one subjects (18.6%) in the esketamine group required dose reduction to 56 mg at some point for all subsequent doses due to: an AE (19 subjects), a tolerability issue (1

subject), or investigator discretion based on expected side effects (1 subject). Ninety-two subjects (81.4%) in the esketamine group did not require a dose reduction.

- Three subjects (2.7%) in the esketamine group received less than the intended 84 mg dose on at least 1 day. Two subjects received a 56 mg dose on Day 1 due to an AE (one subject continued on 84 mg for all subsequent doses; one discontinued treatment after that). One subject received partial doses of esketamine on Days 1, 4, and 7 due to issues with administration of six nasal spray devices.

Clinical Reviewer's Comment: Given that the majority of subjects in the esketamine group (81.4%) received 84 mg, and that subjects who reduced to 56 mg did so at various time points, it does not appear useful to explore a dose-response subgroup analysis.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint of change from baseline to 24 hours total MADRS score showed a 3.82 point (two-sided $p = 0.0064$) greater decline in the esketamine arm compared to placebo, see Table 16. The esketamine arm declined 16.5 points from an average baseline score of 41.3 points. See Table 16 for the placebo arm values. P-values were compared to an alpha level of 0.05. Throughout this Section, negative change indicates improvement.

Table 16. MADRS Total Score at 24 Hours

Dose	Placebo		Esketamine		LS Mean Difference (95% CI)	Two-sided p-value
	N	LS Mean (SE)	N	LS Mean (SE)		
84 mg	112	-12.7 (0.97)	111	-16.5 (0.97)	-3.82 (-6.60, -1.04)	0.0064

Source: Statistical Reviewer.

Statistical Reviewer's Note: *The estimated least squares means (LSmeans) in Table 16 differ from the Applicant's LSmeans (Esketamine 84 mg = - 15.9; Placebo = -12.0) because the Statistical Reviewer used weight proportional to the observed study margins instead of equal weights, the Applicant's choice. Both choices of weights yield the same treatment difference and statistical inference.*

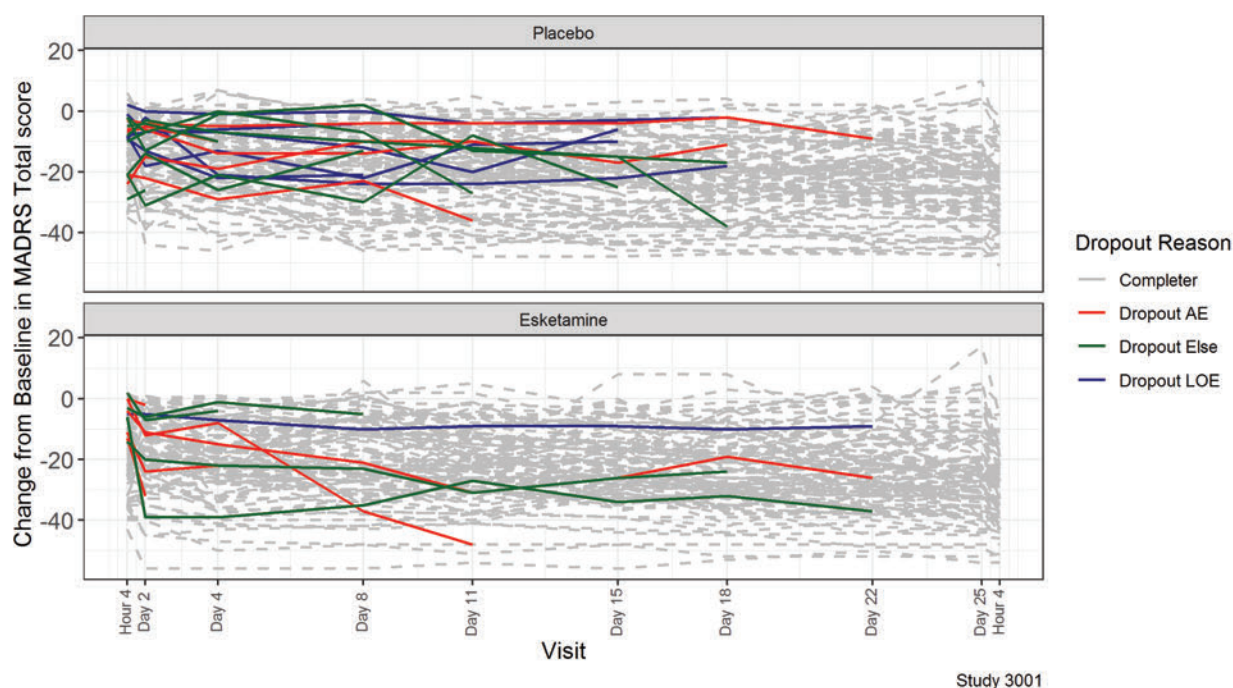
One patient in the placebo arm did not have a 24-hour observation, see Table 17. In this case when only one observation is missing, it is unlikely to have any noticeable effect on the study results assuming LOCF. However, by Day 25, between 14% and 18% of patients dropped out. The LOCF assumption is likely to affect results and was not used by either the Applicant or these Reviewers. Instead, the Applicant's exploratory analyses of the time course of MADRS scores assumed missing at random (MAR) and were conducted with mixed models for repeated measures (MMRM).

Table 17. Missing Observations in the Full Efficacy Analysis Set

Treatment Arm	Day 2		Day 25	
	Observed	LOCF	Observed	LOCF
Placebo	111 (99%)	1 (1%)	92 (82%)	20 (18%)
Esketamine	111 (100%)	0 (0%)	96 (86%)	15 (14%)

Source: Statistical Reviewer.

Although the primary endpoint was evaluated at 1 day post-dose, it is clinically relevant to understand if esketamine demonstrated a persistence of effect through Day 25 compared to placebo, which was an additional secondary endpoint. Figure 3 shows the individual patient MADRS trajectories from Hour 4 to Day 25 with grey lines indicating patients who completed the study and red, green, and blue lines indicating patients who dropped out. Patients who dropped out do not show a systematic pattern or deviation from completers. MAR may be a justifiable assumption for analyzing the MADRS total score during the 25-day double-blind period.

Figure 3. Patient Level MADRS Change Score Trajectories (SUI3001: FAS)

Source: Statistical Reviewer.

Table 18 and Figure 4 present the MADRS total score during the 25-day double-blind period. In Figure 4, both esketamine (black line) and placebo (grey line) arm MADRS scores decrease rapidly over the first 4 days with the esketamine arm improving approximately 19 points and the placebo improving approximately 14 points. The difference between esketamine and

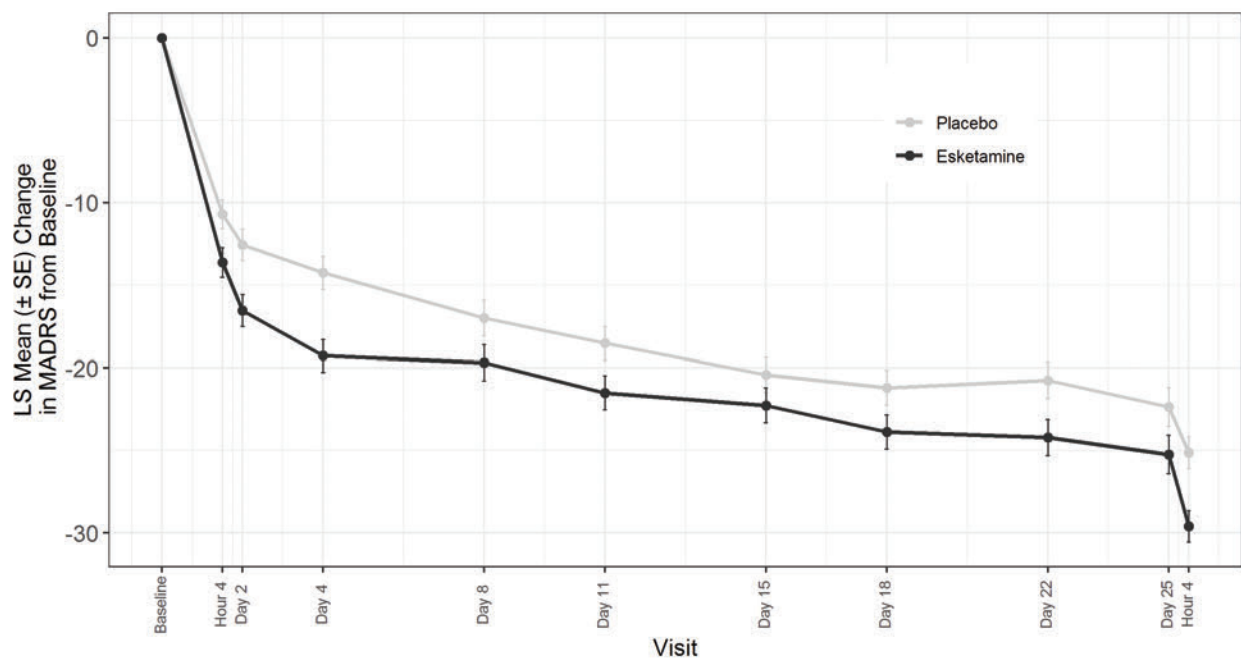
placebo is greatest at Day 4 with a difference of 4.74 points (95% CI: -7.49 to -1.99), see Table 18. Throughout the double-blind period, the esketamine arm had between 1.5 to 4.75 point greater improvement from baseline compared to the placebo arm.

Table 18. Change from Baseline in MADRS Total Score (SUI3001: FAS)

<i>Treatment Arm</i>	<i>Visit</i>	<i>Treatment Effect</i>	<i>SE</i>	<i>Lower 95% CI</i>	<i>Upper 95% CI</i>	<i>Unadjusted p-value</i>
ESK - Placebo	Day 1(DB): 4H	-2.63	1.26	-5.10	-0.16	0.0369
ESK - Placebo	Day 2(DB)	-3.69	1.37	-6.37	-1.00	0.0072
ESK - Placebo	Day 4(DB)	-4.74	1.40	-7.49	-1.99	0.0007
ESK - Placebo	Day 8(DB)	-2.40	1.54	-5.42	0.61	0.1183
ESK - Placebo	Day 11(DB)	-2.70	1.45	-5.55	0.16	0.0639
ESK - Placebo	Day 15(DB)	-1.55	1.51	-4.51	1.40	0.3029
ESK - Placebo	Day 18(DB)	-2.38	1.48	-5.28	0.53	0.1086
ESK - Placebo	Day 22(DB)	-3.17	1.57	-6.24	-0.09	0.0434
ESK - Placebo	Day 25(DB): Predose	-2.59	1.66	-5.84	0.66	0.1177
ESK - Placebo	Day 25(DB): 4H	-4.18	1.36	-6.85	-1.50	0.0022

Source: Statistical Reviewer.

Figure 4. MADRS Total Score - LS Mean ($\pm$ SE) Change from Baseline over Time - Mixed Model for Repeated Measures (SUI3001: FAS Population)

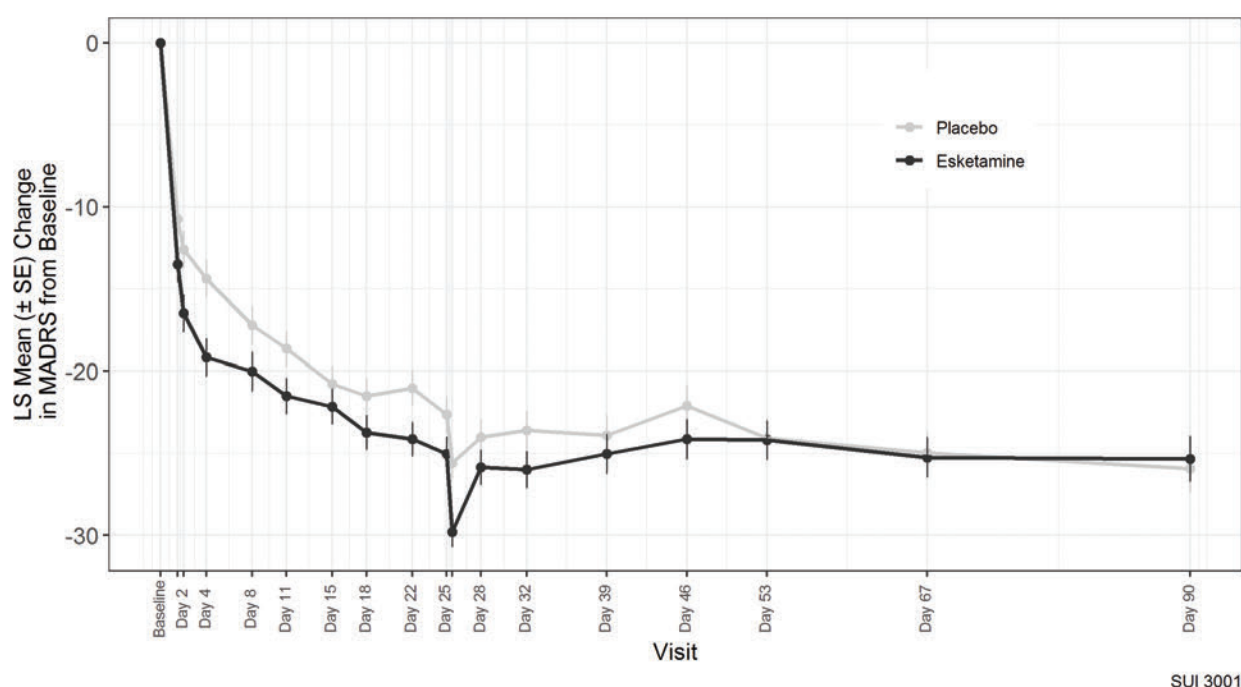


SUI 3001

Source: Statistical Reviewer.

Over the entire 90-day follow-up period, differences between placebo arm and esketamine arm in MADRS total score are no longer present by Day 53, see Figure 5. However, the statistical information about the difference declines as soon as Day 28 because of patients dropping out of the study. These graphs were generated using results of the Statistical Reviewer's mixed effects model for repeated measures (MMRM) analysis, see details in additional statistical analysis section.

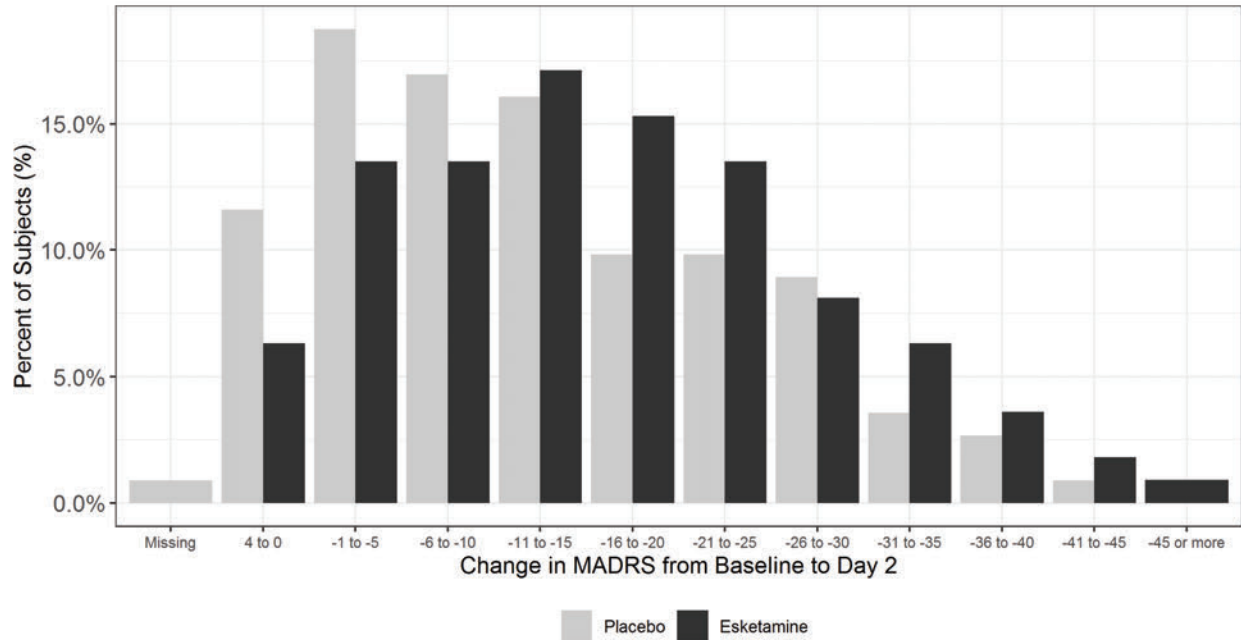
Figure 5. MADRS Total Score - 90 Day Follow-up - LS Mean ($\pm$ SE) Change from Baseline over Time - Mixed Model for Repeated Measures (SUI3001: FAS Population)



Source: Statistical Reviewer.

In SUI3001, 99% of patients completed the 24 hour post-randomization observation and 84% of patients completed the double-blind phase. Using Figure 6., Figure 7., and Figure 23, this Reviewer analyzed the usefulness of esketamine in treating MDSI. The histogram includes categories for patients who showed no improvement or worsening MDD. In addition, patients who dropped out before the specified time are included in the "Missing" category. At one day post-randomization and at both time points on Day 25, the esketamine arm has more patients showing a greater improvement from baseline than placebo. Combined with comparable dropout rates across arms implies that esketamine is useful in treating MDSI. Therefore, esketamine may be more useful than placebo in treating MDSI.

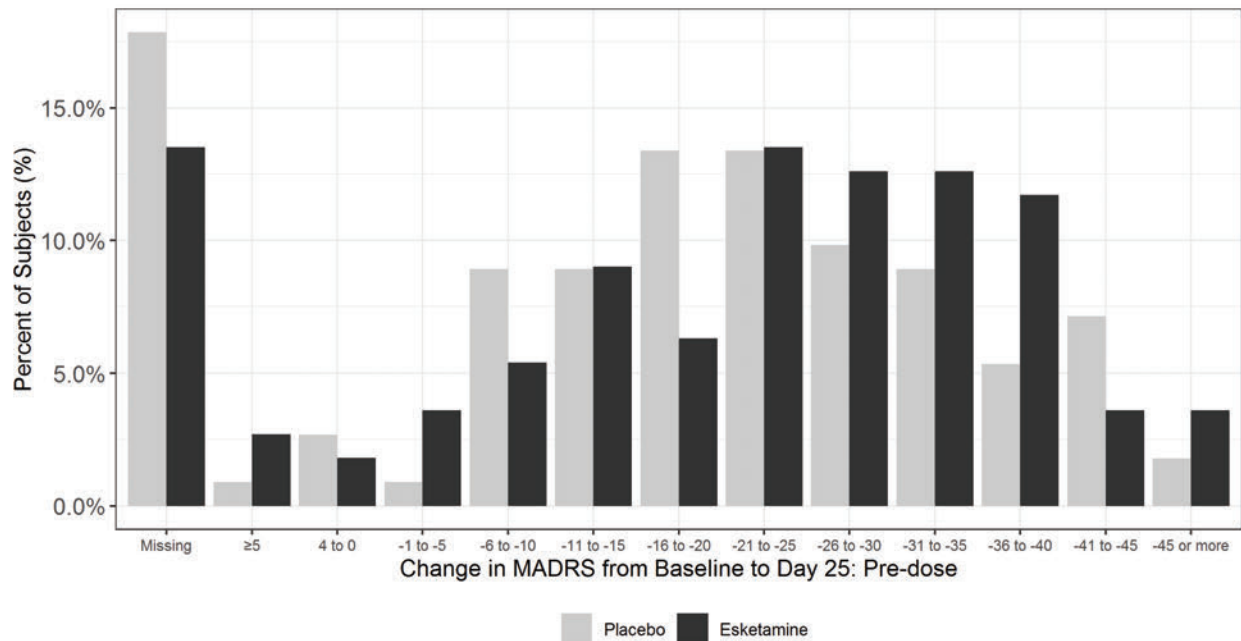
Figure 6. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 24 Hours (SUI3001: FAS)



Study SUI3001

Source: Statistical Reviewer.

Figure 7. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 25 Days Pre-dose (SUI3001: FAS)



Study SUI3001

Source: Statistical Reviewer.

Data Quality and Integrity

The data and datasets were of sufficient quality to permit review. Inspections conducted by the Office of Scientific Investigations did not uncover any data integrity concerns.

Efficacy Results – Secondary and other relevant endpoints

On the pre-specified ranked ANCOVA, the key secondary efficacy endpoint of change from baseline to 24 hours total CGI-SS-R did not show any change (Hodges-Lehmann median difference = 0 (95% CI = -1 to 0, rank ANCOVA p = 0.107), see Table 19. At this point, statistical testing hierarchy stopped because a p-value was greater than 0.05. The Applicant also reported results of a Bayesian Ordinal Item Response Theory model suggesting that the odds of improvement in the esketamine arm are 1.9 times the odds in the placebo arm (95% Credible Interval (CrI): 0.90 to 4.23).

Table 19. Clinical Global Impression - Severity of Suicidality - Revised for SUI3001 and SUI3002 (FAS)

Table 11: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF on Ranks for the Double-blind Treatment Phases in Studies SUI3001 and SUI3002 (Full Efficacy Analysis Sets)						
	Study SUI3001		Study SUI3002		Pooled Studies SUI3001 and SUI3002	
	Placebo + SOC (N=112)	Esk 84 mg + SOC (N=112)	Placebo + SOC (N=113)	Esk 84 mg + SOC (N=114)	Placebo + SOC (N=225)	Esk 84 mg + SOC (N=226)
Baseline						
N	112	111	113	114	225	225
Median	4.0	4.0	4.0	4.0	4.0	4.0
Range	1; 6	1; 6	1; 6	1; 6	1; 6	1; 6
24 Hours (Day 2) LOCF^b						
N	112	112	113	113	225	225
Median	2.5	2.0	3.0	2.0	3.0	2.0
Range	0; 5	0; 6	0; 6	0; 5	0; 6	0; 6
Change, baseline to 24 Hours (Day 2)						
N	112	111	113	113	225	224
Median	-1.0	-1.0	-1.0	-1.0	-1.0	-1.0
Range	-5; 1	-6; 2	-5; 2	-6; 2	-5; 2	-6; 2
Statistical analysis^a						
Hodges-Lehmann Estimate of Treatment Difference		0.0		0.0		0.0
95% CI		-1.00; 0.00		0.00; 0.00		0.00; 0.00
2-sided p-value		0.107		0.379		

Source: Applicant's Integrated Summary of Efficacy.

Statistical Reviewer's Comment: The Applicant's two pre-specified analyses yield different findings about a potential signal of improvement in CGI-SS-R. Two potential

causes of this inconsistency are related to the statistical methods (violations of assumptions underlying the statistical methods) and the ability of CGI-SS-R to measure a patient's suicidal severity and sensitivity to detect change. The Hodges-Lehmann estimator (HL-estimator) estimates a shift parameter describing the difference between two continuous distributions (Rosenkranz, 2010). The CGI-SS-R scores and the change from baseline in CGI-SS-R scores both are discrete distributions parameterized by the probabilities of being in a category. In this case, it is unclear whether the HL-estimator provides an interpretable or consistent estimate of differences between ESK arm and placebo. The rank ANCOVA relies on the distribution of the ranks of the CFB in CGI-SS-R. In Table 20, note that most of the ranks have a large number of ties (ranks with numbers greater than one). The large number of ties may affect the estimation of standard errors. Because of the public health costs of suicide and the Applicant's inclusion of results of a Bayesian ITR model in the label, the statistical reviewer conducted several additional analyses to explore the Applicant's analyses and the time course of CGI-SS-R over the entire 25-day double-blind period.

Table 20. Ranks^a of Change from Baseline to Day 2 in CGI-SS-R (FAS)

Rank	SUI 3001 at Day 2	
	Placebo	Esketamine
1	0	1
6.5	4	6
18.5	5	9
40.5	16	14
75	18	21
122.5	26	30
181.5	39	23
217.5	4	6
223	0	1
224	0	1

^a: Smaller ranks indicate a greater improvement.

Source: Statistical Reviewer.

To further investigate CGI-SS-R, the statistical reviewer conducted analyses on both the CGI-SS-R and MADRS item 10 (suicide item):

- Descriptive plots of the time evaluation of the sample proportions of patients in each CGI-SS-R and MADRS item 10 at each visit in the double-blind period
- Descriptive plots of the time evaluation of the sample proportions of patients in each CGI-SS-R and MADRS item 10 at each visit stratified by prior suicide status in the double-blind period

- Assessment of the assumptions underlying the Applicant's rank-based analysis
- Bayesian longitudinal ordinal regression model (BLOR) of CGI-SS-R and MADRS item 10, see details in Additional Analyses.

The MADRS item 10 assesses suicidal ideation, but not impulsivity, suicidal behavior or risk/protective factors as the CGI-SS-R does (see Table 6). The MADRS item 10 question stem describes a continuation from passive SI to active SI, and specifies that suicide attempts should not in themselves influence the rating; the anchors include:

- 0 – Enjoys life or takes it as it comes.
- 2 – Weary of life. Only fleeting suicidal thoughts.
- 4 – Probably better off dead. Suicidal thoughts are common, and suicide is considered a possible solution, but without specific plans and intentions.
- 6 – Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

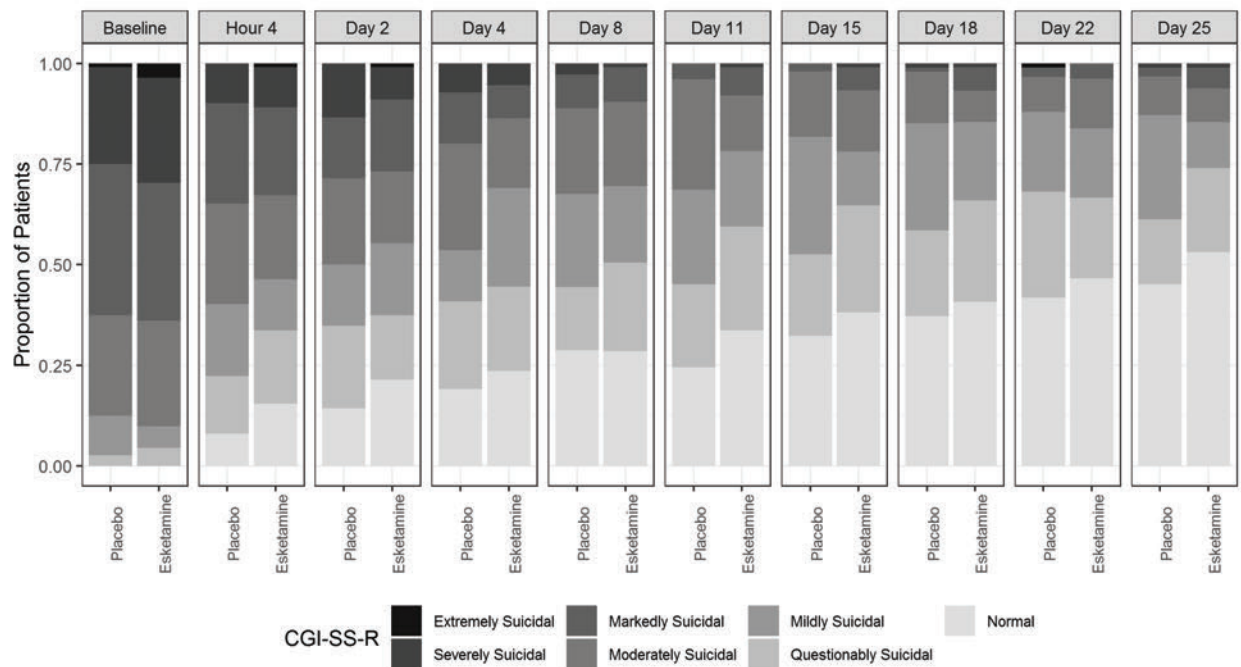
In Figure 8 and Figure 9, the proportion of patients with lower severity of suicidality (lighter grey bars) increases in both esketamine and placebo patients from baseline through Day 25. On the CGI-SS-R (Figure 8), the normal and mildly suicidal categories have slightly higher combined height in the esketamine arm compared to the placebo arm. This pattern is repeated in the MADRS item 10 (combined categories 0 and 1). The greater number of patients with lower scores in the esketamine group suggests that esketamine may be efficacious in improving measures of suicidal severity.

Results of a BLOR analysis conducted by the Statistical Reviewer suggest that patients in the esketamine arm have a lesser chance of being in a higher severity category compared to placebo at 24 hours (OR = 0.54, 95% CrI: 0.24 to 1.08) and at Day 25 (OR = 0.51, 95% CrI: 0.20 to 1.09), see Table 21. This model suggests similar results for the MADRS item 10 with an OR = 0.68 (95% CrI: 0.28 to 1.40) at 24 hours and an OR = 0.66 (95% CrI: 0.25 to 1.49) at Day 25. These analyses suggest that a potential efficacy signal for severity of suicidal ideation and behavior may exist. However, Study 3001 provides little statistical information about a potential signal. This analysis has similar results to the Applicant's ITR analysis for the probability of declining one category.

The results of multiple statistical models are inconclusive. The Applicant's ranked ANCOVA analysis did not detect any greater improvement in the esketamine arm compared to placebo

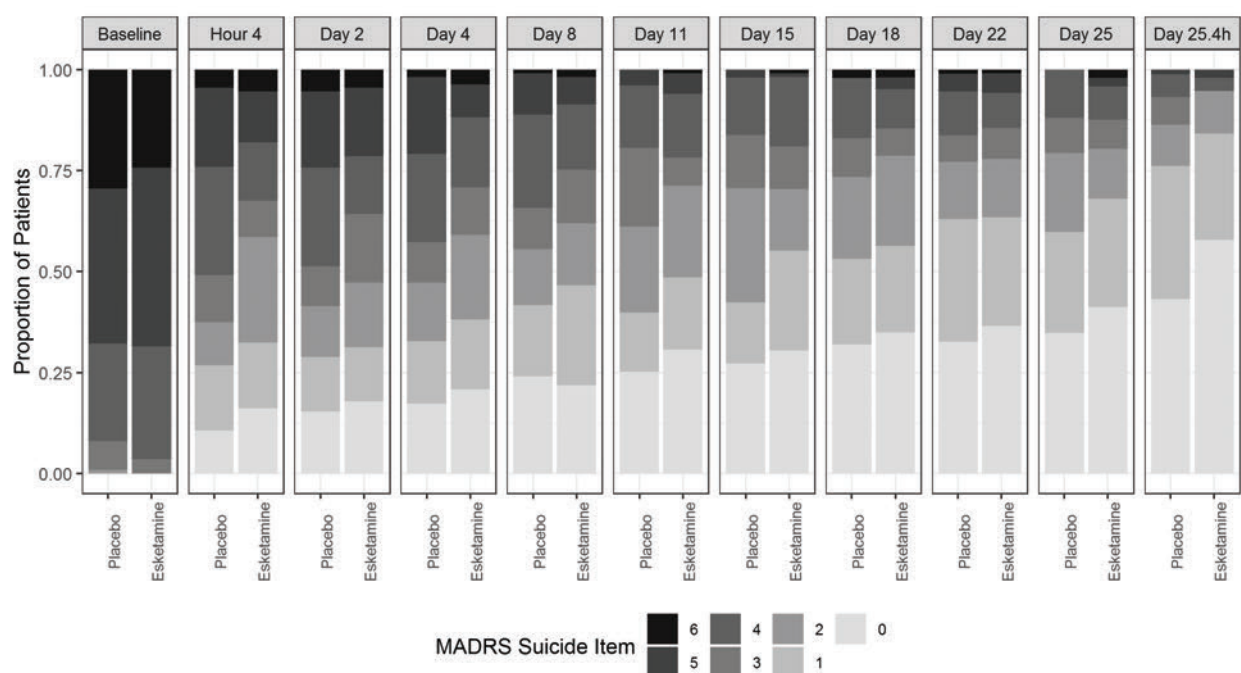
while the Applicant's Bayesian IRT model and the Statistical Reviewer's longitudinal regression model detected a signal of greater improvement in the esketamine arm with high uncertainty. Study 3001 does not provide sufficient evidence for any effects of esketamine on improving severity of suicidality.

Figure 8. Proportion of Patients in CGI-SS-R Category (SUI3001: FAS)



Source: Statistical Reviewer.

Figure 9. Proportion of Patients in MADRS Item 10 Category (SUI3001: FAS)



Source: Statistical Reviewer.

Table 21. Odds Ratio for CGI-SS-R and MADRS Item 10 from a Bayesian Ordinal Longitudinal Model

	Visit	$OR = \frac{Esk_j/Esk_i}{Plb_j/Plb_i}$	95% CI	
CGI-SS-R	Day 2	0.54	0.24	1.08
	Day 25	0.51	0.20	1.09
MADRS Item 10	Day 2	0.68	0.28	1.40
	Day 25	0.66	0.25	1.49

Source: Statistical Reviewer.

See preceding discussion of primary efficacy results regarding the other secondary endpoints of change in the MADRS total score over time (i.e., at 4 hours and through Day 25) and the exploratory endpoints of change in the MADRS total score through Day 90, and change in MADRS individual item scores through Day 25 and Day 90 (i.e., specifically regarding Item 10, suicidal ideation).

Other than the secondary endpoint of CGI-SS-R at Day 2, none of the other secondary (or exploratory) endpoints were controlled for multiplicity, or inform labeling; therefore they are discussed briefly or not reviewed here. Table 22 lists some of the other secondary and

exploratory endpoints. The percentages of subjects with remission of MDD (defined as MADRS total score ≤ 12) or response (defined as $\geq 50\%$ reduction in MADRS total score) were numerically greater in the esketamine group at the timepoints noted except for Day 90; however, at three of the five noted timepoints in each category the CI included zero. The changes from baseline in the BHS and QLDS numerically favored esketamine at Day 25 (although the CI included zero for the BHS and almost did for the QLDS).

Table 22. Trial SUI3001 Other Secondary or Exploratory Endpoints

Endpoint Timepoint	Placebo + SOC	Esketamine + SOC	Difference (95% CI)
Percentage of subjects with remission of MDD (MADRS total score ≤ 12)			
Day 1 (4 hours) ¹	9 (8.0%)	12 (10.7%)	2.7 (-4.96; 10.30)
Day 2 (24 hours) ¹	10 (8.9%)	21 (18.8%)	9.8 (3.42; 23.37)
Day 25 (predose) ¹	38 (33.9%)	46 (41.1%)	7.1 (-5.50; 19.79)
Day 25 (4 hours) ¹	42 (37.5%)	60 (53.6%)	16.1 (3.20; 28.94)
Day 90 ²	45 (49.5%)	47 (46.5%)	-2.9 (-17.06; 11.23)
Percentage of subjects with response ($\geq 50\%$ reduction in MADRS total score) ²			
Day 1 (4 hours)	25 (22.3%)	29 (25.9%)	3.6 (-7.62; 14.76)
Day 2 (24 hours)	30 (26.8%)	38 (33.9%)	7.1 (-4.86; 19.15)
Day 25 (predose)	51 (45.5%)	68 (60.7%)	15.2 (2.26; 28.10)
Day 25 (4 hours)	62 (55.4%)	78 (69.6%)	14.3 (1.74; 26.83)
Day 90	56 (61.5%)	54 (53.5%)	-8.1 (-22.02; 5.87)
Change from baseline in BHS total score (LS mean) ¹			
Day 25 (predose)	-6.0	-7.1	-1.1 (-2.75; 0.61)
Change from baseline in QLDS score (LS mean) ¹			
Day 25 (predose)	-5.3	-6.8	-1.5 (-2.95; -0.03)

Source: Adapted from Trial SUI3001 clinical study report

Note: Endpoints through Day 25 derived from full efficacy analysis set; endpoints at Day 90 derived from follow-up analysis set

Abbreviations: BHS = Beck Hopelessness Scale, CI = confidence interval, LS = least-squares, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, QLDS = Quality of Life in Depression Scale, SOC = standard of care

¹ Other secondary endpoint

² Exploratory endpoint

Clinical Reviewer's Comment: The percentage of subjects with remission of MDD at 24 hours is supportive, although the threshold of MADRS total score ≤ 12 is on the higher end of the literature (Zimmerman et al. 2004a; Zimmerman et al. 2004b), and the CI for percentage of responders included zero. It is unclear what the Applicant meant to

achieve by measurement of the MADRS on Day 25 predose and at 4 hours post-dose; the results are mixed. For example, the percentage of remitters is numerically greater for esketamine at both timepoints, but more so post-dose (where the CI does not include zero). However, the percentage of responders is fairly similarly greater for esketamine at both timepoints (and neither CI includes zero).

Dose/Dose Response

Subjects received 84 mg of esketamine, but were permitted a one-time reduction to 56 mg for the remainder of treatment for tolerability issues. Dose-response was not assessed.

Clinical Reviewer's Comment: *Given that the majority of esketamine subjects (81.4%) did not require a dose reduction (as previously discussed) and that dose reductions occurred at various timepoints, a dose-response analysis does not appear useful.*

Durability of Response

See preceding discussion under primary efficacy results.

Clinical Reviewer's Comment: *Although multiple timepoints in the 25-day double-blind treatment period included 95% confidence intervals that included zero (Table 18), treatment with esketamine was numerically favored over placebo at all timepoints on the primary efficacy endpoint, which is supportive of a durable response.*

Persistence of Effect

See preceding discussion under primary efficacy results.

Clinical and Statistical Reviewer's Comment: *The change from baseline in MADRS total score to Day 90 was an exploratory endpoint. Statistical information declined after Day 28 because of dropouts, and there was no longer a difference from placebo by Day 53 (Figure 5). The continued observation of large improvements from baseline in MADRS total score after completing esketamine treatment on Day 25 could be considered supportive of the Applicant's intended use (i.e., demonstrating an early benefit while awaiting onset of oral antidepressant benefit). However, it is unclear if these observations are driven by the standard of care or esketamine. Without clear pre-specification of a clinical question and estimand for the follow-up data, these findings admit multiple interpretations.*

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See above.

Additional Analyses Conducted on the Individual Trial

The Statistical Reviewer conducted a MMRM analysis on the MADRS total score data for Days 1 to 90. This model included the same covariates as the Applicant's MMRM analysis for the double-blind period (Days 1 to 25). Both an unstructured (UN) covariance matrix and an autogressive order 1 (AR(1)) covariance matrix were used. The AR(1) structure was used because the UN structure failed to converge.

The Bayesian longitudinal ordinal regression model extends equation (1) to longitudinal data with the addition of random effects and a time factor, see equation (2). In both models, an important assumption is the Proportional Odds (PO) Assumption – covariates have same effect (odds ratio) in each category. PO assumptions is explored graphically using plots of the expected covariate means in each outcome category. In Figure 10 and Figure 11, dashed lines indicate expected means if PO holds and the dots are the observed mean. Large deviations between the dots and dashed line indicate PO may not hold.

$$\Pr [Y \geq j | X] = \frac{1}{1 + \exp [-\alpha_j + X\beta]} \#(1)$$

where: J = 7 categories, α_j are the category intercepts, β coefficients, and X is the covariates

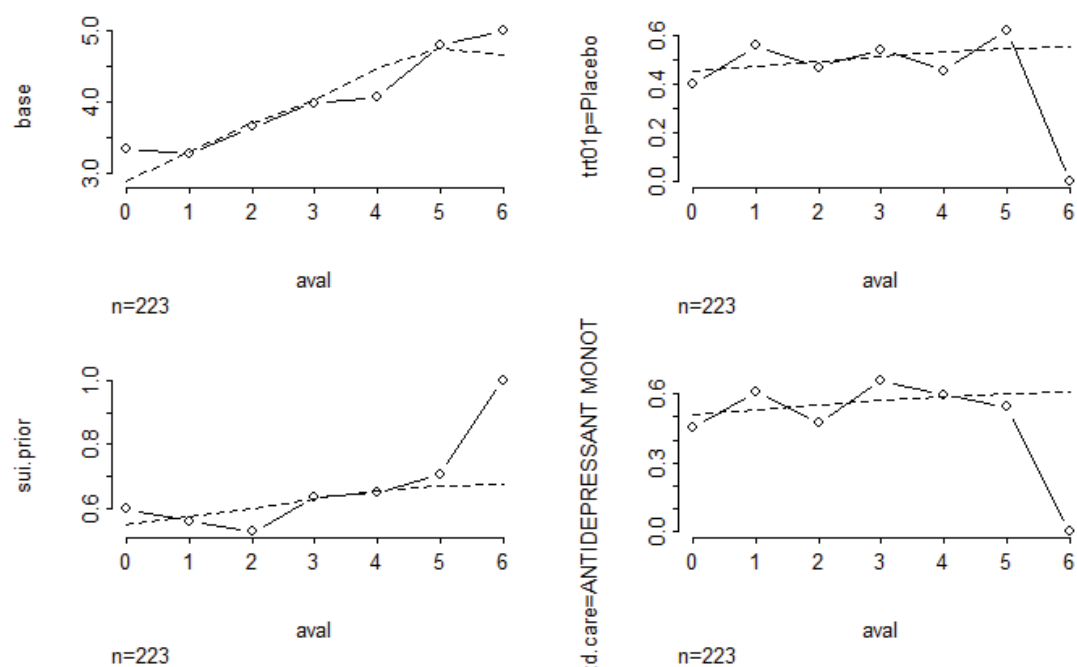
$$\Pr [Y_{it} \geq j | X] = \frac{1}{1 + \exp [-\alpha_j + X\beta + Zb_i]} \#(2)$$

where: b_i is a random effect (intercept only), t indexes the longitudinal observations, time enters model as factor and time by treatment interaction, and the priors are:

- Category intercepts have $t_v = 3, \mu = 0, \sigma = 10$ prior
- Other parameters have non-informative prior

Proportional odds assumption was assessed using graphical descriptions at Days 2 and 25, see Figure 10 and Figure 11. At Day 2, the observed and expected means are reasonably close except for CGI-SS-R = 6 which has only has a few patients in the esketamine arm. However, by Day 25, the observed means have deviated from the expected means implying that the PO assumption may no longer hold. Further research into the impacts of potential time dependence in the PO assumption and its impact on model fit is needed.

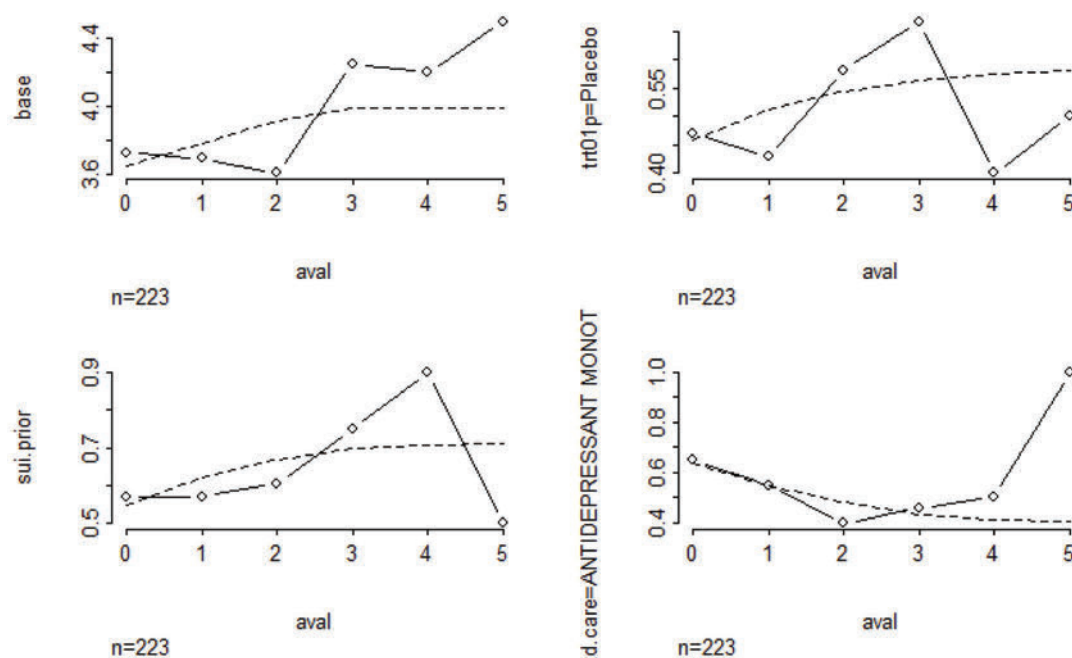
Figure 10. Proportional Odds Plot at Day 2 (SUI3001: FAS)¹



Source: Statistical Reviewer.

¹ In Figure 10 and Figure 11, aval is CGI-SS-R with categories 0-6, base in baseline CGI-SS-R, sui.prior is an factor for prior suicide history (0 – no history, 1 – history), trt01p is the treatment factor, and std.care is the standard of care (antidepressant vs plus antidepressant).

Figure 11. Proportional Odds Plot at Day 25 (SUI3001: FAS)



Source: Statistical Reviewer.

7.2. Trial SUI3002 (ASPIRE II)

7.2.1. Study Design

Trial SUI3002 was nearly identical to Trial SUI3001; see Section 7.1.1 Study Design for a description. Differences included:

- Trial locations, which for Trial SUI3002 included a total of 47 sites in 12 countries: 13 sites in the United States; 5 sites each in Brazil and France; 4 sites each in Argentina, Poland, and Turkey; 3 sites in Spain; 2 sites each in Austria, Belgium, the Czech Republic, and Lithuania; and one site in Canada.
- Basic study design inpatient hospitalization requirement: in some countries, the recommended duration of admission was 14 days to be consistent with local practice (rather than 5 days).
- Exclusion criterion: in some countries, subjects were excluded if they met the criteria for moderate or severe substance or alcohol use disorder within the 12 months before screening (rather than 6 months).

Clinical Reviewer's Comment: Differences between Trial SUI3001 and Trial SUI3002 are unlikely to have a significant impact on findings. As previously noted, the Division agreed in pre-NDA communication with a proposal for 20 to 25% of the study population to be U.S.-based, given similar results across subgroups.

The Statistical Analysis Plan for SUI3002 does not differ from the SUI3001 SAP in any manner that changes the statistical analyses conducted. The Statistical Analysis Plan for SUI3002 does not differ from the SUI3001 SAP in any important manner.

Protocol Amendments

There were two amendments to the original protocol: Amendment 1 (April 20, 2017) included the revisions from Amendments 1 and 2 from Trial SUI3001, and Amendment 2 (January 31, 2018) included the revisions from Amendment 3 from Trial SUI3001 (see 7.1.1 for descriptions).

Clinical Reviewer's Comment: Similarly to Trial SUI3001, the first subject in this study signed informed consent on June 22, 2017, and the last observation for the last subject recorded as part of the database was April 11, 2019. Therefore, Amendment 2 could theoretically impact study results, but the specific revisions appear unlikely to do so. Safety assessment could consider the impact of any subjects taking concomitant prescribed psychostimulants with subgroup analysis; although upon prior and concomitant medication dataset review, it appears one subject in each group was taking methylphenidate, and one subject in each group was taking lisdexamfetamine, so the numbers are unlikely to have an impact.

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study-related information were reviewed by an independent ethics committee or institutional review board before the start of the study. The Applicant attests that the study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

See Appendix 17.2 for details.

Patient Disposition

See Table 23 for trial analysis sets and see Table 24 for subject disposition, including reasons for discontinuation during the double-blind treatment phase (through Day 25). See Figure 12 for the Applicant's diagram of subject flow that includes reasons for discontinuation during follow-

up (through Day 90). Esketamine and placebo will refer to esketamine plus SOC, or placebo plus SOC:

- Of 273 subjects screened, 43 subjects were screen failures.
- Of the 230 subjects randomized, one subject in the esketamine group was not included in the safety analysis set, after withdrawing consent during the double-blind treatment phase before receiving the first dose of study drug.
- Two subjects randomized to the placebo group were not included in the safety analysis set; one was withdrawn due to a major protocol violation (positive urine test for cocaine), and the other withdrawn for “other” reason (subject wanted to stop the study but did not withdraw consent).
- In terms of treatment completion (i.e., through Day 25 double-blind treatment), more subjects completed treatment in the placebo group (81.7%) than the esketamine group (78.3%).
- For the follow-up analysis set (i.e., subjects who entered the follow-up phase or provided AE data post-treatment-phase), slightly more subjects were included in the placebo group (81.7%) than the esketamine group (77.4%).
- In terms of follow-up completion (i.e., through Day 90), slightly more subjects completed follow-up in the placebo group (73.9%) than the esketamine group (70.4%).

Table 23. Trial SUI3002 Analysis Sets

	Placebo + SOC	Esk 84 mg + SOC	Total
All randomized	115	115	230
Safety analysis set	113 (98.3%)	114 (99.1%)	227 (98.7%)
Full efficacy analysis set	113 (98.3%)	114 (99.1%)	227 (98.7%)
Follow-up analysis set	94 (81.7%)	89 (77.4%)	183 (79.6%)

[TSIDEM02.RTF] [JNJ-54135419/SUI3002/DBR_FINAL/RE_CSR/PROD/TSIDEM02.SAS] 09MAY2019, 11:58

Source: Trial SUI3002 clinical study report Table 5, p. 69

Abbreviations: Esk = esketamine, SOC = standard of care

Table 24. Trial SUI3002 Subject Disposition

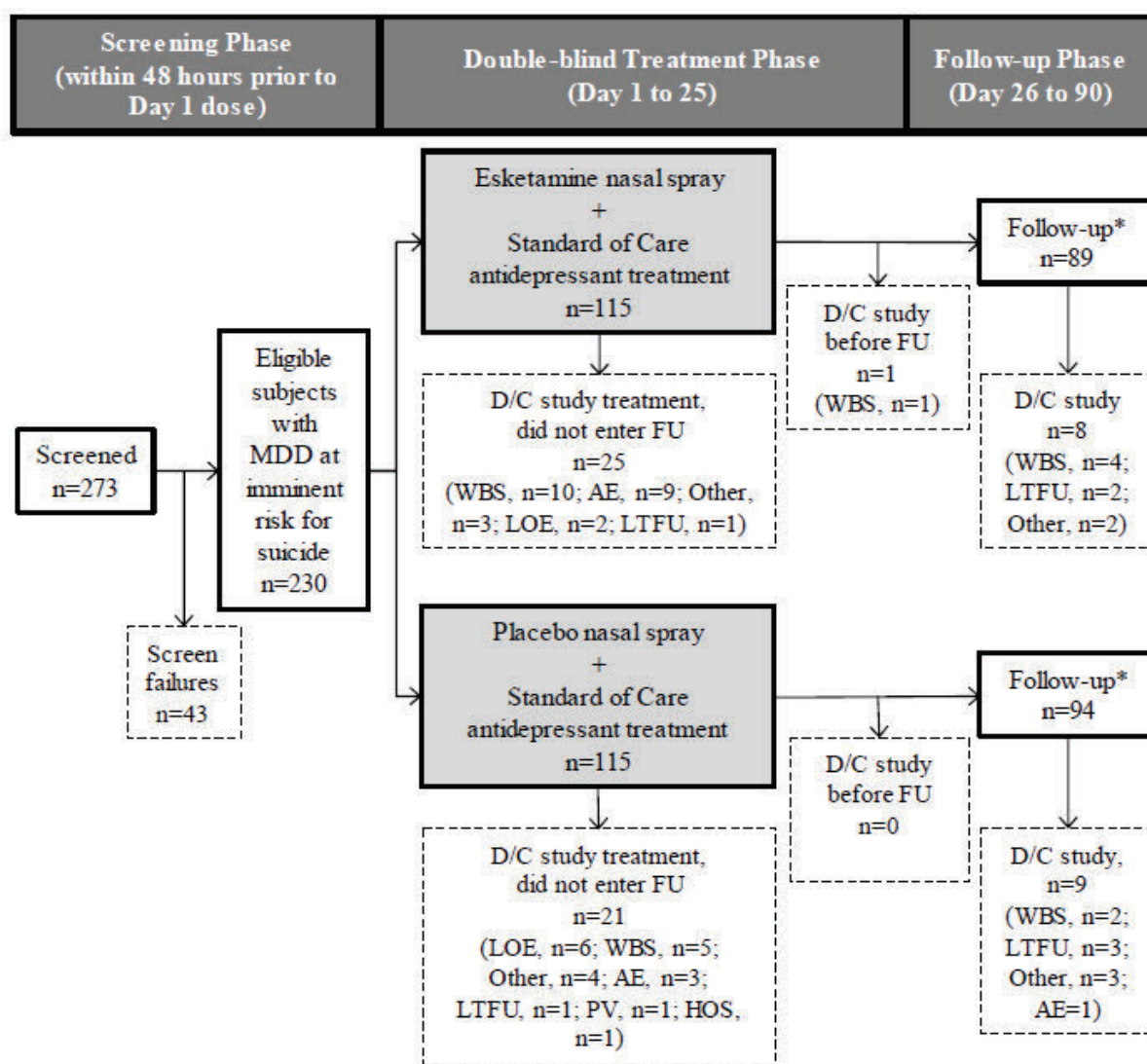
Analysis set: All Randomized	Placebo + SOC 115	Esk 84 mg + SOC 115	Total 230
Completed study treatment	94 (81.7%)	90 (78.3%)	184 (80.0%)
Discontinued study treatment	21 (18.3%)	25 (21.7%)	46 (20.0%)
Reason for discontinuation			
Withdrawal by subject	5 (4.3%)	10 (8.7%)	15 (6.5%)
Adverse event	3 (2.6%)	9 (7.8%)	12 (5.2%)
Lack of efficacy	6 (5.2%)	2 (1.7%)	8 (3.5%)
Other	4 (3.5%)	3 (2.6%)	7 (3.0%)
Lost to follow-up	1 (0.9%)	1 (0.9%)	2 (0.9%)
Change from voluntary to involuntary			
hospitalization	1 (0.9%)	0	1 (0.4%)
Protocol violation	1 (0.9%)	0	1 (0.4%)

Note: 2 subjects in placebo + SOC and 1 subject in esketamine 84 mg + SOC who were randomized but did not receive any study medication is included in this summary.

[TSIDS01A.RTF] [JNJ-54135419\SUI3002\DBR_FINAL\RE_CSR\PROD\TSIDS01A.SAS] 09MAY2019, 11:59

Source: Trial SUI3002 clinical study report Table 6, p. 69

Abbreviations: Esk = esketamine, SOC = standard of care

Figure 12. Trial SUI3002 Subject Flow Diagram

* Subjects entered the follow-up phase or provided adverse event data after the double-blind treatment phase.

AE = adverse event; D/C = discontinued; FU = follow-up phase; HOS = change from voluntary to involuntary hospitalization; LOE = lack of efficacy; LTFU = Lost to follow-up; MDD = major depressive disorder; PV = protocol violation; WBS = withdrawal by subject.

Source: Trial SUI3002 clinical study report Figure 2 (including footnotes), p. 71

Clinical Reviewer's Comment: Nearly equal numbers of subjects between treatment groups completed the first treatment and Day 2 assessment for the full efficacy analysis set, and a similar percentage between groups completed Day 90 assessments. Of note, a greater number of subjects withdrew for AEs during the double-blind phase in the esketamine group than placebo (7.8% versus 2.6%), and more subjects in the placebo group withdrew for lack of efficacy (5.2% versus 1.7%). Esketamine appears to have been

less tolerated. It is possible that if subjects were unintentionally unblinded given the lack of an active placebo, they may have been more inclined to drop out of the study.

Protocol Violations/Deviations

See Table 25 for major protocol deviations for Trial SUI3002, reported in 14.8% of subjects across both treatment arms. Overall, more major protocol deviations occurred in the placebo treatment group than esketamine (19.1% versus 10.4% per pre-database lock; 19.1% versus 11.3% per post-database lock, see below), mostly in the “other” category. One subject in the placebo group was withdrawn for a protocol violation (see Table 24), for a positive urine test for cocaine.

Table 25. Trial SUI3002 Major Protocol Deviations

Analysis set: All Randomized	Placebo + SOC 115	Esk 84 mg + SOC 115	Total 230
Subjects with major protocol deviations	22 (19.1%)	12 (10.4%)	34 (14.8%)
Entered but did not satisfy criteria	4 (3.5%)	4 (3.5%)	8 (3.5%)
Received wrong treatment or incorrect dose	3 (2.6%)	1 (0.9%)	4 (1.7%)
Developed withdrawal criteria but not withdrawn	1 (0.9%)	0	1 (0.4%)
Other	15 (13.0%)	8 (7.0%)	23 (10.0%)

Note: Subjects may appear in more than one category.

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Source: Trial SUI3002 clinical study report Table 9, p. 79

Abbreviations: Esk = esketamine, SOC = standard of care

Regarding subjects who entered but did not satisfy criteria:

- Three subjects in the esketamine group and one subject in the placebo group had a screening period longer than 24 hours but assessment of MINI Question B3 and B10 Current Status was not repeated.
- Two subjects in the placebo group had abnormal BP measurements.
- One subject in the esketamine group committed to the use of condoms and spermicides, which was not considered a highly effective method of contraception.
- One subject in the placebo group had a positive urine test for cocaine (and was withdrawn, as noted above).

Regarding subjects who developed withdrawal criteria but were not withdrawn, one subject in the placebo group should have been withdrawn for BP measurements, but continued to receive study agent.

Regarding subjects who received the wrong treatment or incorrect dose:

- Two subjects in the placebo group received one nasal spray device of esketamine 28 mg instead of placebo (one on Day 1, and one on Day 15).
- Two subjects in the esketamine group received an incorrect dose on Day 1; for one, two of three nasal sprays were noted as partially administered. For the other, one of three nasal sprays were noted as partially administered; this issue was identified after the database lock, and was not included in Table 25 but was documented in the ERRATA.
- One subject in the placebo group did not administer the full dose of the study drug.

Regarding “other” major protocol deviations, there were 23 subjects with 23 deviations. Of note:

- The stratification factor for SOC (AD monotherapy versus AD plus augmentation therapy) was entered incorrectly for 11 subjects from seven study centers (five in the esketamine group and six in the placebo group). Data review noted the majority of errors were by site staff entry mistake, and one from miscommunication.
- The rater separation plan was not followed for six subjects (two in esketamine and four in placebo); efficacy raters reviewed medical charts containing safety assessments or provided clinical care.
- Three subjects were missing Day 2 MADRS and SIBAT assessments (two in placebo and one in esketamine).
- Two subjects in the placebo group did not have a safety assessment performed as scheduled (ECG for one and laboratory for the other).

Clinical Reviewer’s Comment: The incidence of protocol deviations across all treatment arms (range 11.3 to 19.1%) does not appear excessive for a trial of this nature and does not raise significant concerns about study conduct. Although some deviations may impact efficacy findings for individual subjects, most appear unlikely to significantly affect the study conclusions because they occurred at a relatively low rate compared to the overall study population and were relatively balanced between groups. The Applicant did not clarify what actions were taken, if any, to manage the deviations, other than one placebo subject being withdrawn.

Table of Demographic Characteristics

See Table 26 for a summary of full efficacy set demographic and baseline characteristics for Trial SUI3002. Overall, subjects were 59.9% female and 40.1% male. Overall, the mean, median,

and range of ages were similar between groups, including each age bracket. Approximately 80% of subjects were White, and 5 to 6% each were African American, Not Reported, or Other. Approximately 30% of subjects were enrolled in the United States; 10 to 16% each were enrolled in Brazil, Poland, France, and Turkey; and <10% were enrolled in each of the remaining countries. Subjects were generally enrolled equally across groups in each country. Weight and body mass index (BMI) were comparable across groups, with an overall mean BMI of 27.9 ± 6.99 (SD) kg/m^2 .

As randomized AD SOC and as received AD SOC, more subjects overall were assigned to AD plus augmentation therapy than AD monotherapy, and were roughly similar between groups. With as received AD SOC, a number of subjects received both AD monotherapy and AD plus augmentation therapy (8.0% in the placebo group, and 3.5% in the esketamine group).

Table 26. Trial SUI3002 Full Efficacy Analysis Set Demographic and Baseline Characteristics

Demographic Parameters	Placebo + SOC (N=113)^{a,b} n (%)	Esk + SOC (N=114)^c n (%)	Total (N=227)^{d,e} n (%)
Sex			
Female	67 (59.3%)	69 (60.5%)	136 (59.9%)
Male	46 (40.7%)	45 (39.5%)	91 (40.1%)
Age (years)			
Mean (SD)	41.4 (13.43)	40.2 (12.73)	40.8 (13.07)
Median	44.0	41.0	42.0
Min, max	18, 64	18, 61	18, 64
18 to 34	40 (35.4%)	37 (32.5%)	77 (33.9%)
35 to 54	51 (45.1%)	59 (51.8%)	110 (48.5%)
55 to 64	22 (19.5%)	18 (15.8%)	40 (17.6%)
Race			
White	87 (77.0%)	92 (80.7%)	179 (78.9%)
Black or African American	8 (7.1%)	7 (6.1%)	15 (6.6%)
Not reported	8 (7.1%)	6 (5.3%)	14 (6.2%)
Other	6 (5.3%)	6 (5.3%)	12 (5.3%)
Asian	2 (1.8%)	1 (0.9%)	3 (1.3%)
Multiple	0	2 (1.8%)	2 (0.9%)
American Indian or Alaska Native	1 (0.9%)	0	1 (0.4%)
Native Hawaiian or Other Pacific Islander	1 (0.9%)	0	1 (0.4%)
Ethnicity			
Not Hispanic or Latino	76 (71.7%) ^a	79 (73.1%) ^c	155 (72.4%) ^d
Hispanic or Latino	29 (27.4%) ^a	28 (25.9%) ^c	57 (26.6%) ^d
Unknown	1 (0.9%) ^a	1 (0.9%) ^c	2 (0.9%) ^d

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Country			
United States	36 (31.9%)	30 (26.3%)	66 (29.1%)
Brazil	18 (15.9%)	18 (15.8%)	36 (15.9%)
Poland	15 (13.3%)	18 (15.8%)	33 (14.5%)
France	9 (8.0%)	15 (13.2%)	24 (10.6%)
Turkey	10 (8.8%)	13 (11.4%)	23 (10.1%)
Argentina	9 (8.0%)	7 (6.1%)	16 (7.0%)
Spain	5 (4.4%)	5 (4.4%)	10 (4.4%)
Austria	5 (4.4%)	4 (3.5%)	9 (4.0%)
Belgium	2 (1.8%)	1 (0.9%)	3 (1.3%)
Czech Republic	2 (1.8%)	1 (0.9%)	3 (1.3%)
Lithuania	1 (0.9%)	2 (1.8%)	3 (1.3%)
Canada	1 (0.9%)	0	1 (0.4%)
Weight (kg)			
Mean (SD)	80.6 (22.05) ^b	78.6 (19.62)	79.6 (20.83) ^e
Median	78.0 ^b	75.3	77.0 ^e
Range	45, 144	48, 133	45, 144
Body Mass Index (kg/m ²)			
Mean (SD)	28.3 (7.56) ^b	27.6 (6.40)	27.9 (6.99) ^e
Median	26.6 ^b	26.9	26.8 ^e
Range	18, 50	17, 49	17, 50
Underweight (<18.5)	2 (1.8%) ^b	6 (5.3%)	8 (3.6%) ^e
Normal (18.5 to <25)	42 (37.8%) ^b	36 (31.6%)	78 (34.7%) ^e
Overweight (25 to <30)	28 (25.2%) ^b	36 (31.6%)	64 (28.4%) ^e
Obese (30 to <40)	29 (26.1%) ^b	32 (28.1%)	61 (27.1%) ^e
Severe Obesity (≥40)	10 (9.0%) ^b	4 (3.5%)	14 (6.2%) ^e
SOC AD Treatment as Randomized			
AD Monotherapy	43 (38.1%)	45 (39.5%)	88 (38.8%)
AD Plus Augmentation Therapy	70 (61.9%)	69 (60.5%)	139 (61.2%)
SOC AD Treatment as Received			
AD Monotherapy	36 (31.9%)	43 (37.7%)	79 (34.8%)
AD Plus Augmentation Therapy	68 (60.2%)	67 (58.8%)	135 (59.5%)
AD Monotherapy / AD Plus Augmentation Therapy ^f	9 (8.0%)	4 (3.5%)	13 (5.7%)

Source: Adapted from Trial SUI3002 clinical study report Table 7, p. 73, and ADVS dataset

Abbreviations: AD = antidepressant; Esk = esketamine, SD = standard deviation, SOC = standard of care

^a Placebo N=106 for these parameters

^b Placebo N=111 for these parameters

^c Esketamine N=108 for these parameters

^d Total N=214 for these parameters

^e Total N=225 for these parameters

^f Subjects received both AD monotherapy and AD plus augmentation therapy

Clinical Reviewer's Comment: Overall, sex and age parameters were generally representative of U.S. patient populations, and relatively similar between treatment groups. Race and ethnicity parameters were not representative of the U.S. population,

with Hispanic or Latinos somewhat overrepresented (26.6% in the study versus 18.3% in the U.S. population, per the U.S. Census Bureau). This was likely a result of enrollment in Argentina and Brazil (accounting for 22.9% of enrolled subjects overall); the Division did agree (see Section 3.1) to the 29.1% U.S. enrollment achieved by the Applicant. African Americans and Asian populations were underrepresented (6.6% in the study versus 13.4% in the U.S. population, and 1.3% in the study versus 5.9% in the U.S. population, per the U.S. Census Bureau, respectively). A sizable number reported as “other” or did not report (11.5% total).

The Applicant presented SOC AD treatment as randomized, and as received. It is unclear if this is a function of the incorrect stratification as described above in protocol violations, or if investigators changed treatment plans during the study. It would appear the latter was true for the subjects noted to have received both AD monotherapy and AD plus augmentation therapy. This may muddy the subgroup analysis, though the numbers of subjects who received both were small overall (5.7%); however this was larger in the placebo group (8.0 versus 3.5%).

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

See Table 27 for baseline psychiatric history characteristics. Overall, these were similar between treatment groups. Of note, the mean MADRS total score was 39.7 ± 5.48 SD, indicating a severely depressed population (range 29 to 54). The mean duration of the current depressive episode was 47.7 ± 75.30 SD months, with a median of 17.1 and a wide range of 2 to 445 months. The mean number of hospitalizations for depression or suicidality in the past 12 months was 0.5 ± 1.13 SD, with a range of 0 to 12; most subjects (69.2%) had none in the past 12 months, with one hospitalization for 21.1%. Based on the MINI, the largest group (55.1%) had a history of two to five lifetime depressive episodes, and 65.6% had a suicide attempt history. Based on the SIBAT, 26.4% had a suicide attempt in the past month; the ratio was somewhat different between groups, with 31.6% who had in the esketamine group versus 21.2% in the placebo group. MADRS, CGI, MINI, and SIBAT suicidal parameters were generally similar between groups. Based on the CGI-SS-R, the largest group (35.2%) was markedly suicidal, with 27.8% and 21.6% moderately or severely suicidal, respectively.

Table 27. Trial SUI3002 Full Efficacy Analysis Set Baseline Psychiatric History Characteristics

Analysis set: Full Efficacy	Placebo + SOC 113	Esk 84 mg + SOC 114	Total 227
MADRS Total Score			
N	113	114	227
Mean (SD)	39.9 (5.76)	39.5 (5.19)	39.7 (5.48)
Median	40.0	39.0	39.0
Range	(29; 54)	(29; 54)	(29; 54)
MADRS Item 10 - Suicidal Thoughts			
N	113	114	227
0	0	0	0
1	0	0	0
2	1 (0.9%)	1 (0.9%)	2 (0.9%)
3	6 (5.3%)	12 (10.5%)	18 (7.9%)
4	25 (22.1%)	30 (26.3%)	55 (24.2%)
5	56 (49.6%)	53 (46.5%)	109 (48.0%)
6	25 (22.1%)	18 (15.8%)	43 (18.9%)
Duration of Current Depressive Episode, months			
N	106	100	206
Mean (SD)	49.9 (79.36)	45.4 (71.07)	47.7 (75.30)
Median	21.2	16.5	17.1
Range	(2; 445)	(2; 341)	(2; 445)
BHS Total Score			
N	112	112	224
Mean (SD)	15.6 (3.95)	15.5 (4.22)	15.5 (4.08)
Median	16.0	16.5	16.0
Range	(0; 20)	(1; 20)	(0; 20)
CGI-SS-R			
N	113	114	227
Normal, not at all suicidal	0	0	0
Questionably suicidal	3 (2.7%)	1 (0.9%)	4 (1.8%)
Mildly suicidal	6 (5.3%)	10 (8.8%)	16 (7.0%)
Moderately suicidal	33 (29.2%)	35 (30.7%)	68 (30.0%)
Markedly suicidal	42 (37.2%)	48 (42.1%)	90 (39.6%)
Severely suicidal	28 (24.8%)	17 (14.9%)	45 (19.8%)
Among the most extremely suicidal patients	1 (0.9%)	3 (2.6%)	4 (1.8%)
CGI-SR-I			
N	113	114	227
No imminent suicide risk	0	3 (2.6%)	3 (1.3%)
Minimal imminent suicide risk	4 (3.5%)	4 (3.5%)	8 (3.5%)
Mild imminent suicide risk	10 (8.8%)	8 (7.0%)	18 (7.9%)
Moderate imminent suicide risk	33 (29.2%)	30 (26.3%)	63 (27.8%)
Marked imminent suicide risk	43 (38.1%)	37 (32.5%)	80 (35.2%)
Severely imminent suicide risk	21 (18.6%)	28 (24.6%)	49 (21.6%)
Extreme imminent suicide risk	2 (1.8%)	4 (3.5%)	6 (2.6%)
MINI Current Status: Think about suicide			
N	113	114	227
Yes	113 (100.0%)	114 (100.0%)	227 (100.0%)
No	0	0	0

(continued next page)

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MINI Current Status: Think about suicide - Frequency

N	113	114	227
Occasionally	13 (11.5%)	13 (11.4%)	26 (11.5%)
Often	53 (46.9%)	58 (50.9%)	111 (48.9%)
Very Often	47 (41.6%)	43 (37.7%)	90 (39.6%)

	Placebo + SOC	Esk 84 mg + SOC	Total
MINI Current Status: Think about suicide - Intensity			
N	113	114	227
Mild	5 (4.4%)	4 (3.5%)	9 (4.0%)
Moderate	56 (49.6%)	52 (45.6%)	108 (47.6%)
Severe	52 (46.0%)	58 (50.9%)	110 (48.5%)

MINI Current Status: Intend to act on thoughts of killing yourself

N	113	114	227
Yes	113 (100.0%)	114 (100.0%)	227 (100.0%)
No	0	0	0

MINI: Lifetime Suicide Attempt

N	113	114	227
Yes	74 (65.5%)	75 (65.8%)	149 (65.6%)
No	39 (34.5%)	39 (34.2%)	78 (34.4%)

MINI: Number of Episodes of Depression in Life Time

N	113	114	227
1	26 (23.0%)	32 (28.1%)	58 (25.6%)
2-5	67 (59.3%)	58 (50.9%)	125 (55.1%)
6-10	10 (8.8%)	18 (15.8%)	28 (12.3%)
>10	10 (8.8%)	6 (5.3%)	16 (7.0%)

Number of Hospitalization due to Depression or Suicidality in the Past 12 Months

N	113	114	227
Mean (SD)	0.4 (0.85)	0.6 (1.34)	0.5 (1.13)
Median	0.0	0.0	0.0
Range	(0; 5)	(0; 12)	(0; 12)
0	82 (72.6%)	75 (65.8%)	157 (69.2%)
1	21 (18.6%)	27 (23.7%)	48 (21.1%)
2	5 (4.4%)	9 (7.9%)	14 (6.2%)
3	4 (3.5%)	1 (0.9%)	5 (2.2%)
4	0	0	0
5	1 (0.9%)	1 (0.9%)	2 (0.9%)
>5	0	1 (0.9%)	1 (0.4%)

Time from the Last Hospitalization Discharge due to Depression or Suicidality in the Past 12 Months, months

N	31	39	70
Mean (SD)	3.9 (3.70)	3.5 (3.29)	3.7 (3.46)
Median	3.0	2.7	2.9
Range	(0; 12)	(0; 10)	(0; 12)
0 - <2	13 (41.9%)	16 (41.0%)	29 (41.4%)
2 - <4	6 (19.4%)	7 (17.9%)	13 (18.6%)
4 - <7	5 (16.1%)	10 (25.6%)	15 (21.4%)
7 - 12	7 (22.6%)	6 (15.4%)	13 (18.6%)

(continued next page)

SIBAT: Patient Reported Frequency of Suicidal Thinking

N	112	114	226
I have no suicidal thoughts	7 (6.3%)	10 (8.8%)	17 (7.5%)
I have suicidal thoughts a little of the time	15 (13.4%)	14 (12.3%)	29 (12.8%)
I have suicidal thoughts some of the time	33 (29.5%)	35 (30.7%)	68 (30.1%)
I have suicidal thoughts most of the time	42 (37.5%)	42 (36.8%)	84 (37.2%)
I have suicidal thoughts all of the time	15 (13.4%)	13 (11.4%)	28 (12.4%)

SIBAT: Prior Suicide Attempt

N	113	114	227
Yes	72 (63.7%)	78 (68.4%)	150 (66.1%)
No	41 (36.3%)	36 (31.6%)	77 (33.9%)

	Placebo + SOC	Esk 84 mg + SOC	Total
Suicide attempt within the last month			
N	113	114	227
Yes	24 (21.2%)	36 (31.6%)	60 (26.4%)
No	89 (78.8%)	78 (68.4%)	167 (73.6%)

Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.

MADRS item 10 - suicide score ranges from 0 to 6; a higher score indicates a more severe condition.

Duration of current depressive episode is derived from MADRS euthymic baseline.

BHS total score ranges from 0 to 20; a higher score indicates a more severe condition.

CGI-SS-R (score ranges from 0-6; a higher score indicates a more severe condition): "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"

CGI-SR-I (score ranges from 0-6; a higher score indicates a more severe condition): "Considering all aspects of this patient's suicidal thinking, behavior and related contributory/protective factors, what is your best clinical judgment of this patient's imminent risk for suicide within the next 7 days?"

Time from last hospitalization discharge is missing for subjects without hospitalization due to depression or suicidality in the past 12 months.

SIBAT Prior Suicide Attempt from Module 1: "I have made one or more attempts to end my life"

SIBAT Patient Reported Frequency of Suicidal Thinking from Module 5, Question 3: "Which of the following ratings best describes your thinking about suicide right now?"

[TSIDEM04B.RTF] [UNJ-54135419/SUI3002/DBR_FINAL/RE_CSR/PROD/TSIDEM04B.SAS] 01JUN2019, 00:53

Source: Trial SUI3002 clinical study report Table 8 (including Applicant footnotes), p. 75

Abbreviations: BHS = Beck Hopelessness Scale, CGI-SR-I = Clinical Global Impression for Suicide Risk – Imminent, CGI-SS-R = Clinical Global Impression for Severity of Suicidality – Revised, Esk = esketamine, MADRS = Montgomery-Åsberg Depression Rating Scale, MINI = Mini International Neuropsychiatric Interview, SD = standard deviation, SIBAT = Suicidal Ideation and Behavior Assessment Tool, SOC = standard of care

***Clinical Reviewer's Comment:** Baseline psychiatric history characteristics, including severity of depression, hospitalization history, suicide attempt history, and suicidality parameters (e.g., frequency or severity of thinking or CGI scoring) appear generally balanced between treatment groups. Of note, subjects in this study had a higher mean baseline MADRS total score (39.7 ± 5.48 SD) compared to subjects in study TRD3001 (37.6 ± 5.51 SD), which may result from higher scores on Item 10 regarding suicidal thoughts. On a minor note, it appears five subjects did not answer the same way regarding suicide attempt history on the MINI versus the SIBAT. And although subjects had to answer the MINI item B3 (Current Status: Think about suicide) affirmatively for inclusion, 7.5% of subjects answered "I have no suicidal thoughts" on the SIBAT; however, this number is unlikely to impact study results significantly.*

See Table 28 for safety analysis set prior medications of special interest, including ADs; antipsychotics; mood stabilizers and antiepileptics; benzodiazepines; and non-benzodiazepine

hypnotics and anxiolytics. Ninety-one percent of subjects were taking an AD; 41.9% were taking a second-generation antipsychotic; and two-thirds were taking a benzodiazepine. Of note, 16.3% of subjects were taking a first-generation antipsychotic in Trial SUI3002, compared to 3.1% in Trial SUI3001. Between studies, more subjects in Trial SUI3002 were taking olanzapine, lithium, and hydroxyzine than in Trial SUI3001. Overall in Trial SUI3002, the classes were similar between treatment groups, with some individual medication exceptions. More subjects were taking mirtazapine in the esketamine group than placebo (14.9% versus 6.2%).

Table 28. Trial SUI3002 Safety Analysis Set Prior Medications of Special Interest

Medication Class	Placebo + SOC (N=113) n (%)	Esk + SOC (N=114) n (%)	Total (N=227) n (%)
Medication Name (Top 3 used per class or if by >10% of total subjects)			
Antidepressants	103 (91.2%)	103 (90.4%)	206 (90.7%)
Venlafaxine	31 (27.4%)	27 (23.7%)	58 (25.6%)
Escitalopram	20 (17.7%)	19 (16.7%)	39 (17.2%)
Duloxetine	17 (15.0%)	20 (17.5%)	37 (16.3%)
Trazodone	22 (19.5%)	14 (12.3%)	36 (15.9%)
Sertraline	13 (11.5%)	21 (18.4%)	34 (15.0%)
Fluoxetine	11 (9.7%)	14 (12.3%)	25 (11.0%)
Mirtazapine	7 (6.2%)	17 (14.9%)	24 (10.6%)
Antipsychotics (Second Generation)	42 (37.2%)	53 (46.5%)	95 (41.9%)
Quetiapine	26 (23.0%)	33 (28.9%)	59 (26.0%)
Olanzapine	8 (7.1%)	12 (10.5%)	20 (8.8%)
Aripiprazole	10 (8.8%)	8 (7.0%)	18 (7.9%)
Antipsychotics (First Generation)	20 (17.7%)	17 (14.9%)	37 (16.3%)
Mood Stabilizers and Antiepileptics	21 (18.6%)	15 (13.2%)	36 (15.9%)
Lithium	10 (8.8%)	7 (6.1%)	17 (7.5%)
Gabapentin	7 (6.2%)	4 (3.5%)	11 (4.8%)
Lamotrigine	3 (2.7%)	3 (2.6%)	6 (2.6%)
Benzodiazepines	70 (61.9%)	79 (69.3%)	149 (65.6%)
Clonazepam	28 (24.8%)	31 (27.2%)	59 (26.0%)
Lorazepam	22 (19.5%)	25 (21.9%)	47 (20.7%)
Alprazolam	14 (12.4%)	17 (14.9%)	31 (13.7%)
Non-benzodiazepine Hypnotics/Anxiolytics	43 (38.1%)	33 (28.9%)	76 (33.5%)
Zolpidem	20 (17.7%)	13 (11.4%)	33 (14.5%)
Hydroxyzine	15 (3.3%)	10 (8.8%)	25 (11.0%)
Pregabalin	4 (3.5%)	7 (6.1%)	11 (4.8%)

Source: Adapted from Trial SUI3002 clinical study report Attachment TSICM03

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: Overall, prior medication classes of interest appear to be balanced between treatment groups, and the few individual medication exceptions are unlikely to impact study results. As might be expected with subjects of this illness

severity, over half were already taking a first or second generation antipsychotic (presumably either for augmentation purposes, or it appears the doses were low or as-needed (PRN) for a number of subjects on quetiapine, likely off-label for insomnia). It is possible that different local practice patterns among countries between Trial SUI3001 and Trial SUI3002 accounted for at least part of the variation in first generation antipsychotic, olanzapine, lithium, and hydroxyzine usage.

Concomitant or Rescue Medication Use and Treatment Compliance

See Table 29 for safety analysis set treatment phase concomitant medications (including those used as SOC treatment) of special interest, including ADs; second generation antipsychotics; mood stabilizers and antiepileptics; benzodiazepines; and non-benzodiazepine hypnotics and anxiolytics. The Applicant presented separate data for concomitant medications versus SOC received; where these numbers were different, the medication is presented additionally as SOC. (This appears to have made the most difference for trazodone, quetiapine, and gabapentin (which was not used as SOC).)

The Applicant did not specify particular rescue medications, but noted that benzodiazepines and non-benzodiazepine hypnotics and anxiolytics would be of interest. Overall the classes were similar between treatment groups, with some individual medication exceptions. More subjects were taking trazodone in the placebo group than esketamine (overall, 24.8% versus 14.0%; as SOC, 11.5% versus 3.5%).

Table 29. Trial SUI3002 Safety Analysis Set Treatment Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC	Esk + SOC	Total
- Medication as SOC if different usage	(N=113)	(N=114)	(N=227)
	n (%)	n (%)	n (%)
Antidepressants			
Venlafaxine	38 (33.6%)	29 (25.4%)	67 (29.5%)
Venlafaxine as SOC	36 (31.9%)	28 (24.6%)	64 (28.2%)
Trazodone	28 (24.8%)	16 (14.0%)	44 (19.4%)
Trazodone as SOC	13 (11.5%)	4 (3.5%)	17 (7.5%)
Escitalopram (/as SOC)	23 (20.4%)	16 (14.0%)	39 (17.2%)
Duloxetine	13 (11.5%)	22 (19.3%)	35 (15.4%)
Duloxetine as SOC	13 (11.5%)	20 (17.5%)	33 (14.5%)
Sertraline	16 (14.2%)	17 (14.9%)	33 (14.5%)
Sertraline as SOC	15 (13.3%)	16 (14.0%)	31 (13.7%)
Mirtazapine	13 (11.5%)	19 (16.7%)	32 (14.1%)
Mirtazapine as SOC	13 (11.5%)	16 (14.0%)	29 (12.8%)
Bupropion (/as SOC)	10 (8.8%)	14 (12.3%)	24 (10.6%)
Antipsychotics (Second Generation)			
Quetiapine	34 (30.1%)	44 (38.6%)	78 (34.4%)
Quetiapine as SOC	30 (26.5%)	34 (29.8%)	64 (28.2%)
Aripiprazole	14 (12.4%)	13 (11.4%)	27 (11.9%)
Aripiprazole as SOC	14 (12.4%)	11 (9.6%)	25 (11.0%)
Olanzapine	7 (6.2%)	11 (9.6%)	18 (7.9%)
Olanzapine as SOC	6 (5.3%)	6 (5.3%)	12 (5.3%)
Mood Stabilizers and Antiepileptics			
Lithium	9 (8.0%)	7 (6.1%)	16 (7.0%)
Lithium as SOC	8 (7.1%)	6 (5.3%)	14 (6.2%)
Gabapentin (not SOC)	6 (5.3%)	5 (4.4%)	11 (4.8%)
Lamotrigine	3 (2.7%)	3 (2.6%)	6 (2.6%)
Lamotrigine as SOC	1 (0.9%)	2 (1.8%)	3 (1.3%)
Valproic Acid (/as SOC)	2 (1.8%)	1 (0.9%)	3 (1.3%)
Benzodiazepines			
Clonazepam	70 (61.9%)	83 (72.8%)	153 (67.4%)
Clonazepam	31 (27.4%)	36 (31.6%)	67 (29.5%)
Lorazepam	24 (21.2%)	33 (28.9%)	57 (25.1%)
Diazepam	11 (9.7%)	12 (10.5%)	23 (10.1%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Zolpidem	46 (40.7%)	46 (40.4%)	92 (40.5%)
Zolpidem	18 (15.9%)	20 (17.5%)	38 (16.7%)
Hydroxyzine	16 (14.2%)	18 (15.8%)	34 (15.0%)
Pregabalin	4 (3.5%)	4 (3.5%)	8 (3.5%)
Pregabalin as SOC	0	3 (2.6%)	3 (1.3%)

Source: Adapted from Trial SUI3002 clinical study report Attachments TSICM01A, TSICM02A, and TSICM04A

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: The differences between concomitant use versus use as SOC for trazodone, quetiapine, and gabapentin likely stem from their off-label uses as PRNs for insomnia (or also anxiety for gabapentin). Benzodiazepine and non-benzodiazepine hypnotic/anxiolytic use was already of note pre-treatment. Benzodiazepine use increased slightly in the esketamine group on-treatment. Non-benzodiazepine use increased somewhat on-treatment (from 33.5 to 40.5% overall), with a larger increase in the esketamine group (11.5% versus a 2.6% increase in the placebo group). Overall, concomitant medication use during the double-blind phase (including as SOC) appears relatively balanced between treatment groups and unlikely to impact study results.

See Table 30 for follow-up analysis set follow-up phase concomitant medications (including those used as SOC treatment) of special interest, presented in the same manner as for the double-blind phase. Overall, medication use was similar between treatment groups, with some exceptions. More subjects took venlafaxine in the placebo group than esketamine (37.2% versus 24.7%; as SOC, 24.5% versus 13.5%). Of note during the follow-up phase, one subject in the esketamine group received esketamine, four subjects in the placebo group received ketamine, and one subject in the esketamine group received ketamine.

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Table 30. Trial SUI3002 Follow-Up Analysis Set Follow-Up Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC	Esk + SOC	Total
- Medication as SOC if different usage	(N=94)	(N=89)	(N=183)
	n (%)	n (%)	n (%)
Antidepressants			
Venlafaxine (/as SOC)	35 (37.2%)	22 (24.7%)	57 (31.1%)
Trazodone	23 (24.5%)	12 (13.5%)	35 (19.1%)
Trazodone as SOC	11 (11.7%)	4 (4.5%)	15 (8.2%)
Sertraline (/as SOC)	13 (13.8%)	14 (15.7%)	27 (14.8%)
Escitalopram (/as SOC)	16 (17.0%)	10 (11.2%)	26 (14.2%)
Mirtazapine	12 (12.8%)	13 (14.6%)	25 (13.7%)
Mirtazapine as SOC	12 (12.8%)	12 (13.5%)	24 (13.1%)
Duloxetine (/as SOC)	11 (11.7%)	13 (14.6%)	24 (13.1%)
Desvenlafaxine (/as SOC)	11 (11.7%)	10 (11.2%)	21 (11.5%)
Bupropion	11 (11.7%)	9 (10.1%)	20 (10.9%)
Bupropion as SOC	10 (10.6%)	8 (9.0%)	18 (9.8%)
Antipsychotics (Second Generation)			
Quetiapine	31 (33.0%)	38 (42.7%)	69 (37.7%)
Quetiapine as SOC	27 (28.7%)	31 (34.8%)	58 (31.7%)
Aripiprazole	13 (13.8%)	12 (13.5%)	25 (13.7%)
Aripiprazole as SOC	13 (13.8%)	10 (11.2%)	23 (12.6%)
Olanzapine	7 (7.4%)	5 (5.6%)	12 (6.6%)
Olanzapine as SOC	5 (5.3%)	3 (3.4%)	8 (4.4%)
Mood Stabilizers and Antiepileptics			
Lithium	10 (10.6%)	10 (11.2%)	20 (10.9%)
Lithium as SOC	9 (9.6%)	8 (9.0%)	17 (9.3%)
Gabapentin (not SOC)	6 (6.4%)	3 (3.4%)	9 (4.9%)
Lamotrigine	0	4 (4.5%)	4 (2.2%)
Lamotrigine as SOC	0	3 (3.4%)	3 (1.6%)
Valproic Acid (/as SOC)	2 (2.1%)	1 (1.1%)	3 (1.6%)
Benzodiazepines			
Clonazepam	47 (50.0%)	48 (53.9%)	95 (51.9%)
Lorazepam	23 (24.5%)	24 (27.0%)	47 (25.7%)
Diazepam	9 (9.6%)	11 (12.4%)	20 (10.9%)
Diazepam	9 (9.6%)	8 (9.0%)	17 (9.3%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Zolpidem	40 (42.6%)	34 (38.2%)	74 (40.4%)
Hydroxyzine	16 (17.0%)	14 (15.7%)	30 (16.4%)
Melatonin	14 (14.9%)	14 (15.7%)	28 (15.3%)
Melatonin	4 (4.3%)	6 (6.7%)	10 (5.5%)

Source: Adapted from Trial SUI3002 clinical study report Attachments TSICM01A, TSICM02A, and TSICM04A

Abbreviations: Esk = esketamine, SOC = standard of care

Clinical Reviewer's Comment: As during the double-blind phase, the differences between concomitant use versus use as SOC for trazodone, quetiapine, and gabapentin in the follow-up phase likely stem from their off-label uses as PRNs for insomnia (or also anxiety for gabapentin). Overall, concomitant medication use during the follow-up phase (including as SOC) appears relatively balanced between treatment groups and unlikely to impact study results. Interestingly, benzodiazepine use dropped from pre-treatment levels (from 65.6% to 51.9% overall), and non-benzodiazepine use increased from pre-treatment (from 33.5% to 40.4%); it is difficult to speculate what may account for the differences. These changes were not observed in Trial SUI3001, for unclear reasons.

Regarding treatment compliance, the Applicant reported that doses of IN study agent were self-administered by subjects at the study site under the direct supervision of the investigator or designee. The Applicant did not comment upon any observation (or pill counting) of SOC AD treatment during the double-blind inpatient phase, or the double-blind outpatient and follow-up phases.

In terms of exposure, a majority of subjects in both treatment groups received study agent on all 8 dosing days during the double-blind phase (83.2% in the placebo group and 75.4% in the esketamine group). As noted previously, more subjects withdrew in the esketamine group for AEs, and more subjects withdrew in the placebo group for lack of efficacy (see Table 24). See Table 31 for a summary of exposure to study agent by number of days exposed.

Table 31. Trial SUI3002 Safety Analysis Set Summary of Exposure to Study Agent

Number of Days Dosed	Placebo + SOC	Esketamine + SOC
	(N=113) n (%)	(N=114) n (%)
1	3 (2.7%)	8 (7.0%)
2	3 (2.7%)	7 (6.1%)
3	4 (3.5%)	3 (2.6%)
4	5 (4.4%)	3 (2.6%)
5	0	3 (2.6%)
6	4 (3.5%)	0
7	0	4 (3.5%)
8	94 (83.2%)	86 (75.4%)

Source: Adapted from Trial SUI3002 clinical study report Table 10, p. 82

Abbreviations: SOC = standard of care

During the double-blind phase, 21 of 114 (18.4%) of subjects in the esketamine group received less than 84 mg of esketamine on at least one dosing day:

- Fourteen subjects (12.3%) in the esketamine group required dose reduction to 56 mg at some point for all subsequent doses due to an AE/tolerability issue (13 subjects) and a

site error (1 subject). One hundred subjects (87.7%) in the esketamine group did not require a dose reduction.

- Three subjects (2.6%) in the esketamine group had dose reduction due to AE/tolerability on at least one dosing day: two subjects received <3 device administrations on Day 1, and one subject received <3 device administrations on Days 1 and 4.
- Four subjects did not have full doses on one of the dosing days for reasons other than AEs/tolerability: one spray for one device on Day 8 due to site error; subject refused third device on Day 1; one device not fully emptied on Days 1 and 4 per dose gauge; and one device was not administered on Day 14 due to device error.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint of change from baseline to 24 hours total MADRS showed a 3.85 (two-sided $p = 0.0062$) point greater decline in the esketamine arm compared to placebo, see Table 16. The esketamine arm declined 16.0 points from an average baseline score of 39.5 points. See Table 16 for the placebo arm values. P-values were compared to an alpha level of 0.05. Throughout this Section, negative change indicates improvement.

Table 32. MADRS Total Score at 24 Hours (SUI3002: FAS)

Dose	Placebo		Esketamine		LS Mean Difference (95% CI)	Two-sided p-value
	N	LS Mean (SE)	N	LS Mean (SE)		
84 mg	113	-12.1 (0.97)	114	-16.0 (0.97)	-3.85 (-6.60, -1.11)	0.0062

Source: Statistical Reviewer.

Three patients in the esketamine arm and two patients in the placebo arm did not have a 24-hour observation, see Table 17. In this case when only a small number (2-3) observations are missing, it is unlikely to have any noticeable effect on the study results assuming LOCF. However, by Day 25, between 22% and 25% of patients dropped out. The LOCF assumption is likely to affect results and was not used by either the Applicant or these Reviewers. Instead, the Applicant's exploratory analyses of the time course of MADRS scores assumed missing at random (MAR) and were conducted with mixed models for repeated measures (MMRM).

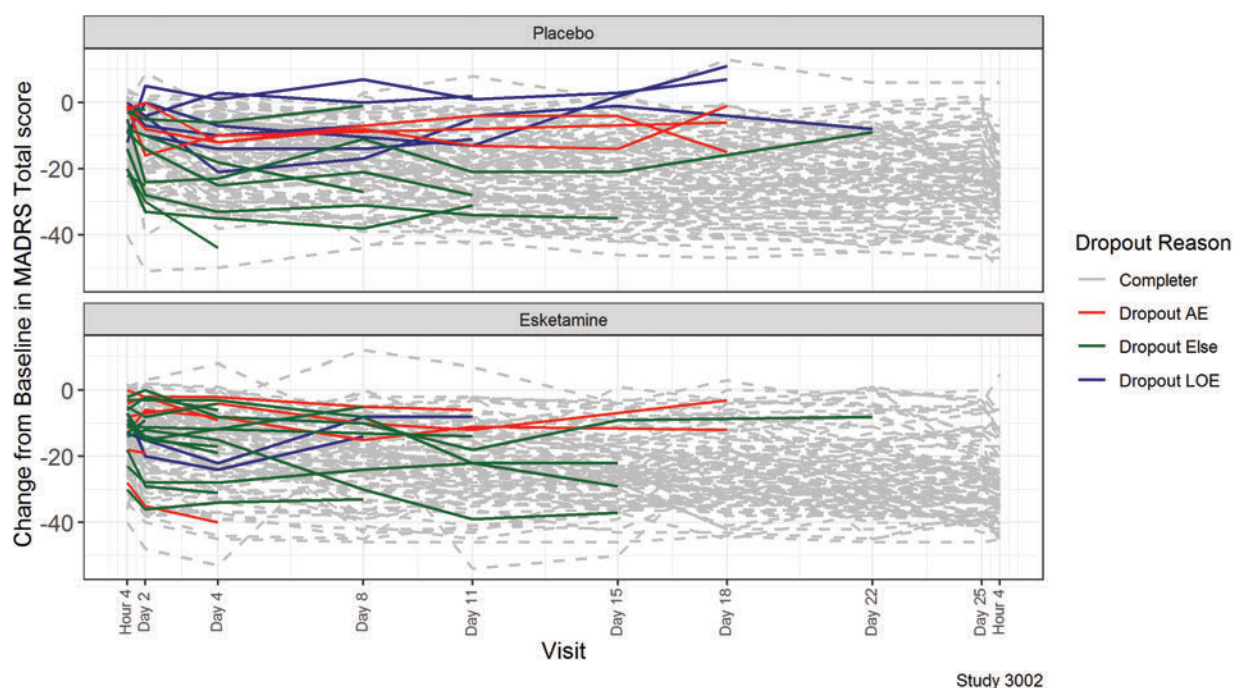
Statistical Reviewer's Comment: Because the MMRM analysis for the entire 25-day double-blind period were considered exploratory, the Applicant did not present results of any sensitivity analyses.

Table 33. Missing Observations in the Full Efficacy Analysis Set (SUI3002: FAS)

Treatment Arm	Day 2		Day 25	
	Observed	LOCF	Observed	LOCF
Placebo	111 (98%)	2 (2%)	88 (78%)	25 (22%)
Esketamine	110 (97%)	3 (3%)	85 (75%)	29 (25%)

Source: Statistical Reviewer.

Although the primary endpoint was evaluated at one day post-dose, it is clinically relevant to understand if ketamine patients still have improved depressive symptoms compared to placebo. Figure 13 shows the individual patient MADRS trajectories from Day 1 to Day 25 with grey lines indicating patients who completed the study and red, green, and blue lines indicating patients who dropped out. Patients who drop out may have smaller changes from baseline compared to completers. MAR may not be a justifiable assumption for analyzing the MADRS total score during the 25-day double-blind period. However, the number of dropouts is small limiting the potential impact of any violations of MAR.

Figure 13. Patient Level MADRS Change Score Trajectories (SUI3002: FAS)

Source: Statistical Reviewer.

Table 34 and Figure 14 present the MADRS total score during the 25-day double-blind period. In Figure 14, both esketamine (black line) and placebo (grey line) arms MADRS scores decrease rapidly over the first 4 days with the esketamine arm improving approximately 17 points and the placebo improving approximately 16 points. The difference between esketamine and

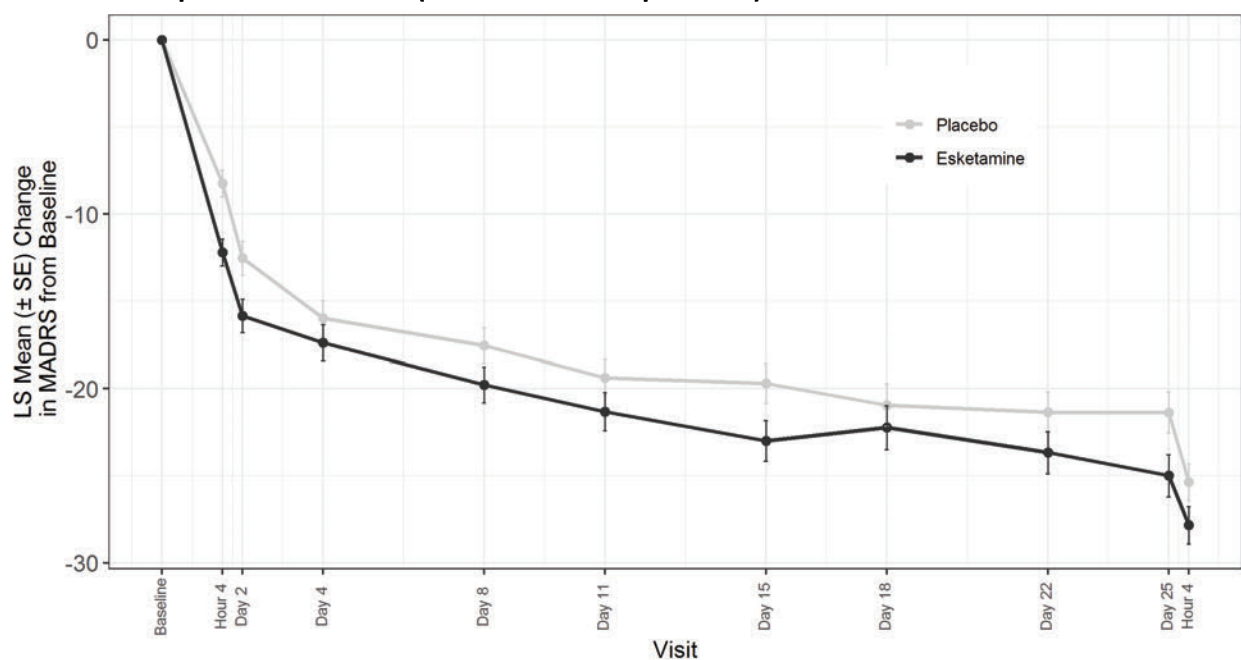
placebo is greatest at Day 1, 4 hours after dosing, with a difference of -3.96 points (95% CI: -6.13 to -1.79), see Table 34. Throughout the double-blind period, the esketamine arm had between 1.3 to 3.6 point greater improvement from baseline compared to the placebo arm.

Table 34. Change from Baseline in MADRS Total Score (SUI3002: FAS)

<i>Treatment Arm</i>	<i>Visit</i>	<i>Treatment Effect</i>	<i>SE</i>	<i>Lower 95% CI</i>	<i>Upper 95% CI</i>	<i>Unadjusted p-value</i>
ESK - Placebo	Day 1(DB): 4H	-3.96	1.11	-6.13	-1.79	0.0004
ESK - Placebo	Day 2(DB)	-3.30	1.36	-5.98	-0.63	0.0155
ESK - Placebo	Day 4(DB)	-1.41	1.47	-4.29	1.46	0.3361
ESK - Placebo	Day 8(DB)	-2.25	1.46	-5.11	0.61	0.1226
ESK - Placebo	Day 11(DB)	-1.95	1.54	-4.96	1.07	0.2051
ESK - Placebo	Day 15(DB)	-3.31	1.65	-6.53	-0.08	0.0445
ESK - Placebo	Day 18(DB)	-1.29	1.75	-4.72	2.14	0.4606
ESK - Placebo	Day 22(DB)	-2.31	1.69	-5.62	1.01	0.1723
ESK - Placebo	Day 25(DB): Predose	-3.63	1.70	-6.95	-0.30	0.0326
ESK - Placebo	Day 25(DB): 4H	-2.48	1.52	-5.46	0.50	0.1031

Source: Statistical Reviewer.

Figure 14. MADRS Total Score - LS Mean ($\pm$ SE) Change from Baseline over Time - Mixed Model for Repeated Measures (SUI3002: FAS Population)

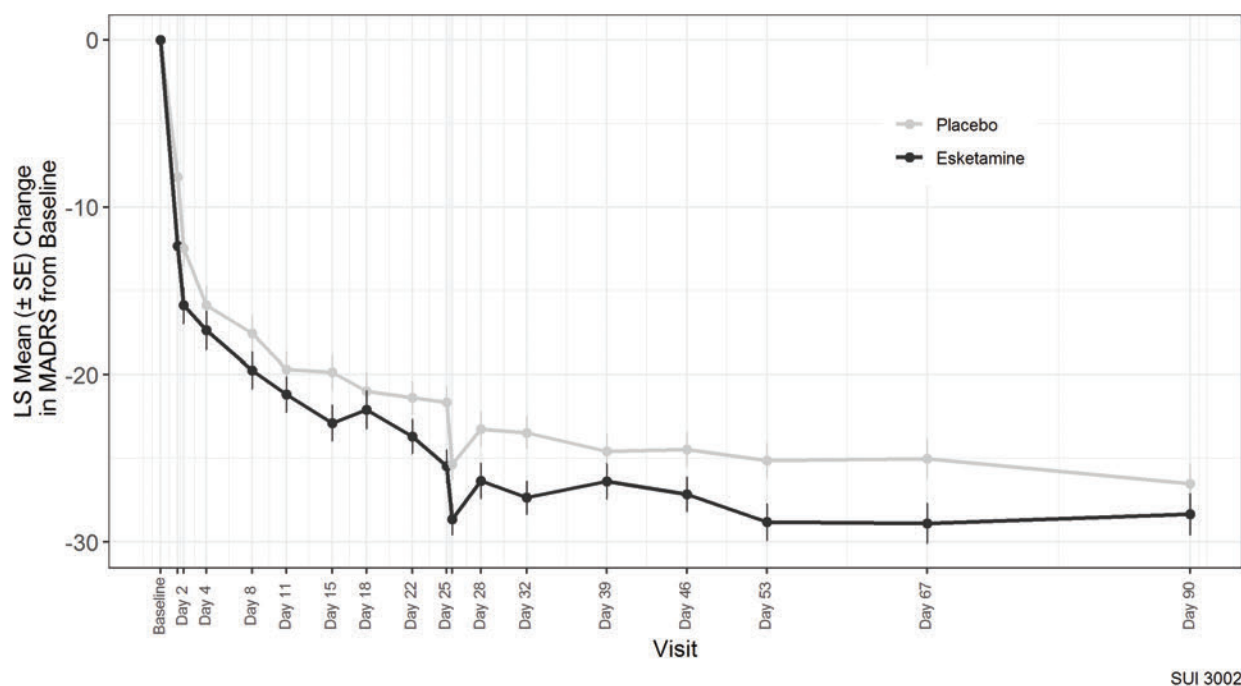


SUI 3002

Source: Statistical Reviewer.

Over the entire 90-day follow-up period, differences between the placebo arm and esketamine arm in MADRS total score are maintained through Day 90, see Figure 15. However, the statistical information about the difference declines as soon as Day 28 because of patients dropping out of the study. These graphs were generated using results of the Statistical Reviewer's mixed effects model for repeated measures (MMRM) analysis, see details in the additional analyses section for SUI3001.

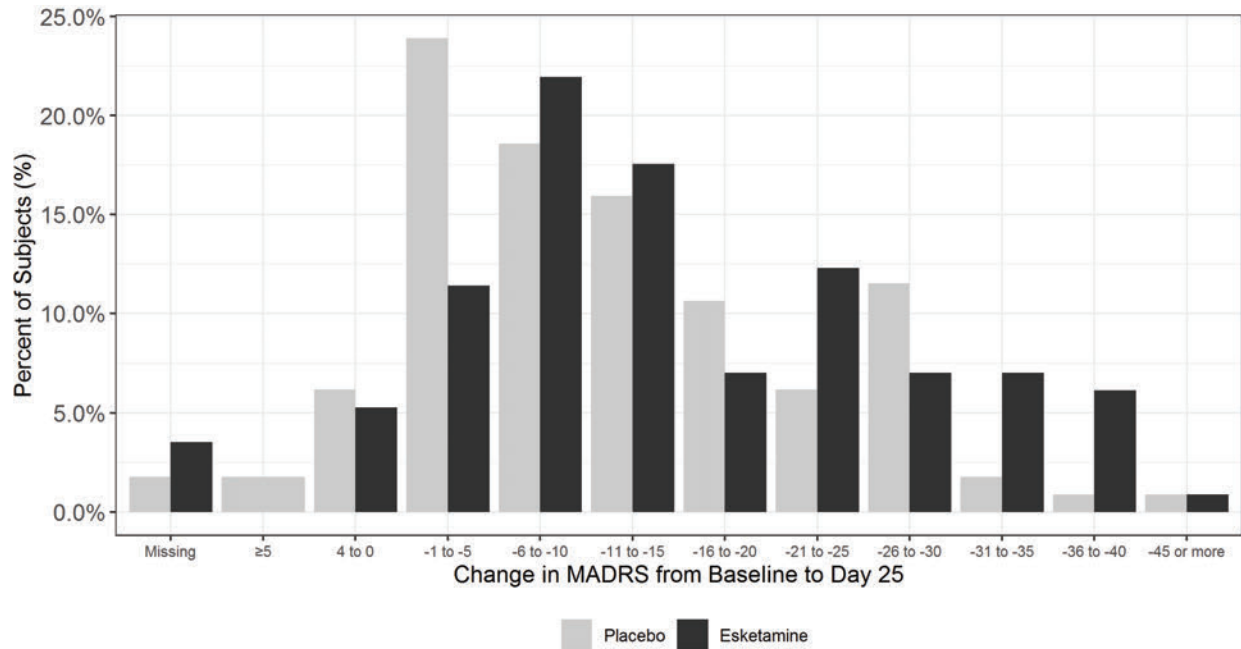
Figure 15. MADRS Total Score - 90 Day Follow-up - LS Mean ($\pm$ SE) Change from Baseline over Time - Mixed Model for Repeated Measures (SUI3002: FAS Population)



Source: Statistical Reviewer.

In SUI3002, 98% of patients completed the 24-hour post-randomization observation and 76% of patients completed the double-blind phase. Using Figure 16 and Figure 17, this reviewer analyzed the usefulness of esketamine in treating MDSI. See description of these histograms under Study 3001. At one day post randomization and at the pre-dose time point on Day 25, the esketamine arm has more patients showing a greater improvement from baseline than placebo. After the Day 25 dose, both treatments showed patients with improved depression symptoms; however, the placebo arm had a greater proportion of patients showing less than a -25 point improvement from baseline. Therefore, esketamine appears more useful than placebo in treating MDSI.

Figure 16. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 24 Hours (SUI3002: FAS)

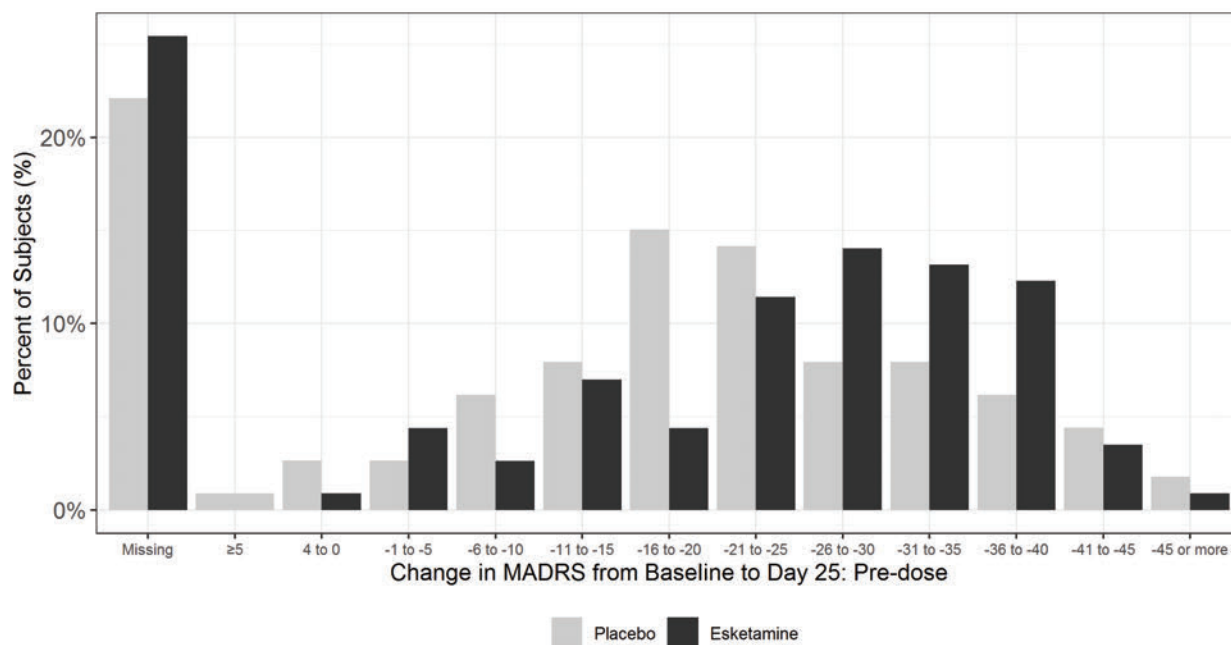


Study SUI3002

Source: Statistical Reviewer.

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Figure 17. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 25 Days Pre-dose (SUI3002: FAS)



Study SUI3002

Source: Statistical Reviewer.

Data Quality and Integrity

The data and datasets were of sufficient quality to permit review. Inspections conducted by the Office of Scientific Investigations did not uncover any data integrity concerns.

Efficacy Results – Secondary and other relevant endpoints

On the pre-specified ranked ANCOVA, the secondary efficacy endpoint of change from baseline to 24 hours total CGI-SS-R did not show any change (Hodges-Lehmann median difference = 0 (95% CI = 0 to 0, rank ANCOVA p = 0.372), see Table 19. At this point, statistical testing hierarchy stopped because a p-value was greater than 0.05. The Applicant also reported results of a Bayesian Ordinal Item Response Theory model suggesting that the odds of improvement in the esketamine arm are 1.9 times the odds in the placebo arm (95% Credible Interval (CrI): 0.90 to 4.23).

Statistical Reviewer's Comment: The Applicant prespecified the same rank analyses as in Study 3001, see Statistical Reviewer's comment under Study 3001. In addition, the 95% CI is degenerate (0 to 0) while the ranked ANCOVA p-value (0.34) indicates uncertainty in the estimates. This result may be caused by the use of HL-estimator on discrete data or the high number of ties in the data. In Table 35, the same pattern of heavily tied ranks as

in Study 3001 is seen. The large number of ties may affect the estimation of standard errors and other statistics. The statistical reviewer conducted several additional analyses to explore the Applicant's analyses and the time course of CGI-SS-R over the entire 25-day double-blind period.

Table 35. Ranks^a of Change from Baseline to Day 2 in CGI-SS-R (FAS)

Rank	Placebo	Esketamine
1	0	1
6.5	4	6
18.5	5	9
40.5	16	14
75	18	21
122.5	26	30
181.5	39	23
217.5	4	6
223	0	1
224	0	1

^a: Smaller ranks indicate a greater improvement.

Source: Statistical Reviewer.

In Figure 18 and Figure 19, the proportion of patients with lower severity of suicidality (lighter grey bars) increases in both esketamine and placebo patients from baseline through Day 25. On the CGI-SS-R, the normal and mildly suicidal categories have slightly higher combined height in the esketamine arm compared to the placebo arm. This pattern is repeated in the MADRS item 10 (combined categories 0 and 1). The greater number of patients with lower scores in the esketamine suggests further investigation of this potential signal is needed.

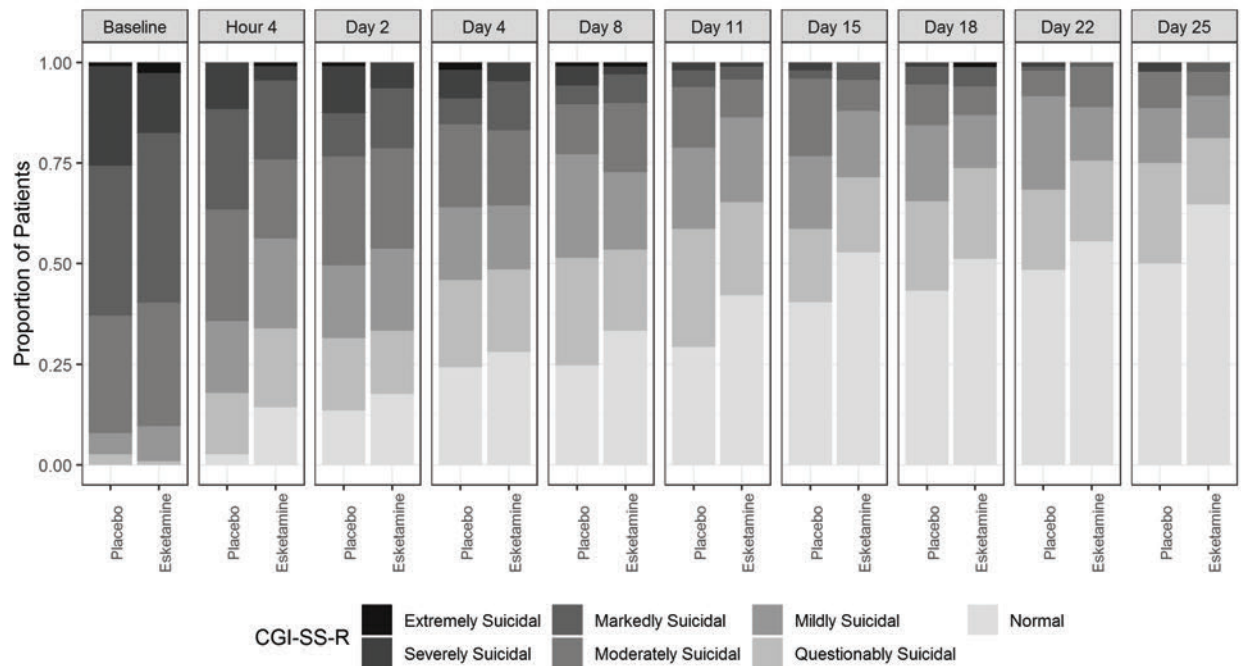
Results of a BLOR analysis conducted by the Statistical Reviewer suggest that patients in the esketamine arm have a lesser chance of being in a higher severity category compared to placebo at 24 hours (OR = 0.78, 95% CrI: 0.37 to 1.52) and at 25 days (OR = 0.58, 95% CrI: 0.23 to 1.23), see Table 36. This model suggests similar results for the MADRS item 10 with an OR = 0.64 (95% CrI: 0.28 to 1.28) at 24 hours and an OR = 0.75 (95% CrI: 0.28 to 1.62) at 25 days. Although all point estimates suggest a potential numerical improvement in suicidal severity in the esketamine arm compared to placebo, the credible intervals include OR = 1 (no effect).

In Figure 20 and Figure 21, PO assumption may be reasonable for CGI-SS-R < 5 for both Days 2 and 25. For CGI-SS-R ≥ 5, PO may no longer be valid. However, the deviations for CGI-SS-R = 5 are not large and the number of patients in CGI-SS-R = 6 is small. Therefore, violations of the PO assumption may not have large impacts on the conclusions from the BLOR.

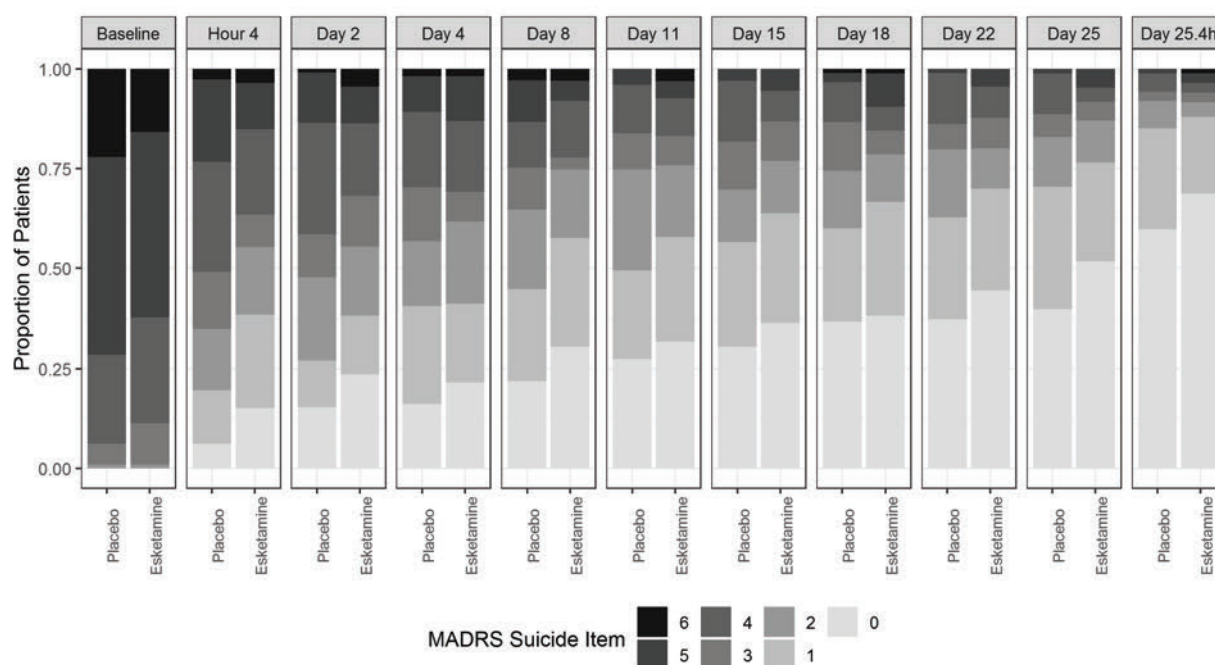
The results of multiple statistical models do not detect a signal of improvement in either CGI-SS-R or MADRS item 10 in contrast to Study 3001, where there is weak evidence for a signal of greater improvement in the esketamine arm.

Statistical Reviewer's Comment: The lack of consistent results on the CGI-SS-R endpoint between Studies 3001 and 3002 may indicate that esketamine does not improve suicidal ideation severity or that the CGI-SS-R has high variability. Further research to understand the measurement properties of the CGI-SS-R for measuring suicide severity and how to design and analyze studies for this endpoint is needed.

Figure 18. Proportion of Patients in CGI-SS-R Category (SUI3002: FAS)



Source: Statistical Reviewer.

Figure 19. Proportion of Patients in MADRS Item 10 Category (SUI3002: FAS)

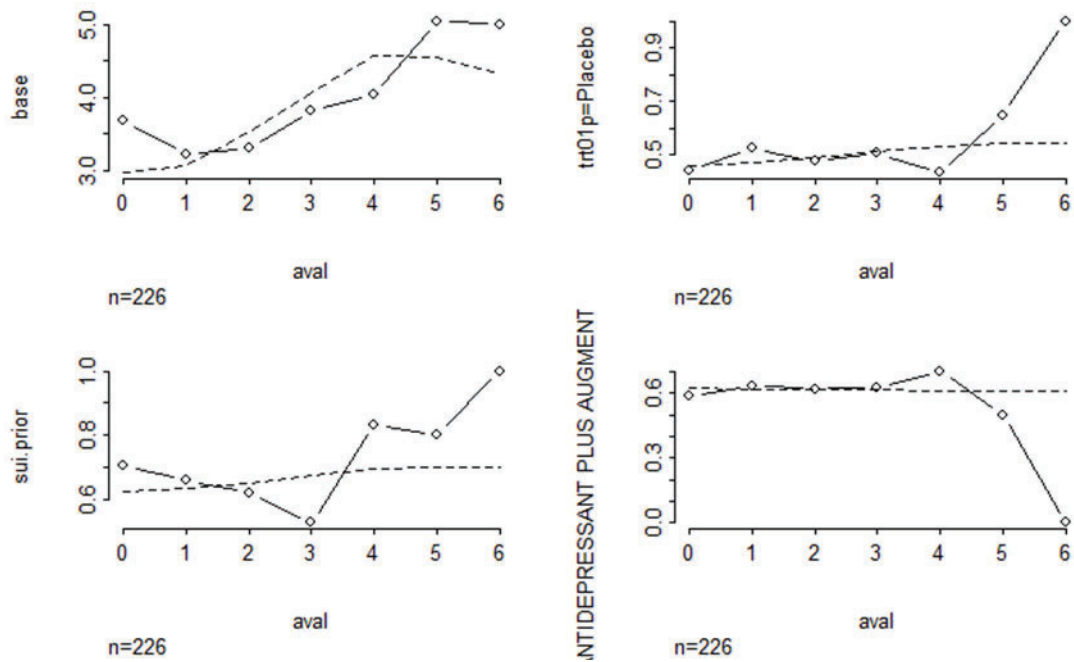
Source: Statistical Reviewer.

Table 36. Odds Ratio for CGI-SS-R and MADRS Item 10 from a Bayesian Ordinal Longitudinal Model (Study 3002: FAS)

	Visit	$OR = \frac{Esk_j/Esk_i}{Plb_j/Plb_i}$	95% CrI	
CGI-SS-R	Day 2	0.78	0.37	1.52
	Day 25	0.58	0.23	1.23
MADRS Item 10	Day 2	0.64	0.28	1.28
	Day 25	0.75	0.28	1.62

Source: Statistical Reviewer.

Figure 20. Proportional Odds Plot at Day 2 (SUI3002: FAS)²

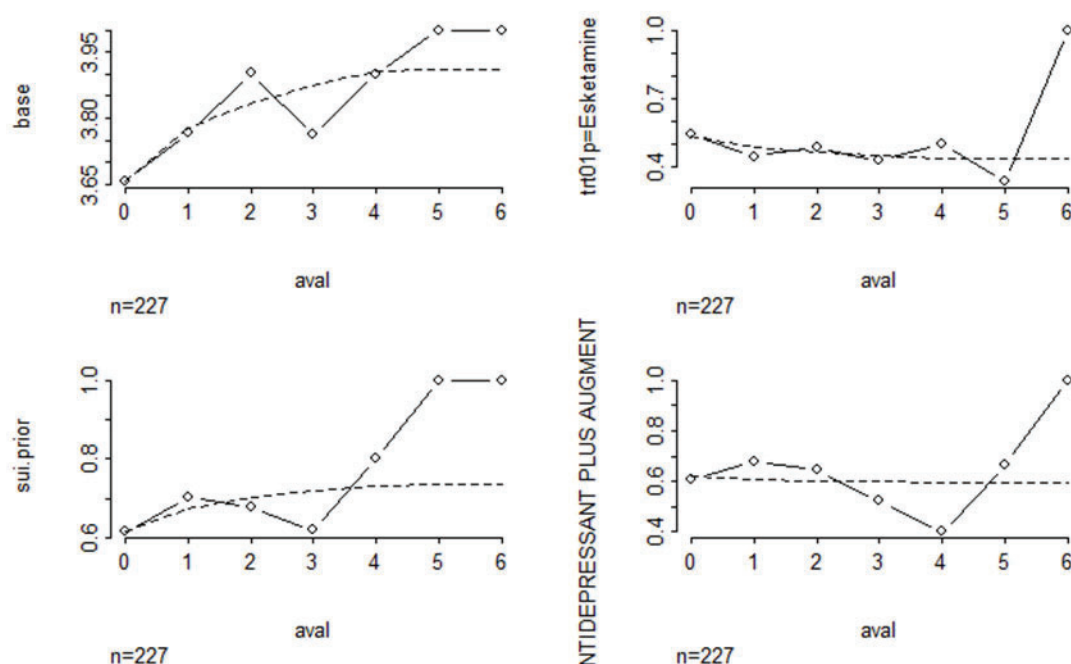


Source: Statistical Reviewer.

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² In Figure 10 and Figure 11, aval is CGI-SS-R with categories 0-6, base in baseline CGI-SS-R, sui.prior is an factor for prior suicide history (0 – no history, 1 – history), trt01p is the treatment factor, and std.care is the standard of care (antidepressant vs plus antidepressant).

Figure 21. Proportional Odds Plot at Day 25 (SUI3002: FAS)



Source: Statistical Reviewer.

See preceding discussion of primary efficacy results regarding the other secondary endpoints of change in the MADRS total score over time (i.e., at 4 hours and through Day 25) and the exploratory endpoints of change in the MADRS total score through Day 90, and change in MADRS individual item scores through Day 25 and Day 90 (i.e., specifically regarding Item 10, suicidal ideation).

Other than the secondary endpoint of CGI-SS-R, none of the other secondary (or exploratory) endpoints were controlled for multiplicity, or inform labeling; therefore they are discussed briefly or not reviewed here. Table 37 lists some of the other secondary and exploratory endpoints. The percentages of subjects with remission of MDD (defined as MADRS total score ≤ 12) or response (defined as $\geq 50\%$ reduction in MADRS total score) were numerically greater in the esketamine group at the timepoints noted except for response at Day 25 (4 hours post-dose); however, at six of the ten noted timepoints the CI included zero. The changes from baseline in the BHS and QLDS numerically favored esketamine at Day 25 (although the CI included zero for the BHS).

Table 37. Trial SUI3002 Other Secondary or Exploratory Endpoints

Endpoint Timepoint	Placebo + SOC	Esketamine + SOC	Difference (95% CI)
Percentage of subjects with remission of MDD (MADRS total score ≤12)			
Day 1 (4 hours) ¹	4 (3.5%)	12 (10.5%)	7.0 (0.40; 13.57)
Day 2 (24 hours) ¹	12 (10.6%)	25 (21.9%)	11.3 (1.83; 20.80)
Day 25 (predose) ¹	31 (27.4%)	49 (43.0%)	15.5 (3.29; 27.81)
Day 25 (4 hours) ¹	42 (37.2%)	54 (47.4%)	10.2 (-2.58; 22.98)
Day 90 ²	48 (51.1%)	51 (57.3%)	6.2 (-8.17; 20.65)
Percentage of subjects with response (≥50% reduction in MADRS total score) ²			
Day 1 (4 hours)	8 (7.1%)	30 (26.3%)	19.2 (9.87; 28.60)
Day 2 (24 hours)	27 (23.9%)	40 (35.1%)	11.2 (-0.58; 22.97)
Day 25 (predose)	54 (47.8%)	67 (58.8%)	11.0 (-1.92; 23.89)
Day 25 (4 hours)	69 (61.1%)	68 (59.6%)	-1.4 (-14.14; 11.31)
Day 90	60 (63.8%)	61 (68.5%)	4.7 (-8.98; 18.40)
Change from baseline in BHS total score (LS mean) ¹			
Day 25 (predose)	-6.6	-7.5	-0.9 (-2.64; 0.91)
Change from baseline in QLDS score (LS mean) ¹			
Day 25 (predose)	-5.1	-6.4	-1.3 (-2.93; 0.27)

Source: Adapted from Trial SUI3002 clinical study report

Note: Endpoints through Day 25 derived from full efficacy analysis set; endpoints at Day 90 derived from follow-up analysis set

Abbreviations: BHS = Beck Hopelessness Scale, CI = confidence interval, LS = least-squares, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, QLDS = Quality of Life in Depression Scale, SOC = standard of care

¹ Other secondary endpoint

² Exploratory endpoint

Clinical Reviewer's Comment: The percentage of subjects with remission of MDD at 24 hours is supportive, although the threshold of MADRS total score ≤12 is on the higher end of the literature (Zimmerman et al. 2004a; Zimmerman et al. 2004b), and the CI for percentage of responders included zero. It is unclear what the Applicant meant to achieve by measurement of the MADRS on Day 25 predose and at 4 hours post-dose; the results are mixed. For example, the percentage of remitters is numerically greater for esketamine at both timepoints, but more so predose (where the CI does not include zero, the opposite result of Trial SUI3001). For responders, esketamine is favored predose and not post-dose (though the CI includes zero for both). It is unclear what, if any, conclusions can be inferred from the mixed results on Day 25.

Dose/Dose Response

Clinical Reviewer's Comment: Given that the majority of esketamine subjects (87.7%) did not require a dose reduction (as previously discussed) and that dose reductions occurred at various timepoints, a dose-response analysis does not appear useful.

Durability of Response

See preceding discussion under primary efficacy results.

Clinical Reviewer's Comment: Although analyses at multiple timepoints in the 25-day double-blind treatment period yielded 95% confidence intervals that included zero (Table 34), treatment with esketamine was numerically favored over placebo at all timepoints on the primary efficacy endpoint, which is supportive of a durable response.

Persistence of Effect

See preceding discussion under primary efficacy results.

Clinical and Statistical Reviewer's Comment: Although the change from baseline in MADRS total score to Day 90 was an exploratory endpoint and statistical information declined after Day 28 because of dropouts (Figure 15), a persistent difference (LS mean difference between esketamine and placebo) between esketamine and placebo was observed along with improved MADRS total score after completing esketamine treatment on Day 25. These observations could be considered supportive of the Applicant's intended use (i.e., demonstrating an early benefit while awaiting onset of oral antidepressant benefit). However, the persistent difference between esketamine and placebo contradicts the observations from Study 3001. To fully characterize the MADRS trajectories and potential treatment effects of esketamine after Day 25, additional studies may be needed.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See above.

Additional Analyses Conducted on the Individual Trial

See discussion under SUI3001.

7.3. Trial SUI2001

7.3.1. Study Design

Trial SUI2001 was a phase 2 proof-of-concept study similar to the phase 3 Trials SUI3001 and SUI3002; see Section 7.1.1 Study Design for a description. Differences included:

- Trial locations: Trial SUI2001 was conducted entirely in the United States, at 11 sites, not internationally as in the phase 3 studies.
- Trial size: Trial SUI2001 was smaller, enrolling 68 subjects as a proof-of-concept study.
- Basic study design duration: the follow-up phase lasted from Day 26 to Day 81, rather than to Day 90 as in the phase 3 studies.
- Eligibility criteria: the required MADRS total score at baseline was lower (≥ 22) compared to the phase 3 studies (> 28); there was no stipulation that if Screening lasted > 24 hours pre-first-dose, then MINI questions regarding suicidality would be repeated prior to randomization to confirm eligibility; MDD diagnosis was based on the DSM-IV-Text Revision edition, rather than the DSM-5.
- Schedule of events and assessments: see Table 38.
- Prohibited medications: prescription amphetamines were not allowed during the double-blind treatment phase, unlike the phase 3 trials post-amendment.
- Primary endpoint: was change from baseline in MADRS total score from baseline (Day 1, pre-dose) to 4 hours post-first dose, rather than to 24 hours post-first-dose as in the phase 3 studies.
- Secondary endpoint: rather than a key secondary of change from baseline in CGI-SS-R score as in the phase 3 studies, Trial SUI2001 included a secondary endpoint of change from baseline in the clinical global judgment of suicide risk (CGJ-SR) using the CGJ-SR score at 24 hours post-first-dose.
- Efficacy assessments: Trial SUI2001 included the Beck Scale for Suicidal Ideation (BSS), and did not include the QLDS, EQ-5D-5L, or TSQM-9.
- Safety assessments: Trial SUI2001 included the clinical outcome safety assessments of a nasal tolerability questionnaire, the Brief Psychiatric Rating Scale (BPRS) for psychotomimetic AEs, and the Bladder Pain/Interstitial Cystitis-Symptom Score (BPIC-SS) for bladder-related AEs. The BPRS is an 18-item rating scale used to assess a range of

psychotic and affective symptoms rated from both observation of the subject and the subject's own report; the 4-item positive symptom subscale (BPRS+: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) was used for the study. The BPIC-SS is an 8-item patient-reported outcome measure with a recall period of 7 days.

Clinical Reviewer's Comment: Notably, the primary endpoint and suicidality-related endpoint were different in Trial SUI2001 compared to the phase 3 trials, in terms of 4 hour versus 24 hour post-dose MADRS total score change from baseline, and the use of the CGJ-SR versus the CGI-SS-R, respectively. Other differences between Trial SUI2001 and the phase 3 trial design are unlikely to impact findings. If indicated, results analysis could consider any potential impact of a lower MADRS baseline total score inclusion criterion, and the lack of repeat MINI suicidality question administration if Screening lasted >24 hours. Safety analysis should examine if the results of the BPRS+, BPIC-SS, and nasal tolerability questionnaire were reassuring enough to lead to their exclusion from the phase 3 trials.

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Table 38. Trial SUI2001 Schedule of Events and Assessments

Phase	Screening	Double-Blind Treatment																Follow Up ^a							
Visit Number	1	2						3	4	5	6 ^a	7 ^b	8 ^b	9 ^b	10 ^b	11 ^b	12 ^b	-	-	13	14	15	16	17	18
Day	1 ^c	1						2	3	4	5	8	11	15	18	22	25	ET ^d		32	39	46	53	67	81
		Pre dose	0 hr	40 min	1 hr	2 hr	4 hr																		
Study Procedures																									
Setting																									
Emergency Room (ER) ^e or other permitted setting	X	X	X	X	X	X	X ^f																		
Inpatient psychiatric unit ^g								X	X	X	X														
Outpatient psychiatric unit												X	X	X	X	X	X	-		X	X	X	X	X	X
Screening/Administrative																									
Informed consent	X																								
Informed consent for optional genetic research samples										X															
Inclusion/exclusion criteria	X	X																							
Medical history and demographics	X																								
Prestudy therapy	X	X																							
Urine pregnancy test for women of childbearing potential ⁱ	X																X	X							X
Urine drug screen ¹	X																								
Alcohol screen (breath) ¹	X																								
Mini International Psychiatric Interview (MINI) ^j	X																								
Question B5 and B9 from MINI (current status) ^{j, k}	X																								
Study Drug Administration																									
Randomization			X																						
Study Drug Administration ^m (intranasal esketamine or placebo)			X ^m							X		X	X	X	X	X	X								
Safety Assessments																									
Physical examination	X																X ^h	X							X
Nasal examination	X					X					X ^{oo}		X ^{oo}	X ^{oo}			X ^{oo}	X			X				

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Phase	Screening	Double-Blind Treatment																		Follow Up ^a						
Visit Number	1	2						3	4	5	6 ^a	7 ^b	8 ^b	9 ^b	10 ^b	11 ^b	12 ^b	-	-	13	14	15	16	17	18	
Day	1 ^c	1						2	3	4	5	8	11	15	18	22	25	ET ^d		32	39	46	53	67	81	
		Pre dose	0 hr	40 min	1 hr	2 hr	4 hr																			
Vital signs ^a	X	X ^o		X ^o	X ^o	X ^o				X ^o		X ^o	X ^o	X ^o	X ^o	X ^o	X ^o	X							X	
12-lead ECG	X ^p				X					X ^q		X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X								
Pulse oximetry ^r		-5 min to 1 hr ^r								X ^r		X ^r	X ^r	X ^r	X ^r	X ^r	X ^r									
Body weight	X																X ^h	X							X	
Clinician Administered Dissociative States Scale (CADSS) ^{j, s}		X		X		X	X			X ^s		X ^s	X ^s	X ^s	X ^s	X ^s	X ^s									
Brief Psychiatric Rating Scale: 4-item (BPRS+) ^{j, s}		X		X		X	X			X ^s		X ^s	X ^s	X ^s	X ^s	X ^s	X ^s									
Modified Observer's Assessment of Alertness/Sedation (MOAA/S) ^{j, t}		X ^t								X ^t		X ^t	X ^t	X ^t	X ^t	X ^t	X ^t									
Bladder Pain/Interstitial Cystitis-Symptom Score (BPIC-SS) ^{cc}		X												X ^h			X ^h				X					
Nasal tolerability questionnaire ¹		X				X				X ^{bb}		X ^{bb}	X ^{bb}	X ^{bb}	X ^{bb}	X ^{bb}	X ^{bb}									
Efficacy Assessments																										
Beck Scale for Suicidal Ideation (BSS): Recall period: Last week, including today ¹		X																								
Beck Scale for Suicidal Ideation (BSS): Recall period: Since last assessment ¹							X	X		X ^h	X	X ^h	X ^h	X ^h	X ^h	X ^h	X ^v	X		X	X	X	X	X	X	
Suicide Ideation and Behavior Assessment Tool (SIBAT) ^w		X					X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Montgomery Asberg Depression Rating Scale (MADRS) (Recall period: 7 days) ^j		X																		X	X	X	X	X	X	X
MADRS (Recall period: Since last assessment) ^j							X ^{dd}	X	X	X ^h	X	X ^h	X ^h	X ^h	X ^h	X ^h	X ^{h,v,dd}	X								
Beck Hopelessness Scale (BHS) Recall: Last 7 days ¹		X									X ^h						X ^h	X							X	

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Phase	Screening	Double-Blind Treatment																Follow Up ^a								
Visit Number	1	2						3	4	5	6 ^a	7 ^b	8 ^b	9 ^b	10 ^b	11 ^b	12 ^b	-	-	13	14	15	16	17	18	
Day	1 ^c	1						2	3	4	5	8	11	15	18	22	25	ET ^d		32	39	46	53	67	81	
		Pre dose	0 hr	40 min	1 hr	2 hr	4 hr																			
Beck Hopelessness Scale (BHS) Recall: Since last assessment ¹							X																			
Clinical Laboratory Assessments																										
Hematology, Chemistry	X ^e																X ^h	X								
Urinalysis	X ^e											X ^h					X ^h	X			X					
Pharmacokinetics																										
Blood sample collection										X ^f																
Biomarkers (optional site participation) ^{aa}																										
Blood sample collection (Inflammation MAP)		X											X ^h				X ^h	X								
Blood sample collection (metabolomics)		X											X ^h				X ^h	X								
Pharmacogenomics (DNA) - Optional																										
Blood sample collection										X ^g																
Ongoing Subject Review																										
Concomitant therapy	Continuous																									
Adverse events	Continuous																									

Footnotes:

^a Visit can be performed +/- 3 days.

^b Visit can be performed +/- 1 day. Intranasal treatment sessions cannot be given on consecutive days.

^c The subject should be screened (i.e., starting with the signing of the informed consent form) within 24 hours prior to intranasal dosing on Day 1. The screening phase may be extended to up to 48 hours prior to the first dose of intranasal study medication upon consultation with the Sponsor's medical monitor.

^d Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit, for reasons other than withdrawal of consent, will have an Early Termination (ET) visit conducted at the time of discontinuation. No additional study visits are required, but the investigator must ensure the subject is appropriately transitioned/monitored for any additional care required.

^e Not applicable for subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or for medical stabilization (following recent suicide attempt). These subjects will receive their first dose of study medication in the inpatient psychiatric unit.

^f For subjects dosed in the ER, it is recommended that subjects not be transferred from the ER to the inpatient psychiatric unit until after the 4 hour postdose assessments are completed.

^g The recommended duration of inpatient hospitalization is 5 days, with shorter or longer hospitalizations permitted if clinically warranted in the investigator's opinion.

^h Performed predose.

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- i In addition the scheduled time points, additional pregnancy, drug, and alcohol testing can be performed at the Investigator's discretion during the study.
- j Clinician-administered assessment.
- k Subjects will be asked to respond to Questions B5 and B9 of the MINI relative to their current state. The response to B5 must refer to the present, whereas the response to B9 may reflect the past 24 hours.
- l Subject-completed assessment.
- m On each dosing day, subjects will self-administer 1 spray into each nostril (i.e., 2 sprays per intranasal device) at each of the following 3 time points: t = 0, 5 minutes and 10 minutes, where time = 0 is defined as the time of the first 100-mcl spray. After Day 1, a one-time decrease to intranasal esketamine 56 mg or intranasal placebo, in a blinded manner, will be permitted if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. In this case, the subject would receive the decreased dose on all remaining dosing days.
- n Blood pressure, heart rate, respiratory rate, and temperature (tympanic recommended).
- o Blood pressure, heart rate, and respiratory rate at predose and at t = 40 minutes, 1 hour, and 2 hours postdose on each dosing day. Temperature at predose only on each dosing day.
- p At Screening, the ECG tracing will be sent to the central ECG laboratory but the investigator or sub-investigator is required to review the ECG locally to determine subject eligibility.
- q Performed predose and at 1 hour postdose on each dosing day from Day 4 to Day 25.
- r On each dosing day, continuous arterial oxygen saturation monitoring by pulse oximetry (SpO2) starting 5 minutes before first spray and, then after the first nasal spray (i.e., t = 0 hour) it will be monitored and documented every 15 minutes for approximately 1 hour postdose.
- s Performed predose, 40 minutes, 2 hours, and 4 hours postdose.
- t Performed every 5 minutes from t = - 5 min (predose) to 1 hour postdose, or longer, if necessary, until the subject has a score of 5. If a score of 5 is reached prior to 1 hour postdose, assessments are to still to continue through 1 hour postdose.
- u This visit is performed at Visit 6 (Day 5) OR on the actual day of discharge from inpatient hospitalization (if discharge does not occur on Day 5). For subjects who remain inpatient on Day 5, only continuous study procedures (adverse event and concomitant therapy recording) are required. If the actual day of discharge coincides with another scheduled study visit, with the exception of the SIBAT, all study procedures for the scheduled visit should be completed and duplicate assessments are not required; in this case, an Unscheduled Visit (that includes all of the required SIBAT modules for the actual day of discharge) should be completed in the electronic device for the SIBAT.
- v Performed at 4 hours postdose.
- w The SIBAT has both clinician-administered and subject-reported modules; not all modules are completed at every visit. A separate "SIBAT Time and Events Schedule" will be provided to all clinical sites (see Section 15. Study Specific Materials) which will outline which module(s) will be performed at each scheduled time point.
- x Samples will be collected for analysis by local laboratory (for eligibility) and central laboratory. If standard of care clinical laboratory tests are performed within 24 hours prior to the Screening visit (i.e., prior to signing of the ICF) the results for laboratory tests required per protocol at Screening can be used for determination of subject eligibility. In this case, after the subject signs the ICF, a sample(s) for the local laboratory is not required, but samples for the central laboratory are still required.
- y A 4 mL venous blood sample will be obtained for pharmacokinetic evaluations at the following time points: 1 sample will be obtained at t = between 30 minutes and 1 hour postdose and 1 sample will be obtained at t = between 2 and 5 hours postdose.
- z The optional pharmacogenomic (DNA) sample should be collected at the specified time point, however if necessary it may be collected at a later time point without constituting a protocol deviation.
- aa Optional site participation based on operational capabilities.
- bb Performed at predose and 2 hours postdose.

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- ^{cc} If a subject has a score greater than 18 on the BPIC-SS with no evidence of a urinary tract infection on urinalysis and microscopy, the subject will be referred to a specialist for evaluation.
- ^{dd} The sleep and appetite items will not be assessed at the 4 hours postdose time point on Day 1 and Day 25. The MADRS scores for the sleep and appetite items recorded predose on the same day will be carried forward.

Source: Trial SUI2001 protocol Time and Events Schedule (including Applicant footnotes), p. 30

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Statistical Analysis Plan

- The primary estimand was defined by the following four components:
 - Population: subjects with MDD who are at imminent risk of suicide
 - Endpoint: change from baseline to 24 hours post first dose (Day 2) in the MADRS total score
 - Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind phase.
 - Summary Measure: the difference in variable least square means.

Statistical Reviewer's Comment: The Applicant's estimand only contains four components instead of the current five components as the SAP was written in 2018 before ICH E9(R1) was finalized in Fall 2019. This estimand is acceptable from a statistics prospective.

- All efficacy analyses were conducted using the Intent-to-treat Analysis Set (ITT). The FAS population consisted of all randomized subjects who received at least one dose of esketamine and have the baseline and 4 hour post-dose MADRS evaluation.
- All statistical tests are carried out at a type I error rate of 10%.

Statistical Reviewer's Comment: The use of a higher type I error rate is acceptable for a learning phase study.

- For the primary endpoint of change in MADRS score from baseline to 4 hours (Δ MADRS), the primary analysis was an ANCOVA analysis. The model included fixed effect terms for treatment arm, baseline MADRS score, center, and standard-of-care antidepressant treatment (i.e., antidepressant monotherapy or an antidepressant plus augmentation therapy). The esketamine treatment effect was estimated using the least squares (LS) mean difference 4 hours from this ANCOVA model.
- The Applicant imputed missing data using last observation carried forward (LOCF).

Statistical Reviewer's Comment: The Applicant's LOCF, single imputation method may be acceptable for the 4-hour endpoint if a small number of patients do not have a 4-hour measurement.

Protocol Amendments

There were five amendments to the original protocol, with noteworthy changes highlighted below:

Amendment 1 (January 29, 2014):

- Removed use of the McLean Screening Instrument for Borderline Personality Disorder
- Allowed initiation of new psychotherapy after the end of the double-blind treatment phase
- Prohibited IN-administered decongestants

Amendment 2 (March 18, 2014):

- Added obsessive compulsive disorder to exclusion criteria
- Use of the BPIC-SS was added as a safety evaluation and secondary objective; if subject has a BPIC-SS score >18, with no evidence of a urinary tract infection on urinalysis and microscopy, subject will be referred for specialist evaluation
- Added pre-dose vital sign measurement on dosing days
- Noted that SIBAT will be both an efficacy and safety evaluation
- Added nasal tolerability questionnaire as a safety evaluation
- Revised MADRS scoring to carry forward the sleep and appetite item answers from pre-dose scores to the 4 hour post-dose scores on Day 1, for the rationale that sleep and appetite items are unlikely to change during a 4 hour interval between assessments
- The prohibited medications list was updated: PRN and chronic dehydroepiandrosterone (DHEA), fish oils, ginkgo, ginseng, and omega-3-fatty acids were allowed; thyroid hormone supplementation was changed from being stable from 6 weeks to being stable for 3 months prior to Day 1

Amendment 3 (July 2, 2014):

- Eligibility criteria updated: to reflect birth control must be used for 3 months (rather than 1 week) after the last dose of study drug, and excluding women who plan to become pregnant or breast-feed with same timeframe; removed allowance of subjects

testing positive for prescribed amphetamines, for subject safety

- Removed prohibition of new psychotherapy initiation during the double-blind phase
- Revised MADRS scoring to carry forward the sleep and appetite item answers from pre-dose scores to the 4 hour post-dose scores on Day 25 (in addition to Day 1)
- Recommended that the same rater does not perform efficacy (MADRS and SIBAT) and safety assessments (BPRS+, CADSS, MOAA/S) for an individual subject
- Added that pertinent individual items (e.g., suicidal thoughts on the MADRS) would be included in efficacy analysis
- The prohibited medications list was updated: statement added advising caution if TCAs prescribed; continuous use of lithium allowed, with statement clarifying not for bipolar disorder as excluded; PRN and continuous use of opioids allowed, with statement clarifying per clinician's judgment.

Amendment 4 (December 11, 2014):

- Screening phase was extended to permit up to 48 hours
- Clarified that inpatient admission could be shorter (or longer) than 5 days if clinically warranted
- Clarified that the inclusion criteria MINI questions B5 referred to present, and B9 may reflect past 24 hours
- Exclusion criteria updated: added subjects exhibiting traits but not meeting full DSM criteria for borderline personality disorder may be eligible on case-by-case basis; revised to moderate to severe alcohol or substance use disorder within 6 months prior to Screening (rather than meeting unspecified severity criteria, at Screening); updated uncontrolled hypertension from SBP >160 to >140 mmHg; updated positive urine screen substances to include PCP; updated to allow subjects with positive test for opiates, benzodiazepines, or barbiturates without prescription on a case-by-case basis
- The prohibited medications list was updated: chloramphenicol and HIV antiretroviral drugs were allowed; dextromethorphan and amphetamines were prohibited; diphenhydramine was allowed for PRN but not chronic use; non-benzodiazepine hypnotics, trazodone PRN, and antipsychotics PRN for insomnia were not allowed within 8 hours of study drug administration; anticoagulants, anticonvulsants, and oral steroids were allowed on a case-by-case basis; thyroid hormone supplementation was changed

back from being stable from 3 months to being stable for 6 weeks prior to Day 1; ECT specifically prohibited

Amendment 5 (October 21, 2015): Corrected error in inclusion criterion description of MINI Question B9.

Clinical Reviewer's Comment: The study period lasted from June 17, 2014, to February 1, 2016. Therefore, Amendments 4 and 5 could theoretically impact study results (Amendment 3 was enacted only 2 weeks after study start), but the specific revisions appear overall unlikely to do so. If indicated, examination of subjects with Screening >24 hours or baseline SBP >140 and ≤160 mmHg could be performed.

7.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study-related information were reviewed by an independent ethics committee or institutional review board before the start of the study. The Applicant attests that the study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

See Appendix 17.2 for details.

Patient Disposition

See Table 39 for Trial SUI2001 analysis sets. For subject disposition (including reasons for discontinuation) during the treatment phase (through Day 25) see Table 40, and during the follow-up phase (through Day 81) see Table 41. Esketamine and placebo will refer to esketamine plus SOC, or placebo plus SOC:

- Of the 94 subjects randomized, 26 were screen failures.
- Of the 68 subjects randomized, one subject in each treatment group was randomized, but did not receive treatment or enter the ITT set (one subject withdrew consent and one subject had an elevated BP prior to study drug administration and was withdrawn).
- Seventy-five percent of the esketamine group completed the double-blind treatment phase, somewhat more than the 68.8% of the placebo group.

- Ninety-one percent of the esketamine group completed the follow-up phase, similar to the 88.9% of the placebo group.
- Intent-to-treat (ITT) and safety analysis sets were the same for the double-blind phase, and for the follow-up phase.

Table 39. Trial SUI2001 Analysis Sets

	Placebo (N=32)	Esketamine 84 mg (N=36)	Total (N=68)
All randomized	32 (100.0%)	36 (100.0%)	68 (100.0%)
ITT	31 (96.9%)	35 (97.2%)	66 (97.1%)
Safety	31 (96.9%)	35 (97.2%)	66 (97.1%)
ITT (FU)	22 (68.8%)	27 (75.0%)	49 (72.1%)
Safety (FU)	22 (68.8%)	27 (75.0%)	49 (72.1%)

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

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Source: Trial SUI2001 clinical study report Table 4, p. 69

Abbreviations: FU = follow-up, ITT = intent-to-treat

Table 40. Trial SUI2001 Treatment Phase Subject Disposition

	Placebo (N=32)	Esketamine 84 mg (N=36)	Total (N=68)
Completed	22 (68.8%)	27 (75.0%)	49 (72.1%)
Withdrawn	10 (31.3%)	9 (25.0%)	19 (27.9%)
Adverse event	1 (3.1%)	5 (13.9%)	6 (8.8%)
Lack of Efficacy	4 (12.5%)	1 (2.8%)	5 (7.4%)
Lost to follow-up	2 (6.3%)	0	2 (2.9%)
Withdrawal of consent	1 (3.1%)	1 (2.8%)	2 (2.9%)
Other	2 (6.3%)	2 (5.6%)	4 (5.9%)

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Source: Trial SUI2001 clinical study report Table 5, p. 70

Table 41. Trial SUI2001 Follow-Up Phase Subject Disposition

	Placebo (N=22)	Esketamine 84 mg (N=27)	Total (N=49)
Completed	20 (90.9%)	24 (88.9%)	44 (89.8%)
Withdrawn	2 (9.1%)	3 (11.1%)	5 (10.2%)
Lost to follow-up	1 (4.5%)	1 (3.7%)	2 (4.1%)
Withdrawal of consent	1 (4.5%)	1 (3.7%)	2 (4.1%)
Other	0	1 (3.7%)	1 (2.0%)

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Source: Trial SUI2001 clinical study report Table 6, p. 71

Clinical Reviewer's Comment: During the double-blind phase, more subjects in the esketamine group withdrew for AEs than the placebo group (13.9% versus 3.1%). Conversely, more subjects in the placebo group withdrew for lack of efficacy than the esketamine group (12.5% versus 2.8%). Esketamine appears to have been less tolerated. It is possible that if subjects were unintentionally unblinded given the lack of an active placebo, they may have been more inclined to drop out of the study. Otherwise, generally similar numbers of subjects completed the double-blind and follow-up phases, and left for other reasons, between groups.

Protocol Violations/Deviations

See Table 42 for major protocol deviations for Trial SUI2001, reported in 27.9% of subjects across both treatment arms. Overall, similar numbers of subjects with major protocol deviations occurred in both treatment groups. No subjects appear to have been withdrawn for protocol violations (see Table 40 and Table 41).

Table 42. Trial SUI2001 Major Protocol Deviations

	Placebo (N=32)	Esketamine 84 mg (N=36)	Total (N=68)
No. of subjects with protocol deviations	9 (28.1%)	10 (27.8%)	19 (27.9%)
Selection criteria not met	1 (3.1%)	1 (2.8%)	2 (2.9%)
Other	9 (28.1%)	9 (25.0%)	18 (26.5%)

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

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Source: Trial SUI2001 clinical study report Table 10, p. 78

Abbreviations: No. = number

Regarding subjects who entered but did not satisfy criteria, one subject in each group was taking a prohibited medication: one subject in the placebo group was taking methylphenidate

during the double-blind phase, and one subject in the esketamine group was taking lithium (which was later removed from the list of prohibited medications in Amendment 3 as noted above).

Regarding subjects who received the wrong treatment or incorrect dose of study drug (which the Applicant did not specify as a separate group in their table), two subjects in the esketamine group received a reduced dose of study drug due to staff error with the IWRS entry (on one dosing day for one subject, and two days for the other).

No subjects developed withdrawal criteria but were not withdrawn. Regarding “other” major protocol deviations, nine were reported in each group, including of note:

- Failure to attend all scheduled site visits during the double-blind phase, resulting in subjects not receiving the designated dose of study drug (3 placebo, 1 esketamine)
- Failure of site to perform/complete all assessments, including at the correct time point, during the double-blind phase, follow-up phase, or at the early termination visit, either because of lack of attendance or site error (7 placebo, 6 esketamine)
- Incomplete analysis of serum and/or urine samples by screening labs to determine subject eligibility (2 esketamine)

Clinical Reviewer’s Comment: Given the relatively small study size, the incidence of protocol deviations across all treatment arms makes for a higher percentage than the phase 3 trials (27.9% overall, with nearly identical numbers between treatment groups, compared to 12.8% and 14.8% overall for Trials SUI3001 and SUI3002, respectively). Although some deviations may impact efficacy or safety findings for individual subjects, most appear unlikely to significantly affect the study conclusions because they occurred at a relatively low rate compared to the overall study population and were relatively balanced between groups. However, the only deviation that occurred in a larger number of subjects was failure of site to perform/complete all assessments, either because of lack of attendance or site error. The Applicant did not clarify what actions were taken, if any, to manage the deviations. The Applicant did not consider any of the deviations to impact the conclusions of the study.

Table of Demographic Characteristics

See Table 43 for a summary of ITT analysis set demographic and baseline characteristics for Trial SUI2001. Overall, subjects were 65.2% female and 34.8% male. Overall, the mean age was similar between groups (overall mean 35.8±13.03 years), and generally similarly distributed among age groups. A little over half of subjects were White, and 37.9% were Black or African American. Almost a quarter of subjects were enrolled at the Atlanta site; around 10% each

were enrolled at New Haven, Birmingham, Cincinnati, Philadelphia, and San Diego; and <10% were enrolled at each of the remaining sites. Subjects were generally enrolled equally across groups at each site. Weight and body mass index (BMI) were generally comparable across groups; the esketamine group was slightly heavier with an overall mean BMI of 29.0 ± 8.08 versus 26.8 ± 6.62 kg/m² for the placebo group.

As randomized AD SOC and as received AD SOC, significantly more subjects overall were assigned to AD monotherapy than AD plus augmentation therapy, and were roughly similar between groups. With as received AD SOC, a number of subjects received both AD monotherapy and AD plus augmentation therapy (9.0% in the placebo group, and 3.6% in the esketamine group).

Table 43. Trial SUI2001 Intent-To-Treat Analysis Set Demographic and Baseline Characteristics

Demographic Parameters	Placebo + SOC (N=31) n (%)	Esk + SOC (N=35) n (%)	Total (N=66) n (%)
Sex			
Female	21 (67.7%)	22 (62.9%)	43 (65.2%)
Male	10 (32.3%)	13 (37.1%)	23 (34.8%)
Age (years)			
Mean (SD)	36.0 (12.82)	35.7 (13.40)	35.8 (13.03)
Median	31.0	32.0	31.5
Min, max	19, 64	19, 64	19, 64
18 to 34	18 (58.1%)	18 (51.4%)	36 (54.5%)
35 to 54	10 (32.3%)	12 (34.3%)	22 (33.3%)
55 to 64	3 (9.7%)	5 (14.3%)	8 (12.1%)
Race			
White	15 (48.4%)	20 (57.1%)	35 (53.0%)
Black or African American	13 (41.9%)	12 (34.3%)	25 (37.9%)
Other	2 (6.5%)	0	2 (3.0%)
Not reported	0	2 (5.7%)	2 (3.0%)
Asian	0	1 (2.9%)	1 (1.5%)
Multiple	1 (3.2%)	0	1 (1.5%)
Ethnicity			
Not Hispanic or Latino	29 (93.5%)	31 (88.6%)	60 (90.9%)
Hispanic or Latino	1 (3.2%)	4 (11.4%)	5 (7.6%)
Not reported	1 (3.2%)	0	1 (1.5%)
Site			
Atlanta, GA	8 (25.8%)	8 (22.9%)	16 (24.2%)
New Haven, CT	4 (12.9%)	5 (14.3%)	9 (13.6%)
Birmingham, AL	4 (12.9%)	3 (8.6%)	7 (10.6%)
Cincinnati, OH	4 (12.9%)	3 (8.6%)	7 (10.6%)
Philadelphia, PA	4 (12.9%)	3 (8.6%)	7 (10.6%)
San Diego, CA	3 (9.7%)	4 (11.4%)	7 (10.6%)

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Iowa City, IA	1 (3.2%)	4 (11.4%)	5 (7.6%)
Baltimore, MD	2 (6.5%)	2 (5.7%)	4 (6.1%)
Hartford, CT	0	2 (5.7%)	2 (3.0%)
Ann Arbor, MI	1 (3.2%)	0	1 (1.5%)
Towson, MD	0	1 (2.9%)	1 (1.5%)
Weight (kg)			
Mean (SD)	76.1 (18.83)	83.5 (23.86)	80.0 (21.79)
Median	75.0	77.1	75.4
Range	48, 110	51, 149	48, 149
Body Mass Index (kg/m ²)			
Mean (SD)	26.8 (6.62)	29.0 (8.08)	28.0 (7.46)
Median	25.0	28.0	26.4
Range	18, 41	17, 48	17, 48
Underweight (<18.5)	2 (6.5%)	1 (2.9%)	3 (4.5%)
Normal (18.5 to <25)	13 (41.9%)	13 (37.1%)	26 (39.4%)
Overweight (25 to <30)	6 (19.4%)	6 (17.1%)	12 (18.2%)
Obese (30 to <40)	9 (29.0%)	12 (34.3%)	21 (31.8%)
Severe Obesity (≥40)	1 (3.2%)	3 (8.6%)	4 (6.1%)
SOC AD Treatment as Randomized			
AD Monotherapy	25 (80.6%)	25 (71.4%)	50 (75.8%)
AD Plus Augmentation Therapy	6 (19.4%)	10 (28.6%)	16 (24.2%)
SOC AD Treatment as Received			
AD Monotherapy	22 (71.0%)	24 (68.6%)	46 (69.7%)
AD Plus Augmentation Therapy	5 (16.1%)	9 (25.7%)	14 (21.2%)
AD Monotherapy / AD Plus Augmentation Therapy*	4 (12.9%)	2 (5.7%)	6 (9.1%)

Source: Adapted from Trial SUI3002 clinical study report Table 7, p. 72, and ADSL and ADVS datasets

Abbreviations: AD = antidepressant; Esk = esketamine, SD = standard deviation, SOC = standard of care

* Subjects received both AD monotherapy and AD plus augmentation therapy

Clinical Reviewer's Comment: Overall, sex and age parameters were generally representative of U.S. patient populations, if perhaps younger with a mean overall age of 35.8±13.03 years, and relatively similar between treatment groups. Race and ethnicity parameters were not representative of the U.S. population, with African Americans overrepresented (37.9% in the study versus 13.4% in the U.S. population, per the U.S. Census Bureau). Hispanic or Latino and Asian populations were underrepresented (7.6% in the study versus 18.3 % in the U.S. population, and 1.5% in the study versus 5.9% in the U.S. population, per the U.S. Census Bureau, respectively).

A significantly larger portion of overall subjects were assigned to SOC AD monotherapy (75.8%) than AD plus augmentation therapy (24.2%). The Applicant presented SOC AD treatment as randomized, and as received, because some subjects did not remain on the SOC AD that was assigned on Day 1 prior to randomization. Even so, the majority received AD monotherapy (69.7%). For unclear reasons, the size of the difference

between the subjects in the two SOC options was larger in this trial than the phase 3 trials.

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

See Table 44 for baseline psychiatric history characteristics. Overall, these were similar between treatment groups. Of note, the mean MADRS total score was 38.6 ± 6.53 SD, indicating a severely depressed population (range 20 to 52; presumably the subject with a score of 20 screened higher). Based on the SIBAT, 62.1% of subjects overall had a history of at least one suicide attempt, and of those subjects, 58.5% had attempted within the past month. MADRS, SIBAT, CGJ-SR, MINI, BSS, and BHS suicidal parameters were similar between groups. The Applicant did not collect MDD episode or hospitalization history as in the phase 3 trials.

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Table 44. Trial SUI2001 Intent-to-Treat Analysis Set Baseline Psychiatric History Characteristics

	Placebo (N=31)	Esketamine 84 mg (N=35)	Total (N=66)
Baseline MADRS Total Score			
N	31	35	66
Mean (SD)	38.8 (7.02)	38.5 (6.17)	38.6 (6.53)
Median	40.0	38.0	38.5
Range	(20; 52)	(27; 49)	(20; 52)
Baseline SIBAT(Module 2): Prior Thought on Suicide, n (%)			
N	31	34	65
Yes	31 (100.0%)	34 (100.0%)	65 (100.0%)
No	0	0	0
Baseline SIBAT(Module 2): Past Suicide Attempts, n (%)			
N	31	35	66
0	10 (32.3%)	15 (42.9%)	25 (37.9%)
≥1	21 (67.7%)	20 (57.1%)	41 (62.1%)
Baseline SIBAT(Module 2): Most Recent Attempts, n (%)			
N	21	20	41
Within The Last Month	13 (61.9%)	11 (55.0%)	24 (58.5%)
1-6 Month Ago	1 (4.8%)	2 (10.0%)	3 (7.3%)
1-5 Years Ago	3 (14.3%)	2 (10.0%)	5 (12.2%)
5-10 Years Ago	1 (4.8%)	2 (10.0%)	3 (7.3%)
More than 10 Years Ago	3 (14.3%)	3 (15.0%)	6 (14.6%)
Baseline SIBAT(Module 6): My Self-Assessment of Suicide Risk: Which rating best describes your intent for suicide right now, n (%)			
N	31	35	66
None	3 (9.7%)	3 (8.6%)	6 (9.1%)
Very weak/Weak/Moderately weak	8 (25.8%)	7 (20.0%)	15 (22.7%)
Mild	6 (19.4%)	6 (17.1%)	12 (18.2%)
Moderate/Moderately strong	9 (29.0%)	10 (28.6%)	19 (28.8%)
Strong	3 (9.7%)	5 (14.3%)	8 (12.1%)
Extremely strong/Extremely strong and constant	2 (6.5%)	4 (11.4%)	6 (9.1%)
Baseline SIBAT(Module 8): Clinical Global Judgment of Suicide Risk, n (%)			
N	31	35	66
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	1 (3.2%)	0	1 (1.5%)
5	16 (51.6%)	15 (42.9%)	31 (47.0%)
6	14 (45.2%)	20 (57.1%)	34 (51.5%)

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	Placebo (N=31)	Esketamine 84 mg (N=35)	Total (N=66)
MINI B5: Think about suicide (killing yourself): Y/N, n (%)			
N	31	35	66
Yes	31 (100.0%)	35 (100.0%)	66 (100.0%)
No	0	0	0
MINI B5: Think about suicide (killing yourself): frequency, n (%)			
N	31	35	66
Occasionally	5 (16.1%)	5 (14.3%)	10 (15.2%)
Often	9 (29.0%)	11 (31.4%)	20 (30.3%)
Very Often	17 (54.8%)	19 (54.3%)	36 (54.5%)
MINI B5: Think about suicide (killing yourself): Intensity, n (%)			
N	31	35	66
Mild	1 (3.2%)	0	1 (1.5%)
Moderate	9 (29.0%)	12 (34.3%)	21 (31.8%)
Severe	21 (67.7%)	23 (65.7%)	44 (66.7%)
MINI B9: Intent to act on thoughts of killing yourself (Y/N), n (%)			
N	31	35	66
Yes	31 (100.0%)	35 (100.0%)	66 (100.0%)
No	0	0	0
Baseline BSS Total Score			
N	31	34	65
Mean (SD)	21.4 (8.28)	24.0 (5.45)	22.8 (7.01)
Median	23.0	25.0	24.0
Range	(1; 38)	(8; 33)	(1; 38)
Baseline BSS-5			
N	31	35	66
Mean (SD)	6.2 (2.61)	7.3 (2.11)	6.8 (2.41)
Median	7.0	8.0	7.0
Range	(1; 10)	(2; 10)	(1; 10)
Baseline BHS Total Score			
N	30	35	65
Mean (SD)	15.5 (4.59)	16.5 (2.91)	16.0 (3.79)
Median	16.0	17.0	17.0
Range	(0; 20)	(9; 20)	(0; 20)

Source: Adapted from Trial SUI2001 clinical study report Table 9, p. 74

Abbreviations: BHS = Beck Hopelessness Scale, BSS = Beck Scale for Suicidal Ideation, MADRS = Montgomery-Åsberg Depression Rating Scale, MINI = Mini International Neuropsychiatric Interview, SD = standard deviation, SIBAT = Suicidal Ideation and Behavior Assessment Tool

Clinical Reviewer's Comment: Baseline psychiatric history characteristics, including severity of depression, suicide attempt history, and suicidality parameters (e.g.,

frequency or severity of thinking or CGJ-SR scoring) appear balanced between treatment groups.

See Table 45 for safety analysis set prior medications of special interest, including ADs, second generation antipsychotics, benzodiazepines, lithium, lamotrigine, buspirone, and hydroxyzine. Unlisted medications include: alprazolam, taken by two (6.5%) placebo subjects and four (11.4%) esketamine subjects; and zolpidem, taken by one (3.2%) placebo subject and three (8.6%) esketamine subjects. Overall, 34 of 66 (51.5%) subjects were taking one of these listed medications, roughly similar between treatment groups.

Table 45. Trial SUI2001 Safety Analysis Set Prior Medications of Special Interest

	Placebo (N=31)	Esketamine 84 mg (N=35)
No. of subjects with prior antidepressants	15 (48.4%)	19 (54.3%)
Mirtazapine	1 (3.2%)	4 (11.4%)
Fluoxetine	3 (9.7%)	3 (8.6%)
Venlafaxine	1 (3.2%)	3 (8.6%)
Aripiprazole	0	2 (5.7%)
Citalopram	1 (3.2%)	2 (5.7%)
Escitalopram	2 (6.5%)	2 (5.7%)
Olanzapine	0	2 (5.7%)
Sertraline	5 (16.1%)	2 (5.7%)
Antidepressants	0	1 (2.9%)
Bupropion	2 (6.5%)	1 (2.9%)
Buspirone	0	1 (2.9%)
Desvenlafaxine	0	1 (2.9%)
Lamotrigine	0	1 (2.9%)
Lithium	0	1 (2.9%)
Quetiapine	2 (6.5%)	1 (2.9%)
Clonazepam	1 (3.2%)	0
Doxepin	1 (3.2%)	0
Duloxetine	1 (3.2%)	0
Hydroxyzine	1 (3.2%)	0
Lorazepam	1 (3.2%)	0
Paroxetine	2 (6.5%)	0
Trazodone	1 (3.2%)	0

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Source: Trial SUI2001 clinical study report Attachment TSICM01

Abbreviations: No. = number

Clinical Reviewer's Comment: Overall, given the small numbers involved, it appears unlikely that the differences between treatment groups in terms of individual medications would make a significant impact.

Concomitant or Rescue Medication Use and Treatment Compliance

See Table 46 and Table 47 for safety analysis set treatment phase and follow-up phase

(respectively) concomitant medications of special interest, including ADs; antipsychotics; mood stabilizers and antiepileptics; benzodiazepines; and non-benzodiazepine hypnotics and anxiolytics. The Applicant presented separate data for concomitant medications versus SOC received; where these numbers were different, the medication is presented additionally as SOC. The Applicant did not specify particular rescue medications, but benzodiazepines and non-benzodiazepine hypnotics and anxiolytics are of interest. Overall, medication use was generally similar between treatment groups, and nearly identical for benzodiazepines and non-benzodiazepine hypnotics and anxiolytics. Three subjects (at three different sites) received haloperidol as a PRN (though one subject appears to have also added it as a standing medication near the end of the follow-up phase on Day 77).

Clinical Reviewer's Comment: Of note but not unexpectedly, benzodiazepine and non-benzodiazepine hypnotic and anxiolytic use increased from pre-treatment during the double-blind phase, then dropped again in the follow-up phase. Overall, concomitant medication use during the double-blind and follow-up phases (including as SOC) appears relatively balanced between treatment groups and unlikely to impact study results.

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Table 46. Trial SUI2001 Safety Analysis Set Treatment Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC	Esk + SOC	Total
- Medication as SOC if different usage	(N=31)	(N=35)	(N=66)
	n (%)	n (%)	n (%)
Antidepressants			
Sertraline (/as SOC)	10 (32.3%)	8 (22.9%)	18 (27.3%)
Fluoxetine (/as SOC)	4 (12.9%)	7 (20.0%)	11 (16.7%)
Citalopram	7 (22.6%)	6 (17.1%)	13 (19.7%)
Citalopram as SOC	6 (19.4%)	6 (17.1%)	12 (18.2%)
Venlafaxine (/as SOC)	4 (12.9%)	4 (11.4%)	8 (12.1%)
Escitalopram (/as SOC)	4 (12.9%)	3 (8.6%)	7 (10.6%)
Bupropion (/as SOC)	5 (16.1%)	2 (5.7%)	7 (10.6%)
Antipsychotics			
Quetiapine	6 (19.4%)	4 (11.4%)	10 (15.2%)
Quetiapine as SOC	6 (19.4%)	3 (8.6%)	9 (13.6%)
Aripiprazole	3 (9.7%)	6 (17.1%)	9 (13.6%)
Aripiprazole as SOC	2 (6.5%)	6 (17.1%)	8 (12.1%)
Haloperidol (not as SOC)	0	3 (8.6%)	3 (4.5%)
Risperidone	0	2 (5.7%)	2 (3.0%)
Risperidone as SOC	0	1 (2.9%)	1 (1.5%)
Mood Stabilizers and Antiepileptics			
Lamotrigine	1 (3.2%)	2 (5.7%)	3 (4.5%)
Lamotrigine as SOC	0	1 (2.9%)	1 (1.5%)
Lithium	0	2 (5.7%)	2 (3.0%)
Lithium as SOC	0	1 (2.9%)	1 (1.5%)
Gabapentin (not as SOC)	2 (6.5%)	0	2 (3.0%)
Benzodiazepines			
Lorazepam	10 (32.3%)	10 (28.6%)	20 (30.3%)
Clonazepam	5 (16.1%)	5 (14.3%)	10 (15.2%)
Alprazolam	3 (9.7%)	3 (8.6%)	6 (9.1%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Hydroxyzine	5 (16.1%)	4 (11.4%)	9 (13.6%)
Zolpidem	3 (9.7%)	4 (11.4%)	7 (10.6%)
Diphenhydramine	3 (9.7%)	3 (8.6%)	6 (9.1%)

Source: Adapted from Trial SUI2001 clinical study report Attachments TSICM02 and TSICM03

Abbreviations: Esk = esketamine, SOC = standard of care

Table 47. Trial SUI2001 Safety Analysis Set Follow-Up Phase Concomitant Medications of Special Interest

Medication Class			
Medication Name (Top 3 used per class, or if by >10% of total subjects)	Placebo + SOC	Esk + SOC	Total
- Medication as SOC if different usage	(N=22)	(N=27)	(N=49)
	n (%)	n (%)	n (%)
Antidepressants			
Sertraline (/as SOC)	6 (27.3%)	6 (22.2%)	12 (24.5%)
Fluoxetine	1 (4.5%)	8 (29.6%)	9 (18.4%)
Fluoxetine as SOC	1 (4.5%)	6 (22.2%)	7 (14.3%)
Citalopram	3 (13.6%)	5 (18.5%)	8 (16.3%)
Citalopram as SOC	3 (13.6%)	4 (14.8%)	7 (14.3%)
Venlafaxine (/as SOC)	4 (18.2%)	3 (11.1%)	7 (14.3%)
Escitalopram (/as SOC)	4 (18.2%)	2 (7.4%)	6 (12.2%)
Antipsychotics			
Quetiapine	7 (31.9%)	5 (18.5%)	12 (24.5%)
Quetiapine as SOC	6 (27.3%)	4 (14.8%)	10 (20.4%)
Aripiprazole (/as SOC)	1 (4.5%)	5 (18.5%)	6 (12.2%)
Haloperidol (not as SOC)	0	2 (7.4%)	2 (4.1%)
Risperidone (/as SOC)	0	1 (3.7%)	1 (2.4%)
Mood Stabilizers and Antiepileptics			
Lamotrigine	2 (9.1%)	3 (11.1%)	5 (10.2%)
Lamotrigine as SOC	1 (4.5%)	2 (7.4%)	3 (6.1%)
Gabapentin (not as SOC)	1 (4.5%)	0	1 (2.4%)
Lithium (/as SOC)	0	1 (3.7%)	1 (2.4%)
Benzodiazepines			
Lorazepam	2 (9.1%)	4 (14.8%)	6 (12.2%)
Clonazepam	2 (9.1%)	3 (11.1%)	5 (10.2%)
Alprazolam	2 (9.1%)	0	2 (4.1%)
Non-benzodiazepine Hypnotics / Anxiolytics			
Diphenhydramine	2 (9.1%)	4 (14.8%)	6 (12.2%)
Hydroxyzine	3 (13.6%)	2 (7.4%)	5 (10.2%)
Zolpidem	2 (9.1%)	1 (3.7%)	3 (6.1%)

Source: Adapted from Trial SUI2001 clinical study report Attachments TSICM05 and TSICM06

Abbreviations: Esk = esketamine, SOC = standard of care

Regarding treatment compliance, the Applicant reported that doses of IN study agent were self-administered by subjects at the study site under the direct supervision of the investigator or designee. The investigator or designee maintained a log of all study medication dispensed and returned, and drug supplies were inventoried and accounted for throughout the study.

In terms of exposure, 64.5% of subjects in the placebo group and 74.3% of subjects in the esketamine group received study agent on all 8 days during the double-blind phase. As noted

previously, more subjects in the esketamine group withdrew for AEs, and more subjects withdrew for lack of efficacy in the placebo group. See Table 48 for a summary of exposure to study agent by number of days exposed.

Table 48. Trial SUI2001 Intent-To-Treat Set Summary of Exposure to Study Agent

Number of Days Dosed	Placebo + SOC (N=31) n (%)	Esketamine + SOC (N=35) n (%)
1	1 (3.2%)	4 (11.4%)
2	2 (6.5%)	0
3	0	2 (5.7%)
4	1 (3.2%)	0
5	1 (3.2%)	1 (2.9%)
6	3 (9.7%)	1 (2.9%)
7	3 (9.7%)	1 (2.9%)
8	20 (64.5%)	26 (74.3%)

Source: Adapted from Trial SUI2001 clinical study report Table 11, p. 79

Abbreviations: SOC = standard of care

During the double-blind phase, five of 35 (14.3%) of subjects in the esketamine group had a dose reduction from 84 to 56 mg; three subjects for an AE, and two subjects were reduced in error as noted previously in major protocol deviations.

Clinical Reviewer's Comment: It appears a larger portion of esketamine subjects who discontinued treatment did so after the first dose. Overall, a larger percentage of esketamine subjects received all eight doses compared to the placebo group, though a large percentage (19.4%) of placebo subjects received 6 to 7 doses. For the two subjects with reduced doses in error, the Applicant had noted that occurred on one day for one subject and two days for the other. For the three subjects who reduced dose for AEs, the Applicant did not specify, but presumably the reduction was for all subsequent doses as per protocol. If necessary a subgroup analysis of subjects receiving 56 mg doses of esketamine may be performed.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint of change from baseline to 4 hours total MADRS score showed a 5.3 (two-sided $p = 0.015$) point greater decline in the esketamine arm compared to placebo, see Table 49. The esketamine arm declined 14 points from an average baseline score of 38.5 points. See Table 49 for the placebo arm values. P-values were compared to an alpha level of 0.10.

Table 49. MADRS Total Score: Change From Baseline to 4-Hour Post-dose ANCOVA LOCF (SUI2001: ITT)

	Placebo (N=31)	Esketamine 84 mg (N=35)
Baseline(DB)		
N	31	35
Mean (SD)	38.8 (7.02)	38.5 (6.17)
Median (Range)	40.0 (20; 52)	38.0 (27; 49)
Day 1(DB): 4H		
N	31	35
Mean (SD)	29.7 (11.28)	25.1 (9.67)
Median (Range)	30.0 (3; 52)	23.0 (7; 48)
Change from Baseline to Day 1(DB): 4H		
N	31	35
Mean (SD)	-9.1 (8.38)	-13.4 (9.03)
Median (Range)	-6.0 (-25; 0)	-14.0 (-32; 1)
P-value (minus Placebo)(a)		0.015
Diff. of LS Means (SE)		-5.3 (2.10)

(a) Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), antidepressant therapy (AD monotherapy, AD plus augmentation therapy) and analysis center as factors, and baseline value as a covariate.

Note: Negative change in score indicates improvement.

Note: Baseline is the predose, Day 1 value.

Source: Applicant's CSR.

Data Quality and Integrity

The data were of sufficient quality to permit review.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoint of MADRS total score change from baseline to 24 hours (Day 2) showed a 7.2 (two-sided $p = 0.015$) point greater decline in the esketamine arm compared to placebo, see Table 50. The esketamine arm declined 19 points from an average baseline score of 38.5 points. See Table 50 for the placebo arm values. P-values were compared to an alpha level of 0.10.

Table 50. MADRS Total Score: Change From Baseline to 24-Hours Post-dose ANCOVA LOCF (SUI2001: ITT)

	Placebo (N=31)	Esketamine 84 mg (N=35)
Baseline(DB)		
N	31	35
Mean (SD)	38.8 (7.02)	38.5 (6.17)
Median (Range)	40.0 (20; 52)	38.0 (27; 49)
Day 2(DB)		
N	31	35
Mean (SD)	26.0 (12.85)	19.2 (11.23)
Median (Range)	25.0 (4; 49)	18.0 (3; 42)
Change from Baseline to Day 2(DB)		
N	31	35
Mean (SD)	-12.8 (9.77)	-19.3 (12.02)
Median (Range)	-10.0 (-33; 1)	-19.0 (-41; 1)
P-value (minus Placebo)(a)		0.015
Diff. of LS Means (SE)		-7.2 (2.85)

(a) Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), antidepressant therapy (AD monotherapy, AD plus augmentation therapy) and analysis center as factors, and baseline value as a covariate.

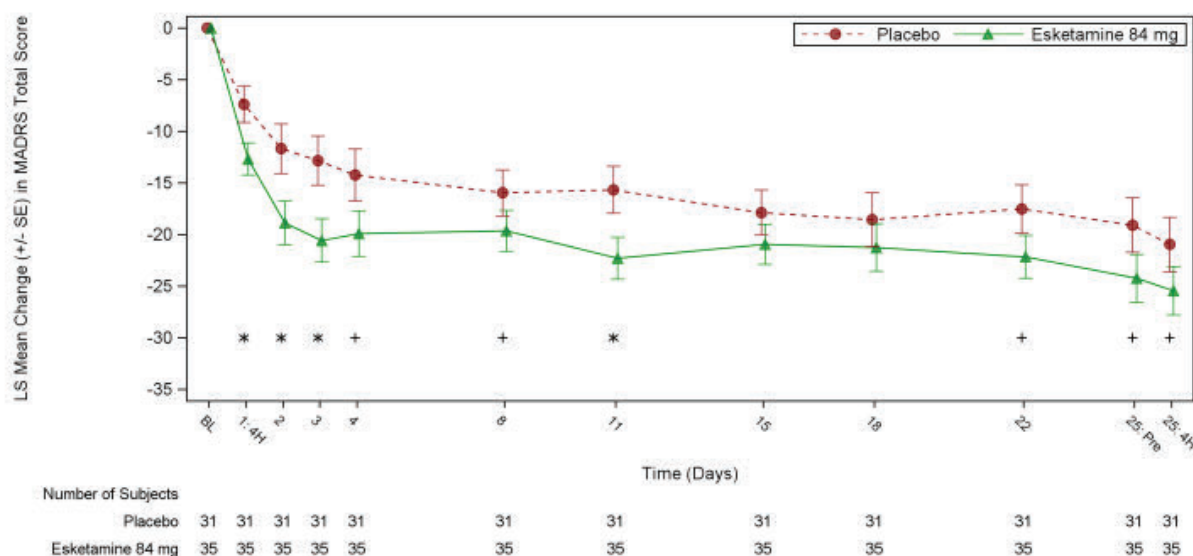
Note: Negative change in score indicates improvement.

Note: Baseline is the predose, Day 1 value.

Source: Applicant's CSR.

Clinical Reviewer's Comment: The primary efficacy endpoint of change from baseline in MADRS total score at 4 hours and the secondary endpoint at 24 hours were both statistically significant, and both with a substantial amount of treatment difference, especially at 24 hours.

On the secondary efficacy endpoint of MADRS total score change from baseline to endpoint of the double-blind phase (Day 25), esketamine's separation from placebo fell short of statistical significance, with a LS-means treatment difference of -4.5 (two-sided p-value = 0.159), for a total decrease of -26.4 points from baseline for the esketamine group. See Figure 22 for MADRS total score change from baseline over the double-blind treatment phase.

Figure 22. MADRS Total Score – LS Mean ($\pm$ SE) Change from Baseline over Time – ANCOVA LOCF (SUI2001: ITT)

Note: LS Mean and SE were based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), antidepressant therapy

(AD monotherapy, AD plus augmentation therapy) and analysis center as factors, and baseline value as a covariate.

Note: Negative change in score indicates improvement.

Note: Baseline is the predose, Day 1 value

Note: + two-sided $p < 0.2$, * two-sided $p < 0.05$.

Source: Applicant's CSR

Dose/Dose Response

Clinical Reviewer's Comment: Given that the majority of esketamine subjects (85.7%) did not require a dose reduction (as previously discussed) and that dose reductions occurred at various timepoints, a dose-response analysis does not appear useful.

Durability of Response

Clinical Reviewer's Comment: As seen in Figure 22, treatment with esketamine was numerically favored over placebo at all timepoints in the double-blind phase on the primary efficacy endpoint, which is supportive of a durable response, although as noted the treatment difference failed to reach statistical significance at the endpoint of the double-blind phase.

Persistence of Effect

On the exploratory efficacy endpoint of change in MADRS total score from baseline to endpoint of the follow-up phase (Day 81), esketamine's separation from placebo fell short of statistical significance, with a LS-means treatment difference of -4.1 (two-sided p-value = 0.211), for a total decrease of -26.4 points from baseline for the esketamine group

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Given Trial SUI2001's supportive study status in the MDSI program, other efficacy results will not be reviewed here.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted on SUI2001.

7.4. Integrated Review of Effectiveness

7.4.1. Assessment of Efficacy Across Trials

In Trial SUI3001 and Trial SUI3002, esketamine plus standard of care demonstrated statistical superiority on the primary endpoint (MADRS total score change from baseline to 24 hours (Day 2)) compared to placebo nasal spray plus standard of care. Esketamine plus standard of care did not demonstrate superiority on the key secondary endpoint (CGI-SS-R change from baseline to 24 hours (Day 2)) compared to placebo nasal spray plus standard of care.

Primary Endpoints

Table 51 summarizes the primary endpoint efficacy results from the phase 3 MDSI studies.

Table 51. Primary Efficacy Results for Change From Baseline in MADRS Total Score at 24 Hours

Study	Placebo		Esketamine		LS Mean Difference (95% CI)	Two-sided p-value
	N	LS Mean (SE)	N	LS Mean (SE)		
SUI3001	112	-12.7 (0.97)	111	-16.5 (0.97)	-3.82 (-6.60, -1.04)	0.0064
SUI3002	113	-12.1 (0.97)	114	-16.0 (0.97)	-3.85 (-6.60, -1.11)	0.0062

Source: Statistical Reviewer

Abbreviations: CI = confidence interval, LS = least-squares, MADRS = Montgomery-Åsberg Depression Rating Scale, SE = standard error

Clinical Relevance of Primary Endpoint:

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 commonly used range follows (Herrmann et al. 1998):

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

In Trial SUI3001, the mean baseline MADRS total score was 41.3 ± 5.87 (SD) for the esketamine group, and, in Trial SUI3002, was 39.5 ± 5.19 (SD), reflecting the severity of illness in this population. Treatment response is generally defined in most research literature as a $\geq 50\%$ reduction in symptoms (e.g., MADRS total score; Riedel et al. 2010). The mean numerical differences from baseline MADRS total score to 24 hours in Trial SUI3001 and Trial SUI3002 (i.e., -16.5 and -16.0, respectively) fall short of that definition of response (i.e., $\geq 50\%$ reduction in total scores would be differences of -20.6 and -19.6, respectively); rather, the study differences represent a 40.0% and a 40.5% reduction in total scores, respectively.

The overall context of these results is clearly important in evaluating clinical meaningfulness, including the intended use, the timing of evaluation, the population, and the persistence of effect. In the studies, esketamine treatment was started with initiation or optimization of oral antidepressant treatment (either as monotherapy or with augmentation), with the intention to demonstrate benefit while awaiting onset of action of standard antidepressants. (Reportedly oral antidepressant effects should start Week 2 and increase from there, although some meta-analyses indicate response as early as the end of Week 1 (Taylor et al. 2006).) Therefore the timing of the evaluation, at 24 hours, is much sooner than other antidepressant evaluations (generally conducted at 4 to 6 weeks). This is a significantly ill population, with mean baseline MADRS scores higher than most previous antidepressant trials' mean baseline scores of 28 to 36 (and the TRD3001 study's mean baseline score of 37.6) including symptoms requiring inpatient psychiatric admission; so a 40% reduction in symptoms is clinically meaningful. Finally, as previously mentioned, the Division had indicated in presubmission communication that persistence of effect would be important to evaluating clinical meaningfulness. On the additional secondary endpoint of MADRS total score change from baseline through Day 25, esketamine demonstrated numerically larger reductions, and a greater number of subjects demonstrating greater improvement, in MADRS total score than placebo. In terms of durability, subjects in both groups continued to improve through Day 25, such that the Day 25 predose change from baseline in MADRS total score was -24.3 and -25.3 for Trial SUI3001 and Trial SUI3002, respectively, in the esketamine group. Although the measurements at every timepoint during the 25-day double-blind phase were not prespecified in the SAP, the results can be considered supportive because esketamine had a numerically greater treatment effect during this period. On the exploratory endpoint of MADRS total score change from baseline through Day 90, a difference from placebo ended by Day 53 in SUI3001, but persisted through Day 90 in SUI3002; statistical information decreased starting at Day 28 because of dropouts. The

reduction in MADRS total scores appeared to persist for both groups, which may support the durability of esketamine's efficacy. However, the contradictory results between SUI3001 and SUI3002 do not allow for determining if the persistent MADRS decline is driven by the effects from the standard of care plus oral antidepressant therapy or by esketamine.

Secondary and Other Endpoints

On the key secondary endpoint (CGI-SS-R change from baseline to 24 hours (Day 2), esketamine plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in the phase 3 MDSI studies; see Table 19 and Section 7.2.2 for results. Given these results, the review team recommends a Prescribing Information Limitation of Use to state: *the effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato.*

It is unclear why esketamine treatment failed to separate from placebo on the key secondary endpoint. Standard of care treatment with an inpatient psychiatric admission may provide a powerful benefit of its own in reducing acute suicidal ideation or behavior. Another possibility is that suicidal ideation, as a core diagnostic symptom of MDD, is reduced as a consequence of adequate treatment of MDD in general – and therefore difficult to separate as a specific treatment effect. The statistical reviewer noted that the lack of consistent results on the CGI-SS-R endpoint between Studies SUI3001 and SUI3002 may indicate that esketamine does not reduce suicidal ideation and behavior, or that the CGI-SS-R has high variability as a measurement of the effect.

Other than the key secondary endpoint, none of the other secondary (or exploratory) endpoints were controlled for multiplicity, or inform labeling; therefore, they are discussed briefly or not reviewed here. See Table 22 and Table 37 for the results of selected other secondary and exploratory endpoints. In both phase 3 MDSI studies, the percentage of subjects with remission of MDD at 24 hours is supportive, although the threshold of MADRS total score ≤ 12 is on the higher end of the literature (Zimmerman et al. 2004a; Zimmerman et al. 2004b), and the 95% confidence interval for percentage of responders included zero.

Subpopulations

The Applicant analyzed the primary and key secondary efficacy results in the phase 3 MDSI studies by the following baseline demographic and clinical variables: sex, race, age group, region, country, baseline MADRS total score (above median versus at or below median), standard of care antidepressant therapy (AD monotherapy or AD plus augmentation therapy) as randomized, baseline prior suicide attempt (lifetime, reported on the SIBAT), and baseline suicide attempt in the last month.

As noted by the Applicant, for the primary efficacy endpoint of change from baseline to 24 hours (Day 2) in MADRS total score, in general results (LS mean difference) directionally favored treatment with esketamine plus standard of care across studies and when pooled. Many subpopulation trends were either inconsistent between SUI3001 and SUI3002, involved 95% confidence intervals that included zero, or were too small of a subpopulation for any clear inference. For example, males demonstrated a somewhat larger treatment effect than females in SUI3001, but sex subpopulation results were nearly identical in SUI3002 (and relatively close when pooled). Regarding age, subjects ages 55 to 64 demonstrated greater treatment effect than subjects ages 18 to 34 or ages 55 to 64 in SUI3001, but age subpopulation results were much closer in SUI3002 (and when pooled). Regarding race, Black subjects demonstrated greater treatment effect in both trials than other racial subpopulations but were a very small subpopulation in the studies (i.e., 10 subjects in the pooled esketamine group). A baseline MADRS total score >median and a baseline SIBAT prior suicide attempt appeared to be associated with a greater treatment effect in SUI3001 and when pooled, but not notably in SUI3002. AD monotherapy appeared to be associated with a greater treatment effect (than AD monotherapy plus augmentation) in SUI3002, but not notably in SUI3001 or when pooled. By region (in both studies and when pooled), subjects from North America (i.e., the United States, as only one subject was enrolled from Canada) appear to have demonstrated greater treatment effect than subjects from other regions, although the 95% confidence intervals for Asia and South America (and Europe in SUI3001) included zero.

Thus, the subpopulation results are unclear regarding the primary efficacy endpoint. However, although the studies were not designed to support efficacy conclusions across subgroups, factors that hypothetically might be associated with a greater magnitude of treatment effect (i.e., greater change from baseline to 24 hours (Day 2) in MADRS total score) appear to be North American regionality, a baseline MADRS total score >median, and a baseline SIBAT prior suicide attempt.

As noted by the Applicant, for the key secondary endpoint of change from baseline to 24 hours (Day 2) in the CGI-SS-R score, in general results (OR estimates) directionally favored treatment with esketamine plus standard of care across studies and when pooled. However, in keeping with the overall failure to demonstrate statistically significant superiority on the key secondary endpoint, nearly all of the subpopulation OR 95% confidence intervals included or were near to 1.

Additional Efficacy Considerations

Considerations on Benefit in the Postmarket Setting

Esketamine has been marketed in the United States since its approval in March 2019 for the treatment of TRD. In addition to a PMR to characterize the long-term effects on cognitive

function and urinary symptoms (to be fulfilled by the completion of the 3-year Study TRD3008), the Applicant has made a PMC to conduct a study evaluating the efficacy of esketamine monotherapy for the treatment of TRD. Some potential postmarket considerations are as follows:

- Given the MDSI study population, clinicians may attempt to utilize esketamine for the treatment of suicidal ideation and behavior despite the program's failure to demonstrate esketamine plus standard of care superiority to placebo plus standard of care on the key secondary endpoint of change from baseline to 24 hours (Day 2) on the CGI-SS-R. However, the recommended Limitations of Use statement in the Prescribing Information as described above is clear on this point.
- Given the more rapid onset of action compared to other antidepressants, clinicians (especially in overfilled emergency rooms and inpatient psychiatric units), insurance companies, or patients may seek to start treatment with esketamine in the emergency room or other acute care setting, but then avoid a clinically warranted inpatient admission (or shorten one) – which was part of the standard of care in the MDSI studies. However, the recommended Limitations of Use statement in the Prescribing Information as described above (and the recommended study description in Section 14 in the Prescribing Information, including study design) are clear.
- The MDSI program studies allowed subjects to have a smooth transition between inpatient and outpatient esketamine treatment and receive all eight treatments twice-weekly as scheduled. In real-world clinical practice, it is well known that arranging stepdown transition of care can be complicated (e.g., it may be difficult to find an outpatient clinician who is in the patient's insurance network or who has appointment availability). Realistically, availability of outpatient clinics that provide esketamine treatment is likely as dependent upon the geographic area's mental health resources as any other follow-up. It will be incumbent upon the Applicant, health care facilities, and insurance companies to facilitate smooth transitions of care and ensure that patients complete the recommended course of treatment as indicated.
- The MDSI program studies examined 4-week treatment periods. The Applicant did not collect data on potential continuation of treatment beyond 4 weeks, which is consequently lacking in subjects without TRD. Findings from the follow-up period do not yield a consistent picture of the persistence of esketamine's efficacy. However, neither the esketamine nor placebo arm appreciably worsened during the study period as described above.
- Although elderly patients and adolescents were not studied in the phase 3 MDSI trials, clinicians may attempt to use esketamine in these populations even without labeled indications. The TRD study in elderly patients did not demonstrate any unusual safety

concerns compared to younger populations, and the Applicant is currently conducting Study SUI2002 in patients ages 12 to 17.

- Esketamine carries risks of abuse and misuse. Although not primarily to prevent misuse and diversion, these risks are currently mitigated with the REMS program.
- Among international enrollment, subjects in the United States (North America) demonstrated superiority on the primary efficacy endpoint with esketamine plus standard of care versus placebo plus standard of care.

Other Relevant Benefits

As noted in the Analysis of Current Treatment Options (Section 2.2), only ECT appears to also demonstrate a rapid onset of action. Esketamine may be preferable to ECT for patients, given the latter's use of general anesthesia, seizure induction, and risk of memory loss.

7.4.2. Integrated Assessment of Effectiveness

The two adequate and well-controlled phase 3 Trials SUI3001 and SUI3002 (and supportive phase 2 Trial SUI2001) presented by the Applicant meet the statutory standard for substantial evidence of effectiveness for esketamine plus standard of care with regard to the primary efficacy endpoint, change from baseline to 24 hours (Day 2) on the MADRS total score. The MDSI program studies did not demonstrate evidence of effectiveness regarding the key secondary endpoint (CGI-SS-R change from baseline to 24 hours (Day 2)).

As described above, the MADRS is a well-established scale for assessing symptom severity in MDD. Subjects in the phase 3 MDSI trials demonstrated a mean MADRS baseline score in the severe range, with symptoms warranting inpatient psychiatric admission. In the context of the more rapid time to onset of benefit than other antidepressants for this severely ill population, the LS-means treatment differences demonstrated in the studies (with supportive information regarding the durability of effect) are clinically meaningful for esketamine's intended use: as means to provide more rapid relief for patients while awaiting onset of benefit of other antidepressants.

Given the positive findings on the primary endpoint but not the key secondary endpoint, and the population studied, we recommend that the Prescribing Information Indication & Use statement be: *for the treatment of depressive symptoms in adult patients with MDD with acute suicidal ideation or behavior*, with a Limitation of Use statement as described above. Given that the MDSI population is likely to represent a significantly more ill population than the general MDD population, we recommend inclusion of the MDSI population in the Indications & Use statement rather than MDD alone, along with a description of the population studied in Section 14. We recommend that the efficacy results be presented in Section 14 as a line graph illustrating the change in MADRS total score over time for treatment arms, as well as a

tabulation comparing baseline MADRS total scores, change from baseline at 24 hours, and placebo-subtracted differences with confidence intervals.

7.5. Review of Safety

7.5.1. Safety Review Approach

The safety data supporting this application are based on the Applicant's ISS. The ISS presents an analysis of primary safety data across the pooled phase 3 trials SUI3001 and SUI3002, and of phase 2 Trial SUI2001. All three were randomized, double-blind, placebo-controlled, multicenter studies of esketamine 84 mg in adults with MDSI; the studies are described in more detail in Sections 7.1, 7.2, and 7.3, respectively. The Agency did not issue any clinical holds for these studies during the development program. Additional supporting data were presented from ongoing TRD studies (the open-label extension TRD3008, TRD3006, and TRD2005) and the pediatric study SUI2002; Table 2 and Table 3 (Section 6.1) list all relevant Applicant-submitted studies. The safety review also examined the 120-day safety update report for the supplement submitted on January 30, 2020; the PADERs submitted on March 31, 2020; January 3, 2020; September 27, 2019; and July 2, 2019; and any relevant information from the 12-month REMS assessment submitted on March 5, 2020. The Integrated Assessment of Safety (Section 7.5.11) summarizes the review of safety and provides an overall safety assessment, and the Benefit-Risk Assessment (Section 1.3) weighs the safety findings against clinical need and the possibility of effective treatment for this product. The Applicant provided safety data from all trials at submission and no mid-review safety update was required.

The original NDA review for esketamine focused primarily on issues of sedation, dissociation, cardiovascular AEs including increased BP, impaired cognition, liver injury, bladder-related AEs, and suicidal ideation or behavior (SIB).

7.5.2. Review of the Safety Database

Overall Exposure

See Table 52 for the total safety population composition for the completed phase 2/3 MDSI studies. See Table 53 for the extent of drug exposure in pooled trials SUI3001 and SUI3002. See Table 48 (Section 7.3.2) for the extent of drug exposure in Trial SUI2001 (note the ITT population was the same as the safety population).

Table 52. Total Completed Phase 2/3 MDSI Safety Population, Size, and Denominators

Clinical Trial	Placebo (n=256)	Esketamine (n=262)	Total (n=518)
Phase 3 total	225	227	452
SUI3001	112	113	225
SUI3002	113	114	227
Phase 2			
SUI2001	31	35	66

Source: Clinical Reviewer-created from Trial SUI3001, SUI3002, and SUI2001 clinical study reports

Abbreviations: MDSI = major depressive disorder, without psychotic features, assessed to be at imminent risk for suicide (i.e., with suicidal ideation and intent)

Table 53. Extent of Drug Exposure for Pooled Trials SUI3001 and SUI3002

Number of Days Dosed	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
1	6 (2.7%)	13 (5.7%)
2	4 (1.8%)	7 (3.1%)
3	9 (4.0%)	5 (2.2%)
4	10 (4.4%)	3 (1.3%)
5	2 (0.9%)	4 (1.8%)
6	6 (2.7%)	2 (0.9%)
7	3 (1.3%)	9 (4.0%)
8	185 (82.2%)	184 (81.1%)

Source: Adapted from Integrated Summary of Safety Table 6, p. 31

Abbreviations: SOC = standard of care

According to the Applicant, the combined cumulative exposure to esketamine in the pooled trials was 13.8 patient-years, based on 227 subjects who received at least one dose. According to the Applicant, across the completed phase 2/3 MDSI trials, the combined cumulative exposure to esketamine was 15.8 patient-years, based on 262 subjects who received at least one dose.

According to the Applicant, in the completed TRD studies, 1,708 subjects received at least one dose of esketamine in the six completed phase 2/3 studies (including 1,601 subjects in phase 3 studies). The combined cumulative exposure to esketamine in the completed phase 3 TRD studies was 601 patient-years; across the completed phase 2/3 TRD trials, the combined cumulative exposure to esketamine was 611 patient-years. In the ongoing open-label long-term extension Trial TRD3008, based on cumulative reporting through the cutoff of December 31, 2018, 1,140 subjects received esketamine; 1,039 subjects were exposed to treatment for at least 6 months, and 927 subjects were exposed for at least 12 months. The combined cumulative exposure to esketamine in Trial TRD3008 as of the cutoff is 1,198 patient-years. (As

of the 120-day safety update cutoff date of October 2, 2019, an additional 8 patients received esketamine for a total of 1,148 subjects.) See Table 54 for the extent of cumulative drug exposure across all ongoing and completed phase 3 TRD trials.

Table 54. Extent of Cumulative Drug Exposure for Ongoing and Completed Phase 3 TRD Trials

	Intranasal Esk 28 mg + Oral AD (N=254)	Intranasal Esk 56 mg + Oral AD (N=1739)	Intranasal Esk 84 mg + Oral AD (N=1279)
Duration, months			
≤Month 1 (≤Day 28)	212 (83.5%)	1089 (62.6%)	310 (24.2%)
≥ 6 months (180 days) exposure	26 (10.2%)	410 (23.6%)	756 (59.1%)
≥ 12 months (365 days) exposure	15 (5.9%)	239 (13.7%)	595 (46.5%)
Mean (SD)	2.1 (5.51)	4.6 (7.73)	11.7 (10.05)
Median	0.3	0.5	11.0
Range	(0; 33)	(0; 39)	(0; 37)
Total exposure (subject years)	40	611	1151

Note: The duration of exposure to each dose is defined as exposure stop date-exposure start date+1. For subjects who received a flexible dose, the duration was calculated as the date before the dose increase/decrease-date start at that dose+1. If a subject received a dose multiple times during the course of treatment the durations were summed to obtain the final duration.

Note: Some of the study designs included flexible dosing and/or allowed dose modifications during the course of treatment. Subject who received at least one dose of esketamine at more than one dose level, would be counted in multiple dose categories (28 mg, 56 mg, or 84 mg). Thus, the number of subjects added across dose categories exceeds the total number of subjects in the TRD studies.

Adapted from Appendix Q150_EX_POOL_T257

Source: Integrated Summary of Safety Table 4, p. 29 (including footnotes)

Abbreviations: AD = antidepressant, Esk = esketamine, SD = standard deviation, TRD = treatment-resistant depression

Adequacy of the Safety Database

The safety population included all subjects who received at least one dose of study medication. The Applicant pooled data from the phase 3 trials SUI3001 and SUI3002, but presented the phase 2 trial SUI2001 separately given the differences in design (inclusion of subjects with baseline MADRS score ≥22, compared to phase 3 score >28) and population (U.S.-only population, compared to phase 3 international). The Division agreed with this approach in a May 2019 Written Response letter.

The demographic characteristics of the phase 3 study populations were previously discussed with individual trial results (see Table 10, Table 26, and Table 43 and corresponding discussion in Sections 7.1.2, 7.2.2, and 7.3.2, for trials SUI3001, 3002, and 2001, respectively). Although race and ethnicity demographics did not closely mirror the U.S. general population, the results appear sufficiently generalizable for the purpose of the safety assessment.

Clinical Reviewer's Comment: Although the Applicant's trial design duration and proposed label recommendation for esketamine in patients with MDSI is a 4-week course of treatment, the proposed label also notes that "patients who also have TRD should be evaluated to determine the need for continued treatment with" esketamine "beyond 4 weeks." Given the likely overlap in the MDSI and TRD populations, it appears possible to become a long-term treatment and thus subject to ICH E1A guideline recommendations. The overall exposure to esketamine in the TRD program (as per Table 54) exceeds the minimum 300 to 600 subjects with 6 months' exposure and 100 subjects with 12 months' exposure.

7.5.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data were of sufficient integrity and quality for review. OSI had no issues of note on inspections.

Categorization of Adverse Events

The Applicant coded AEs by system organ class and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 for their ISS submission, which was the version used in phase 3 trials SUI3001 and SUI3002. When SUI2001 data was not pooled with the phase 3 trials, the Applicant retained the Version 18.0 used in Trial SUI2001. AEs and serious AEs (SAEs) were appropriately defined. Regarding suicidality, the Division agreed with the Sponsor's plan at the end-of-phase-2 meeting (see Section 3.1) not to treat the initial episode of suicidality as an AE unless there was a worsening of severity from baseline (as well as not report the initial per-protocol hospitalization as an SAE unless extension of admission beyond 5 days was due to a subject's clinical worsening). AEs were collected as per the schedules in Table 4 and Table 38. The severity of AEs was classified based on the following:

- Mild: awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Moderate: sufficient discomfort is present to cause interference with normal activity.
- Severe: extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The Applicant's treatment-emergent AE (TEAE) definition did not include AEs if they occurred or increased in severity during the follow-up phase. Per the Applicant, TEAEs of special interest were examined separately and grouped in the following categories, determined based on the

known pharmacological properties and safety profile of esketamine: TEAEs suggestive of abuse potential, increased BP, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, and anticipated dosing-related AEs.

In a pre-submission communication, the Division agreed with the Applicant's proposal to capture suicide-related events and differentiate them from those that are part of the underlying illness. The Division agreed with the Applicant's plan not to count the initial episode of SI/B as an AE, unless there was a worsening from baseline severity; future suicide-related events would only be counted as an AE if they reoccurred after full resolution of prior SI/B, or if they met criteria for an SAE. The initial per-protocol hospitalization would not be counted as an SAE, unless the duration of admission was extended beyond 5 days due to clinical worsening.

The Applicant grouped related PTs for an analysis of Applicant-determined adverse drug reactions (ADRs) for all esketamine phase 2/3 studies (TRD and MDSI), but did not group PTs for their ISS AE analysis. I grouped related PTs for ISS AE analysis as per Table 55. The majority of my groupings aligned with the Applicant's groupings for ADRs, with exceptions as noted in the table footnotes. I only included PTs that occurred in the MDSI data.

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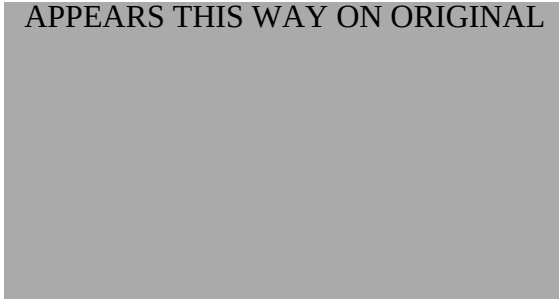


Table 55. Preferred Term Groupings for Trials SUI3001, SUI3002, and SUI2001

Grouped Preferred Term	Included Preferred Terms
Abdominal pain ¹	Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness ²
Amnesia ¹	Amnesia, memory impairment, retrograde amnesia
Anxiety ³	Agitation, anxiety, anxiety disorder, fear, feeling jittery ² , nervousness, panic attack, psychomotor hyperactivity ⁴ , tension ⁴
Blood pressure decreased ¹	Blood pressure decreased, hypotension
Blood pressure increased	Blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, hypertension
Depression ¹	Depressed mood ² , depression, depressive symptom ² , major depression ²
Dissociation	Depersonalization/derealization disorder, derealization, diplopia, dissociation, dissociative disorder ² , dysesthesia, feeling cold, feeling hot, hallucination, hallucination auditory, hallucination visual, hallucinations mixed ⁴ , hyperacusis, paresthesia, paresthesia oral, pharyngeal paresthesia, photophobia, time perception altered, tinnitus, vision blurred
Dizziness	Dizziness, dizziness exertional, dizziness postural
Dysarthria	Dysarthria, slow speech
Dysgeusia	Dysgeusia, hypogeusia
Emotional distress ³	Crying, dysphoria, emotional distress
Headache	Headache, tension headache ⁵
Hyperhidrosis ⁴	Cold sweat ⁴ , diaphoresis ⁵ , hyperhidrosis
Hypoesthesia	Hypoesthesia, hypoesthesia oral, intranasal hypoesthesia, pharyngeal hypoesthesia
Insomnia ¹	Initial insomnia, insomnia, middle insomnia, terminal insomnia
Irritability ¹	Anger, hostility, irritability ³
Lethargy	Fatigue, lethargy, psychomotor retardation ⁴
Mental impairment ⁴	Confusional state, disturbance in attention, mental impairment
Nasal discomfort	Nasal discomfort, nasal dryness, nasal pruritis
Pollakiuria	Micturition urgency ⁴ , pollakiuria
Psychosis ¹	Acute psychosis ² , delusion ² , paranoia ² , psychotic disorder ² , psychotic symptom
Rash ¹	Rash, rash erythematous, rash generalized, rash pruritic, rash vesicular
Sedation	Altered state of consciousness ² , sedation, somnolence, stupor ⁴
Tachycardia	Heart rate increased, sinus tachycardia ⁴ , tachycardia
Throat irritation ⁴	Oropharyngeal pain, throat irritation
Tremor	Postural tremor ⁵ , tremor

Source: Clinical Reviewer-adapted from Integrated Summary of Safety, Attachment 1, p. 573, for MDSI data only

¹ Grouping added by clinical reviewer

² Preferred term reported in SUI2001 only

³ Clinical reviewer moved irritability from Applicant's anxiety grouping to independent grouping

⁴ Applicant added preferred term or grouping for MDSI analysis not included in either TRD analysis or TRD labeling

⁵ Preferred term added to Applicant's grouping by clinical reviewer

Clinical Reviewer's Comment: The Applicant's AE and SAE definitions, and monitoring and severity determinations, appear reasonable. I did not agree with the Applicant's definition of TEAEs for the treatment phase: the Applicant did not consider AEs that occurred on Days 26 or 27 as TEAEs, even though they occurred within 2 days after the last dose of study drug, and would have been considered TEAEs between previous doses with similar timing. Thus, I included AEs on Days 26 and 27 in my treatment-phase TEAE analysis.

The Applicant's verbatim-to-PT mapping appeared reasonable upon examination, and did not require any recoding prior to grouping. The PT "depression suicidal" was coded separately from suicidal ideation, presumably as another way to differentiate the underlying condition. However, there is likely some difficulty in determining the intention of the investigators for a verbatim term such as "worsening of MDD with suicidal ideation" or "worsening depression with worsening suicide ideations with plan and intent," as those verbatim terms could refer to a worsening of the underlying condition, or could refer to a specific worsening or re-occurrence of SI. If the latter, those events were not captured as an AE of suicidal ideation, as they were coded as depression suicidal. Accordingly, I listed the PTs "depression suicidal" and "suicidal ideation" separately, but also as a grouped total.

It is possible that AEs occurring during the initial per-protocol hospitalization (if they did not prolong the stay) may have escaped categorization as SAEs, even if they would have been triggers for a hospital admission from an outpatient setting.

Routine Clinical Tests

Standard clinical laboratory assessments (i.e., hematology, chemistry, urinalysis) were collected at screening and pre-dose on Day 25/early termination at the end of the double-blind phase; in Trial SUI2001, urinalysis was also collected on Days 11 and 39. Urine pregnancy testing for women of childbearing potential and urine drug screen were performed at screening and Day 25/early termination in all trials, and urine pregnancy was repeated at Day 81 in Trial SUI2001. An alcohol breath screen was completed at screening in Trial SUI2001.

Vital signs and ECG were collected as per Table 4 for the phase 3 trials, and per Table 38 for Trial SUI2001. Vital signs included temperature, respiratory rate (RR), heart rate (HR), and BP. In the phase 3 trials, pulse oximetry was recorded on IN dosing days every 15 minutes from 5 minutes pre-dose to 90 minutes post-dose (in Trial SUI2001, measurements extended to 60 minutes post-dose); if oxygen saturation levels were <93% at any point, measurements were recorded every 5 minutes until levels returned to ≥93% or until the subject was referred for appropriate medical care, as indicated. A nasal examination was performed at screening and Day 25/early termination in all trials, and on Days 1, 8, 15, 18, and 39 in Trial SUI2001.

Additional safety assessments as described per Section 7.1.1 and Section 7.3.1 included the MOAA/S and the CADSS in all trials, and the BPRS+ and BPIC-SS in Trial SUI2001.

Clinical Reviewer's Comment: The clinical laboratory assessments, additional safety assessments, and collection schedule for labs, vital signs, and ECG were reasonable. The Applicant did not specify why the BPRS+ and BPIC-SS were performed in Trial SUI2001 and not the phase 3 trials.

7.5.4. Safety Results

Deaths

A total of eight deaths have been reported in subjects who received esketamine across all completed and ongoing MDSI and TRD studies. Information was collected from relevant case report forms (CRFs), CSRs, and the ISS.

- One death occurred in the MDSI development program, in Trial SUI3001 at a U.S. site (b) (6). Subject (b) (6) in the esketamine treatment group was a 53 year-old Asian female with MDSI who completed suicide by hanging on Day 27 (follow-up phase), 3 days after her final dose of esketamine in the treatment phase. An autopsy was not performed. She had a history of MDD, anxiety, insomnia secondary to depression, perimenopause, constipation, and dry mouth. She had a history of five previous suicide attempts, with three in the past 9 months and the most recent attempt by overdose occurring in the 30 days prior to screening (screening occurred on the inpatient unit); she had been psychiatrically hospitalized four times in the preceding 12 months for depression or suicidality.

She received the full eight treatments of 84 mg esketamine, with the first six while inpatient until her discharge to home on Day 17. She appears to have entered the study taking escitalopram (for the previous 1 to 2 months), and was selected for antidepressant monotherapy SOC; she appears to have started on a cross-titration to desvenlafaxine for 6 days before study entry, then switched to bupropion SOC AD monotherapy, which was titrated incrementally to 300 mg daily near the end of the double-blind phase, before decreasing to 150 mg daily on Day 22. Other concomitant medications included prior and ongoing oral contraceptive, estradiol, low-dose trazodone PRN insomnia, and lorazepam PRN insomnia that was increased from 1 mg at study entry to 2 mg on Day 3.

Per the Applicant CIOMS report, on Day 24, her last esketamine dosing day, the subject reported having had depressed mood and anxiety during (b) (6) (on Day 22). According to her husband, she may have been depressed and anxious after spending time with friends and family (feeling like everyone else's life was better than hers). Her MADRS total score had decreased from 41 at baseline to 6 by Day 17; it did

increase slightly to 9 on Day 24 pre-dose, then decreased to 3 at 4 hours post-dose. Her MADRS item 10 score, which had dropped from 4 at baseline to 0 by Day 8, did increase to 1 on Day 24 pre-dose, but returned to 0 at 4 hours post-dose. Her CGI-SS-R score had decreased from 4 at baseline to 0 by Day 8, where it remained. Her MOAA/S score never dropped below 5. Her CADSS score consistently increased at 40 minutes post-dose (to a high of 32 on Day 4, but generally trended downward to a high of 13 on Day 24), and almost or fully returned to a score of 0 by 1.5 hours post-dose.

Clinical Reviewer's Comment: It is theoretically possible that the subject experienced an esketamine withdrawal after treatment completion that contributed to her suicide, but that theory is not supported by the fact that her MADRS scores trended downward between study visits with similar intervals (i.e., 3 days), which demonstrated no major sign of rapidly, severely worsening depression between treatments. Additionally, the subject had a notable history of five previous suicide attempts, with three in the past 9 months and the most recent within 30 days of study entry, suggesting a high risk of future attempt. The reason for her SOC AD bupropion decrease from 300 mg to 150 mg is not clear, but it is possible that the AD was worsening her anxiety, which could also be a risk factor for suicide. Her lorazepam PRN insomnia dose was increased from 1 to 2 mg, which could indicate increased anxiety.

- Three completed suicides were reported in the TRD program in the esketamine groups and evaluated in the original NDA submission; they occurred at 4, 12, and 20 days after the most recent dose of esketamine.
- Three additional deaths were reported in the TRD program in the esketamine groups and evaluated in the original NDA submission, including a case of myocardial infarction, a case of acute respiratory and heart failure, and a case of multiple injuries following a motorcycle accident (which occurred 1 day (~28 hours) after the most recent dose of esketamine; per the study report, the subject had a fall after hitting a tree).

Clinical Reviewer's Comment: The original NDA review examined the three suicides and three additional deaths and did not consider them related to esketamine, and no clear drug-related trend was identified. As per the DPV postmarket drug safety surveillance summary including data from multiple Periodic Adverse Drug Experience Reports (PADERs), a postmarketing case was reported of a subject who accidentally drove her car into an all-terrain vehicle 1 to 3 days following an esketamine treatment; thus, one may consider it possible that the motorcycle accident death from the TRD program, occurring 1 day after the most recent dose of esketamine, could have been related to esketamine-induced sedation or dissociation. However, the subject in the motorcycle accident had MOAA/S scores that were consistently 5 (the most alert) from Day 1, 45

minutes post-dose onward. His CADSS total score did increase from 0 at baseline to 24 on Day 1 at 40 minutes post-dose, but returned to 0 by 1.5 hours post-dose, remained 0 on Days 4 and 8, and only increased to 3 and 4 on Days 11 and 15 at 40 minutes post-dose, respectively, while returning to 1 and 0 at 1.5 hours post-dose, respectively. His scores do not suggest a later-onset notable case of sedation or dissociation that could have contributed to the motorcycle accident, though the possibility cannot be excluded. Also, the motorcycle death occurred relatively early in treatment, after five doses of esketamine on Day 16, when that subject's most recent MADRS score was 30 (decreased from a baseline of 38), so the possibility of a suicide cannot be excluded.

- One additional death in the esketamine group was reported in the ongoing open-label TRD3008 study since the original NDA submission, a case of poly-trauma (per the ISS, the 59-year-old Bulgarian male subject was hit by an automobile while riding a bicycle; per the study report narrative, the subject “met an accident”), which occurred 6 days after the most recent esketamine dose. That subject (Subject (b) (6)) had had mild AEs of sedation on several occasions.

Clinical Reviewer's Comment: Given that 6 days had passed after the most recent dose of esketamine, it appears unlikely the automobile-bicycle collision was sedation- or dissociation-related. The possibility that Subject (b) (6) automobile-bicycle collision death was a suicide cannot be excluded. However, his most recent MADRS score was 4 on Day 358 (after 21 doses of esketamine over approximately 1 year), which is less suggestive of a potential suicide.

Serious Adverse Events

For pooled studies SUI3001 and SUI3002, the Applicant separated SAEs and AEs by double-blind treatment phase (Days 1 through 25) versus follow-up phase (Days 26 through 90), and discussed subjects who had discontinued separately from their phase totals. (There was one instance of a Day 25 event categorized as follow-up, and two instances of a Day 26 event categorized as treatment.) As previously noted, I expanded the treatment phase to Days 1 through 27, to consistently capture (S)AEs that may have occurred within the 2 days following the last Day 25 dose (and adjusted follow-up to Days 28 through 90). For subjects who discontinued during the treatment phase, I included any (S)AEs that occurred within 2 days following their last dose in the treatment phase totals, and noted others separately. For subjects who were not included in the follow-up analysis set population (with a flag), I did not include their (S)AEs. For subjects who discontinued during the follow-up phase but were included in the follow-up analysis set population (with a flag), I included their S(AE)s. Information was collected from relevant case report forms (CRFs), CSRs, and the ISS.

SAEs reported in the pooled phase 3 MDSI studies during the treatment phase (as described

above) for the Safety Analysis Set are summarized in Table 56, including groupings as per Table 55. The PTs depression suicidal and suicidal ideation are listed separately as per pre-submission communication, but also as a grouped total.

Table 56. Serious Adverse Events During the Treatment Phase, Safety Analysis Set, in Pooled Trials SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Psychiatric disorders	9 (4.0%)	10 (4.4%)
Suicide attempt	3 (1.3%)	4 (1.8%)
Depression suicidal	1 (0.4%)	2 (0.9%)
Suicidal ideation	4 (1.8%)	2 (0.9%)
Grouped: depression suicidal, suicidal ideation	5 (2.2%)	4 (1.8%)
Depersonalization/derealization disorder	0	1 (0.4%)
Depression	2 (0.9%)	1 (0.4%)
Completed suicide	0	1 (0.4%)
Aggression	1 (0.4%)	0
Metabolism and nutrition disorders	0	1 (0.4%)
Diabetic ketoacidosis	0	1 (0.4%)
Cardiac disorders	2 (0.9%)	0
Arrhythmia	1 (0.4%)	0
Pericardial effusion	1 (0.4%)	0
Hepatobiliary disorders	1 (0.4%)	0
Hypertransaminasaemia	1 (0.4%)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.4%)	0
Pneumothorax	1 (0.4%)	0

Source: Adapted from Integrated Summary of Safety Table 14, p. 48, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

Clinical Reviewer's Comment: The completed suicide is discussed above under deaths. Overall, numbers of SAEs are low, either more frequent in the placebo group or nearly equal between groups, and in one case, an expected AE from esketamine (depersonalization/derealization disorder).

Not included in the treatment phase table are discontinued subjects whose SAE occurred more than 2 days after their last dose. One subject (b) (6) discontinued on Day 1 (due to an AE of transient elevation of blood pressure) after (b) (6) of esketamine, and on Day 26 reported the SAEs suicide attempt, multiple injuries, and subarachnoid hemorrhage (after a jumping suicide attempt). One subject (b) (6) discontinued on Day 1 (due to nonserious AEs of confusional state, sedation, hypoesthesia, and pharyngeal hypoesthesia) after one dose of esketamine, and on Day 9 reported the SAE suicidal ideation. One subject (b) (6)

withdrew on Day 6 (due to other reasons: subject opted for ECT) after two doses of esketamine (last dose on Day 4), and on Day 14 reported the SAE suicidal ideation.

One discontinued subject (b) (6) in Trial SUI3002 had a notable SAE (acute psychosis) that technically occurred more than 2 days after his last dose, but he had a related nonserious AE (mild psychotic symptom) within 2 days of his last dose. The subject was a 22-year-old Turkish male who was withdrawn on Day 10 for lack of efficacy, after he received three total doses of esketamine (last dose on Day 8). The subject had a history of overdose attempt 18 days prior to study entry, and was on venlafaxine monotherapy as his AD SOC. He had a nonserious AE of euphoric mood on Day 1 that resolved by Day 3, which is when the investigator noted a nonserious AE of moderate worsening depression ("started to become introvert...negativism started"). On Day 10, nonserious AEs of mild psychotic symptom and moderate insomnia were reported; he received mirtazapine for the latter. On Day 12, the SAE of acute psychosis was reported, which was described as paranoid persecutory ideation. It appears he was not discharged until Day 80, and over the course of his admission received treatment with aripiprazole, olanzapine, quetiapine, chlorpromazine, and eventually ECT.

Clinical Reviewer's Comment: Regarding subjects whose SAEs occurred more than 2 days after drug discontinuation, the suicide attempt and the cases of suicidal ideation appear to have occurred long enough after the last dose of esketamine not to suggest a withdrawal effect, especially after only 1 to 2 doses. The acute psychosis is difficult to interpret; in that subject, a nonserious AE of mild psychotic symptom was reported on Day 10, two days after the subject's third and final esketamine dose, with acute psychosis on Day 12. It is possible that the introversion and negativism noted on Day 3, following the euphoric mood from Day 1 to 2, were an early, more subtle sign of emerging psychosis. Considering potential causality, racemic ketamine is known to have the potential to be psychotomimetic. However, the subject's age and MDD are consistent with the potential for psychotic symptoms, which confounds any inference of drug-induced causality. In the literature, an outpatient sample estimated an incidence of psychotic depression of 5.3% among depressed patients (Gaudiano et al. 2011), and an inpatient sample estimated the incidence as high as 25% (Coryell et al. 1984) (though the latter is an older sample).

SAEs reported in the pooled phase 3 MDSI studies during the follow-up phase (as described above) for the Follow-up Analysis Set are summarized in Table 57, including groupings as per Table 55. The PTs depression suicidal and suicidal ideation are listed separately as per pre-submission communication, but also as a grouped total.

Table 57. Serious Adverse Events During the Follow-Up Phase, Follow-up Analysis Set, in Pooled Trials SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=185) n (%)	Esketamine + SOC (N=190) n (%)
Psychiatric disorders	14 (7.6%)	20 (10.5%)
Suicide attempt	3 (1.6%)	7 (3.7%)
Suicidal ideation	6 (3.2%)	5 (2.6%)
Depression suicidal	5 (2.7%)	5 (2.6%)
<i>Grouped: depression suicidal, suicidal ideation</i>	<i>11 (5.9%)</i>	<i>10 (5.3%)</i>
Depression*	2 (1.1%)	4 (2.1%)
Acute stress disorder	0	1 (0.5%)
Homicidal ideation	1 (0.5%)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (0.5%)
Hemothorax	0	1 (0.5%)
Infections and infestations	3 (1.6%)	0
Erysipelas	1 (0.5%)	0
Pyelonephritis	1 (0.5%)	0
Staphylococcal bacteremia	1 (0.5%)	0
Injury, poisoning, and procedural complications	1 (0.5%)	0
Overdose	1 (0.5%)	0
Musculoskeletal and connective tissue disorders	1 (0.5%)	0
Rhabdomyolysis	1 (0.5%)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.5%)	0
Papillary thyroid cancer	1 (0.5%)	0
Nervous system disorders	1 (0.5%)	0
Encephalopathy	1 (0.5%)	0

Source: Adapted from Integrated Summary of Safety Table 15, p. 49, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

* As per Table 55 groupings

Clinical Reviewer's Comment: Overall, psychiatric disorder SAEs were mostly similar between groups, except suicide attempts (7 in esketamine versus 3 in placebo). Upon examination, the suicide attempts in the esketamine group were reported on Days 29, 30, 36, 49, 60, 64, and 86. In the placebo group, they were reported on Days 28, 37, and 39. One might be tempted to conjecture about a potential withdrawal effect from esketamine predisposing to suicide attempt, but the fact that the placebo group attempts were also relatively early in the follow-up phase doesn't support that theory (also, the groups were roughly equal regarding suicidal ideation). The suicide attempts may, however, signal a need for caution while discontinuing treatment in this population. The Applicant did not collect baseline data to determine whether the subjects met TRD criteria (in which case they may continue esketamine after the 4-week treatment phase as per current labeling). However, the Applicant asserts that literature

suggests approximately 30% of patients with MDSI would also have TRD, and notes that 53% of subjects in the pooled phase 3 studies were assigned to oral AD plus augmentation therapy, suggesting that they had required at least a second-line therapy.

During the treatment phase of Trial SUI2001, in the esketamine group, three subjects (8.6%) reported SAEs of suicidal ideation (on Days 9, 15, and 26, the last of which was counted by the Applicant in the follow-up phase, but occurred the day following the last esketamine dose); one subject (2.9%) reported agitation, and one subject reported depressive symptoms. No placebo subjects reported any SAEs during the double-blind phase. During the follow-up phase, in the placebo group, three subjects (13.6%) reported suicide attempt; one subject (4.5%) reported suicidal ideation; and one subject reported cellulitis. No subjects in the esketamine group reported any SAEs in the follow-up phase (other than the suicidal ideation mentioned above under treatment phase).

Clinical Reviewer's Comment: Three subjects reported suicidal ideation in the esketamine group during the treatment phase of Trial SUI2001, while three subjects reported suicide attempts and one suicidal ideation in the placebo group during the follow-up phase. In the phase 3 trials described above, roughly equal numbers of subjects reported suicidal ideation or depression suicidal between groups during the treatment phase, so there does not appear to be a clear signal for suicidal ideation as an esketamine AE (as considered separately from suicide attempts, as discussed above).

According to the Applicant, during the ongoing, open-label extension study TRD3008 (through the interim CSR cutoff date of December 31, 2018), five of 453 subjects (1.1%) reported one or more SAEs during the induction phase, including: back pain (two subjects (0.4%)); and completed suicide (discussed above), urinary bladder polyp, and hypertensive emergency (one subject (0.2%) each). During the long-term optimization/maintenance phase, 87 of 1101 (7.9%) subjects reported one or more SAEs, with depression (11 subjects (1.0%)) and anxiety (five subjects (0.5%)) the most common, followed by major depression, suicidal ideation, and suicide attempt (three subjects (0.3%) each). Other SAEs reported by more than one subject included: cholelithiasis and pneumonia (three subjects (0.3%) each); and infection, lower limb fracture, overdose, carotid artery aneurysm, headache, atrial fibrillation, myocardial infarction, pancreatitis acute, asthma, stress urinary incontinence, and vertigo (two subjects (0.2%) each). Between December 31, 2018 and April 20, 2019, 17 subjects reported 19 SAEs: cholelithiasis and suicidal ideation (two subjects each); and anaphylactic reaction, abortion spontaneous, bronchitis chronic, depression, colitis, exposure during pregnancy, face injury, fall, intentional overdose, lung disorder, meniscus injury, muscle rupture, nodule, rotator cuff syndrome, and suicide attempt (one subject each). According to the Applicant's 120-day safety update, between April 20, 2019 and the clinical cutoff date of October 2, 2019, additional SAEs during the optimization/maintenance phase reported in more than one subject included suicide attempt (five subjects), depression (four subjects), cholelithiasis, suicidal ideation, and umbilical hernia (two subjects each).

According to the Applicant, during the ongoing, blinded pediatric study SUI2002, a subject reported the SAE psychotic disorder, and her treatment was unblinded as esketamine. Per the Applicant, Subject (b) (6) is a 17-year-old female with a psychiatric history significant for MDD, anxiety, suicidal intent, and four previous suicide attempts (including two attempts within 30 days of screening). On Day 18, the first symptoms of clinically significant dissociation were reported to start; she remained in the study and received all eight doses of the study medication. Three days after the final dose of study medication, she experienced psychotic symptoms, which progressively worsened. After unblinding, the site reported an SAE of “psychotic episode” (coded term psychotic disorder). She was treated with aripiprazole. Her symptoms improved and were reported to end 14 days later.

Also during the ongoing, blinded pediatric study SUI2002, 20 of 47 randomized subjects reported 24 SAEs of suicidal ideation (ten subjects), suicide attempt (seven subjects), and one subject each reported intentional self-injury, toxicity to various agents, psychotic disorder (detailed above), depression suicidal, major depression, and suicidal behavior. According to the Applicant’s 120-day safety update, between April 20, 2019 and the clinical cutoff date of October 2, 2019, an additional nine subjects reported seven SAEs of suicidal ideation (four subjects), suicide attempt (three subjects), and one subject each reported alcohol intoxication, bipolar disorder, HIV infection, and major depressive disorder.

According to the Applicant’s 120-day safety update, as of the October 2, 2019 clinical cutoff date, one subject in study TRD3006 reported an SAE of “recurrent depressive disorder, currently a severe episode without psychiatric symptoms.” In study TRD2005, unblinded data since the sNDA safety identified one esketamine subject who had a multiple-complaint SAE that was later diagnosed as conversion disorder, and ankle fracture and uterine leiomyoma in one placebo subject each. Since the April 20, 2019 sNDA cutoff date, an additional three subjects reported four SAEs: fracture and suicide attempt (one esketamine subject each), and suicidal ideation and suicide attempt in one placebo subject.

Clinical Reviewer’s Comment: The overall SAE frequencies are small in study TRD3008. The case of psychotic disorder in SUI2002 is of note, though like the case in the adult Turkish subject in Trial SUI3002 discussed above, the subject’s age and MDD are consistent with the potential for emerging psychosis, confounding any causality inference.

Dropouts and/or Discontinuations Due to Adverse Effects

Study drug discontinuations due to AEs in the pooled phase 3 MDSI studies during the treatment phase are summarized in Table 58, including groupings as per Table 55. The PTs depression suicidal and suicidal ideation are listed separately as per pre-submission communication, but also as a grouped total. Per the Applicant, in the pooled phase 3 studies SUI3001/3002, 6.2% of subjects in the esketamine group versus 3.6% of subjects in the placebo

group experienced AEs leading to discontinuation of study drug. The most common AE cause for discontinuation in the esketamine group was the grouping dissociation, depersonalization/derealization disorder, hallucination visual (six subjects (2.6%) total).

Table 58. Adverse Events Leading to Study Drug Discontinuation During the Treatment Phase in Pooled Studies SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Psychiatric disorders	3 (1.3%)	7 (3.1%)
Dissociation ¹	0	6 (2.6%)
Confusional state	0	1 (0.4%)
Aggression	1 (0.4%)	0
Depression suicidal	1 (0.4%)	0
Suicidal ideation	1 (0.4%)	0
<i>Grouped: depression suicidal, suicidal ideation</i>	<i>2 (0.9%)</i>	<i>0</i>
Gastrointestinal disorders	0	4 (1.8%)
Nausea	0	2 (0.9%)
Dyspepsia	0	1 (0.4%)
Paresthesia oral	0	1 (0.4%)
Vomiting	0	1 (0.4%)
Nervous system disorders	0	4 (1.8%)
Dizziness ¹	0	2 (0.9%)
Sedation ¹	0	2 (0.9%)
Headache	0	1 (0.4%)
Hypoesthesia ^{1,2}	0	1 (0.4%)
Respiratory, thoracic, and mediastinal disorders	1 (0.4%)	3 (1.3%)
Nasal discomfort	0	1 (0.4%)
Throat irritation	0	1 (0.4%)
Pneumothorax	1 (0.4%)	0
Investigations	1 (0.4%)	2 (0.9%)
Blood pressure increased ¹	1 (0.4%)	2 (0.9%)
Cardiac disorders	3 (1.3%)	0
Arrhythmia	1 (0.4%)	0
Atrioventricular block first degree	1 (0.4%)	0
Pericardial effusion	1 (0.4%)	0
Hepatobiliary disorders	1 (0.4%)	0
Hypertransaminasemia	1 (0.4%)	0

Source: Adapted from Integrated Summary of Safety Attachment TSFAE06A_SCS, p. 218, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

¹ As per Table 55 groupings

² The same subject reported both PTs in the grouping, which were counted once for the PT grouping, but separately for System Organ Class totals (i.e., Nervous system disorders and Respiratory, thoracic, and mediastinal disorders)

Per the Applicant, in Trial SUI2001, five subjects (14.3%) in the esketamine group versus one subject (3.2%) in the placebo group discontinued because of AEs in the double-blind treatment phase. In the esketamine group, AEs leading to discontinuation included dizziness, dysgeusia, aggression, agitation, ventricular extrasystoles, nausea, and dyspnea (one subject each). In the placebo group, one subject experienced AEs of dissociative disorder and panic attack leading to study discontinuation and withdrawal.

According to the Applicant's 120-day safety update (as of the October 2, 2019 clinical cutoff date) in the ongoing open-label extension study TRD3008, during the induction phase, eight subjects (1.7%) experienced one or more AEs leading to discontinuation, including blood pressure increased (three subjects), and one subject each reported agitation, dissociation, dizziness, euphoric mood, fatigue, hepatic enzyme increased, hypertensive emergency, and hypoesthesia. During the optimization/maintenance phase, 43 subjects (3.9%) experienced one or more AEs leading to discontinuation, including dissociation (four subjects), blood pressure increased, depression, major depression, mania (three subjects each), and anxiety and suicidal ideation (two subjects each).

Clinical Reviewer's Comment: As noted previously in Sections 7.1.2, 7.2.2, and 7.3.2, more subjects discontinued because of AEs in the phase 2/3 MDSI studies in the esketamine group than placebo, which is not unexpected. The AE most frequently leading to discontinuation (still relatively low at 2.6% of subjects) was the dissociation grouping, which could also potentially include the one subject who reported confusional state, though the Applicant grouped the latter PT with mental impairment.

Significant Adverse Events

Adverse Events Leading to Dose Reduction or Interruption

In the MDSI studies, subjects started with 84 mg, and could make a one-time dose reduction at any time for all remaining doses. Dose reductions or interruptions due to AEs in the pooled phase 3 MDSI studies during the treatment phase are summarized in Table 59, including groupings as per Table 55. Per the Applicant, in the pooled phase 3 studies SUI3001/3002, 15.4% of subjects in the esketamine group versus 1.8% of subjects in the placebo group experienced AEs leading to dose reduction or interruption of study drug. In the esketamine group, the most common AE reasons included dissociation (5.7%), nausea (4.8%), dizziness and dizziness postural grouped (3.5%), sedation and somnolence grouped (3.5%), vomiting (2.2%), and blood pressure increased and blood pressure systolic increased grouped (1.8%).

Table 59. Adverse Events Leading to Dose Reduction or Interruption During the Treatment Phase in Pooled Studies SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Psychiatric disorders	2 (0.9%)	16 (7.0%)
Dissociation	0	13 (5.7%)
Confusional state	0	1 (0.4%)
Disorientation	0	1 (0.4%)
Inappropriate affect	0	1 (0.4%)
Mutism	0	1 (0.4%)
Suicide attempt	1 (0.4%)	1 (0.4%)
Tension	1 (0.4%)	0
Nervous system disorders	0	15 (6.6%)
Dizziness*	0	8 (3.5%)
Sedation*	0	8 (3.5%)
Dysgeusia	0	2 (0.9%)
Hypoesthesia	0	1 (0.4%)
Lethargy	0	1 (0.4%)
Psychomotor hyperactivity	0	1 (0.4%)
Gastrointestinal disorders	0	13 (5.7%)
Nausea	0	11 (4.8%)
Vomiting	0	5 (2.2%)
Investigations	0	4 (1.8%)
Blood pressure increased*	0	4 (1.8%)
General disorders and administration site conditions	1 (0.4%)	2 (0.9%)
Feeling abnormal	0	1 (0.4%)
Gait disturbance	1 (0.4%)	1 (0.4%)
Product intolerance	0	1 (0.4%)
Thirst	0	1 (0.4%)
Ear and labyrinth disorders	0	1 (0.4%)
Vertigo	0	1 (0.4%)
Infections and infestations	0	1 (0.4%)
Tooth abscess	0	1 (0.4%)
Musculoskeletal and connective tissue disorders	0	1 (0.4%)
Muscle rigidity	0	1 (0.4%)
Respiratory, thoracic, and mediastinal disorders	1 (0.4%)	1 (0.4%)
Nasal discomfort	0	1 (0.4%)
Epistaxis	1 (0.4%)	0
Skin and subcutaneous tissue disorders	0	1 (0.4%)
Erythema	0	1 (0.4%)

Source: Adapted from Integrated Summary of Safety Attachment TSFAE09_SCS, p. 231, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

* As per Table 55 groupings

Per the Applicant, in Trial SUI2001, three subjects in the esketamine group reduced their dose because of AEs, including two subjects for dizziness, and one subject for anxiety, chest discomfort, feeling abnormal, and hyperacusis.

Clinical Reviewer's Comment: The most common AEs leading to dose reduction or interruption are consistent with current labeling from the original TRD application.

Severe Adverse Events

Severe AEs occurring in $\geq 1\%$ of subjects in any treatment group in the pooled phase 3 MDSI studies during the treatment phase are summarized in Table 60, including groupings as per Table 55. The PTs depression suicidal and suicidal ideation are listed separately as per pre-submission communication, but also as a grouped total. Per the Applicant, in the pooled phase 3 studies SUI3001/3002, 13.7% of subjects in the esketamine group versus 5.8% of subjects in the placebo group experienced severe AEs. In the esketamine group, the most common severe AEs occurring at a rate greater than placebo included: dissociation (derealization, dissociation, hallucination visual grouped) (4.8%); blood pressure increased (grouped with blood pressure systolic increased) (2.2%); nausea (2.2%); anxiety (1.8%); and suicide attempt (1.3%).

Table 60. Severe Adverse Events Occurring During the Treatment Phase in $\geq 1\%$ of Subjects in Any Treatment Group in Pooled Studies SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Psychiatric disorders	10 (4.4%)	20 (8.8%)
Dissociation*	0	11 (4.8%)
Anxiety	1 (0.4%)	4 (1.8%)
Suicide attempt	2 (0.9%)	3 (1.3%)
Depression*	4 (1.8%)	2 (0.9%)
Suicidal ideation	3 (1.3%)	1 (0.4%)
Grouped: depression suicidal, suicidal ideation	4 (1.8%)	2 (0.9%)
Gastrointestinal disorders	0	7 (3.1%)
Nausea	0	5 (2.2%)
Investigations	0	5 (2.2%)
Blood pressure increased*	0	5 (2.2%)

Source: Adapted from Integrated Summary of Safety Table 12, p. 43, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

* As per Table 55 groupings

In Trial SUI2001 during the treatment phase, severe AEs were reported in five subjects (14.3%) in the esketamine group versus 1 subject (3.2%) in the placebo group. In the esketamine group, dysgeusia was reported by three subjects (8.6%), suicidal ideation by two subjects (5.7%), and agitation, dissociation, feeling drunk, major depression, nausea, paraesthesia, somnolence,

throat irritation, and vertigo by one subject each (3.2%).

Clinical Reviewer's Comment: Severe AE distributions are generally in line with overall AEs and AEs leading to discontinuation or dose reduction/interruption. For the phase 3 MDSI data, note that suicide attempt occurred in only one more subject in the esketamine group than placebo (i.e., three versus two subjects, respectively).

Treatment Emergent Adverse Events and Adverse Reactions

Table 61 summarizes AEs occurring during the treatment phase in $\geq 2\%$ of subjects in the esketamine group and at a greater rate than subjects in the placebo group in pooled studies SUI3001/3002. As before, I included AEs for subjects who dropped out if the AE occurred within 2 days of their last dose. Some AEs have additional PT grouping data for consideration (i.e., adding dysuria to pollakiuria). AEs are listed both with Table 55 PT groupings and without (to align with the TRD-label PT groupings), where applicable. In some cases, when ungrouped to align with the TRD label, only one PT from the grouping may have still qualified for $\geq 2\%$ frequency table inclusion, which may or may not be the same PT as the overall grouping PT.

Table 61. Adverse Events Occurring During the Treatment Phase in $\geq 2\%$ of Subjects Treated with Esketamine + SOC and at a Greater Rate than Subjects Treated with Placebo + SOC in Pooled Studies SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Nervous system disorders		
Dizziness ¹	34 (15.1%)	103 (45.4%)
Sedation ^{1,3}	27 (12.0%)	66 (29.1%)
Dysgeusia ¹	29 (12.9%)	46 (20.3%)
Hypoesthesia ¹	4 (1.8%)	30 (13.2%)
Lethargy ¹	4 (1.8%)	10 (4.4%)
Lethargy ²	4 (1.8%)	8 (3.5%)
Mental impairment ¹	0	9 (4.0%)
Confusional state ²	0	5 (2.2%)
Psychiatric disorders		
Dissociation ^{1,3}	30 (13.3%)	108 (47.6%)
Anxiety ¹	21 (9.3%)	34 (15.0%)
Anxiety ²	20 (8.9%)	32 (14.1%)
Euphoric mood	1 (0.4%)	17 (7.5%)
Emotional distress ¹	0	11 (4.8%)
Dysphoria ²	0	5 (2.2%)
Intentional self-injury	4 (1.8%)	7 (3.1%)
Gastrointestinal disorders		
Nausea	31 (13.6%)	60 (26.4%)

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Spravato (esketamine) nasal spray

Vomiting	12 (5.3%)	26 (11.5%)
Constipation	14 (6.2%)	22 (9.7%)
Dry mouth	6 (2.7%)	8 (3.5%)
Toothache	2 (0.9%)	5 (2.2%)
Investigations		
Blood pressure increased ¹	14 (6.2%)	34 (15.0%)
Respiratory, thoracic, and mediastinal disorders		
Throat irritation ¹	8 (3.6%)	18 (7.9%)
Oropharyngeal pain ²	3 (1.3%)	10 (4.4%)
Throat irritation ²	5 (2.2%)	9 (4.0%)
Ear and labyrinth disorders		
Vertigo	1 (0.4%)	14 (6.2%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis ¹	5 (2.2%)	11 (4.8%)
Hyperhidrosis ²	4 (1.8%)	10 (4.4%)
General disorders and administration site conditions		
Feeling drunk	1 (0.4%)	8 (3.5%)
Feeling of relaxation	3 (1.3%)	5 (2.2%)
Cardiac disorders		
Tachycardia ¹	2 (0.9%)	8 (3.5%)
Tachycardia ²	2 (0.9%)	7 (3.1%)
Renal and urinary disorders		
Pollakiuria ^{1,4}	2 (0.9%)	5 (2.2%)
Grouped: pollakiuria ¹ , dysuria	2 (0.9%)	7 (3.1%)
Musculoskeletal and connective tissue disorders		
Myalgia	1 (0.4%)	5 (2.2%)

Source: Clinical Reviewer-created from Integrated Summary of Safety ADAE dataset and Spravato label information
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

¹ As per Table 55 groupings

² If grouped term ungrouped to align with treatment-resistant depression label groupings

³ If ungrouped to align with treatment-resistant depression label groupings, no change would occur

⁴ If ungrouped to align with treatment-resistant depression label groupings, pollakiuria would not qualify for inclusion in the table (most frequent occurrence as micturition urgency 4 (1.8%) in esketamine + SOC versus 0 in placebo + SOC)

***Clinical Reviewer's Comment:** Treatment-phase AEs occurring in the esketamine group at ≥2% frequency and greater than with placebo appear generally similar to the AEs from the comparable TRD labeling. More dizziness was reported in the MDSI population (45.4% versus 29% TRD label), more sedation (29.1% versus 23%), more dissociation (48% versus 41%), slightly more euphoric mood (7.5% versus 4%), more constipation (9.7% versus 3%), and more blood pressure increased (15% versus 10%). Higher AE incidences in the MDSI population may be the result of a higher proportion of subjects receiving the maximum 84 mg dosage, as the TRD studies included fixed-dose 56 mg and 84 mg groups and a flexible-dose 56-to-84 mg group.*

AEs not included in TRD labeling but included here are: emotional distress (which, if ungrouped to align with TRD label groupings, would still be included as dysphoria), intentional self-injury, toothache, feeling of relaxation, and myalgia. The emotional distress grouping occurrence was twice greater than placebo (which had no occurrences); and with a frequency of 4.8%, could represent a safety signal worth further monitoring. If emotional distress was ungrouped to align with TRD labeling, sub-PT dysphoria occurrence was twice greater than placebo (no occurrences), but of overall low frequency (2.2%). Intentional self-injury occurrence was not twice greater than placebo (3.1% versus 1.8%) and of relatively low overall frequency, so it is difficult to know if that represents a safety signal; it may have resulted from the characteristics or acutely-ill nature of the MDSI population.

AEs from the TRD label that did not qualify for table inclusion with the MDSI population include diarrhea, headache, tremor, insomnia, feeling abnormal, and nasal discomfort (occurrence equal to or more frequent with placebo); and dysarthria (occurrence <2%: three subjects in the esketamine group (1.3%)).

In Trial SUI2001, the most common AEs (as grouped according to Table 55) during the treatment phase in the esketamine group (N=35) at rates higher than placebo were: dissociation (21 subjects (60%)); dizziness (14 subjects (40%)); nausea (13 subjects (37.1%)); headache (12 subjects (34.3%)); dysgeusia (11 subjects (31.4%)); sedation (10 subjects (28.6%)); anxiety (8 subjects (22.9%)); vomiting (7 subjects (20%)); euphoric mood, throat irritation, and vertigo (4 subjects (11.4% each)); and diarrhea, dry mouth, feeling abnormal, hyperhidrosis, insomnia, nasal discomfort, and suicidal ideation (3 subjects (8.6%) each).

According to the Applicant, in the ongoing open-label extension study TRD3008 (N=1,140 as of the interim CSR cutoff date 31 December 2018), during the induction phase and the optimization/maintenance phase, the most common ($\geq 5\%$ of subjects) AEs by PT were: dizziness (25.4%), nausea (24.2%), headache (23.0%), dissociation (20.9%), somnolence (18.7%), dysgeusia (16.6%), vertigo (14.8%), nasopharyngitis (14.3%), vomiting (10.8%), anxiety and blood pressure increased (10.6% each), back pain (9.1%), diarrhea (8.8%), hypoesthesia (8.7%), vision blurred (8.4%), hypoesthesia oral (7.5%), upper respiratory tract infection (7.4%), paresthesia (7.3%), fatigue and urinary tract infection (7.2% each), sedation (6.6%), nasal discomfort (6.5%), arthralgia and insomnia (5.9% each), influenza (5.8%), cough (5.4%), dizziness postural (5.2%), and paresthesia oral (5.0%). According to the Applicant's 120-day safety update (N=1,148 as of the clinical cutoff date 2 October 2019), the most common ($\geq 10\%$ of subjects) AEs during the induction and the optimization/maintenance phases were generally similar to the interim CSR for TRD3008.

Clinical Reviewer's Comment: The most common treatment-phase AEs in Trial SUI2001 were generally similar to those observed in the phase 3 MDSI trials or the TRD label data. Suicidal ideation occurred in three subjects (8.6%) in the esketamine group compared to

one subject (3.2%) in the placebo group, but does not appear to be a signal based upon the phase 3 MDSI data (in which suicidal ideation occurred more frequently in placebo than esketamine (4.4% versus 3.5%)). The most common AEs in study TRD3008 are generally consistent with the most common AEs in the phase 2/3 MDSI studies (except headache was more frequent in placebo in the phase 3 studies, thus is not represented in Table 61); several terms were not grouped for the TRD3008 CSR data and the datasets were not available (i.e., dizziness and dizziness postural; dissociation, paresthesia, paresthesia oral, and vision blurred; somnolence and sedation; hypoesthesia and hypoesthesia oral).

The Applicant presented data regarding the occurrence and resolution of AEs on IN dosing days in the phase 3 MDSI trials. According to the Applicant, in the esketamine group, 94.9% of AEs that occurred on IN dosing days also resolved on the same day (compared to 85.2% of AEs in the placebo group). The AEs with at least 50 total occurrences in the esketamine group were similar to the most commonly occurring AEs ($\geq 10\%$ of subjects reporting the event): dizziness, dysgeusia, somnolence, nausea, headache, paresthesia, hypoesthesia, sedation, dissociation, and blood pressure increased. Of those, $\geq 95\%$ of the events had onset on a dosing day except for nausea (89.1%) and headache (62.3%).

Clinical Reviewer's Comment: *As expected, many of the frequent esketamine-related AEs demonstrate an onset on IN dosing days, and reassuringly the majority of dosing-day AEs resolve same-day.*

Laboratory Findings

Hematology, Chemistry, and Urinalysis

In the phase 2/3 MDSI studies, serum hematology and chemistry and urinalysis were collected at screening and on Day 25 at the end of the double-blind treatment phase. No hematology, chemistry, or urinalysis laboratory measurements demonstrated any significant difference in mean baseline or double-blind change-from-baseline scores, and no clinically significant changes, between the esketamine and placebo groups in the phase 2/3 studies.

Upon examination of outliers for potential differences between groups in the phase 3 MDSI studies, three subjects in the esketamine group demonstrated platelet values below the markedly-abnormal value of $100 \times 10^9/L$ at Day 25 compared to no subjects in the placebo group (range of 52 to $98 \times 10^9/L$ and changes-from-baseline range of -177 to $-214 \times 10^9/L$). However, all three subjects were taking at least one concomitant medication with thrombocytopenia or decreased platelet count labeled as a reported potential adverse reaction. Four additional subjects demonstrated values below the reference range but above markedly abnormal (three esketamine and one placebo: range of 125 to $136 \times 10^9/L$), but their changes-from-baseline were much smaller: range of -15 to $3 \times 10^9/L$.

One subject in the placebo group demonstrated a white blood cell (WBC) count ($2.32 \times 10^9/L$) below the markedly-abnormal value of $2.5 \times 10^9/L$ at Day 25 compared to no subjects in the esketamine group. Seventeen additional subjects demonstrated values below the reference range but above markedly abnormal (15 esketamine and two placebo: range of 2.7 to $3.76 \times 10^9/L$). Among the esketamine subjects, six demonstrated a change from baseline $>1 \times 10^9/L$; of those, five subjects were taking at least one concomitant medication with leukopenia labeled as a reported potential adverse reaction. The sixth subject's reported race was black or African-American, which could indicate the presence of benign ethnic neutropenia (of note, baseline WBC count was already below-range at $2.99 \times 10^9/L$ (lower end of range $3.8 \times 10^9/L$)).

One SAE in the phase 3 MSDI trials was related to laboratory investigations as per Table 56: hypertransaminasemia in a placebo subject. Table 62 lists AEs related to laboratory findings in the phase 3 MDSI studies. Most related AEs were either reported equally between treatment groups, or more often in placebo; two AEs were reported in one esketamine subject each but in no placebo subjects. Of those, the neutrophil count decreased case appears to have been nonsignificant, with a low-normal baseline value ($2.21 \times 10^9/L$) decreased to a still-within-reference-range low-normal Day 25 measurement ($1.97 \times 10^9/L$; lower end of range $1.96 \times 10^9/L$). The blood lactate dehydrogenase increased case did not increase greatly beyond the upper end of the reference range (from a baseline value of 167 U/L increased to a Day 25 measurement of 299 U/L (upper end of range 234 U/L), which normalized by a Day 39 measurement of 233 U/L).

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Table 62. Adverse Events Related to Treatment Phase Laboratory Findings in Pooled Studies SUI3001 and SUI3002

MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Hepatic enzyme increased	2 (0.9%)	2 (0.9%)
Alanine aminotransferase increased	1 (0.4%)	1 (0.4%)
Aspartate aminotransferase increased	1 (0.4%)	1 (0.4%)
Blood creatinine phosphokinase increased	1 (0.4%)	1 (0.4%)
Hypoglycemia	1 (0.4%)	1 (0.4%)
Blood lactate dehydrogenase increased	0	1 (0.4%)
Neutrophil count decreased	0	1 (0.4%)
Hyperglycemia	3 (1.3%)	0
Hypercholesterolemia	2 (0.9%)	0
Hypertransaminasemia*	1 (0.4%)	0
Blood folate decreased	1 (0.4%)	0
Hematocrit decreased	1 (0.4%)	0
Hypertriglyceridemia	1 (0.4%)	0
Iron deficiency	1 (0.4%)	0
Proteinuria	1 (0.4%)	0
Transaminases increased	1 (0.4%)	0
Vitamin D deficiency	1 (0.4%)	0

Source: Clinical Reviewer-created from Integrated Summary of Safety ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

*Serious adverse event

In Trial SUI2001, no SAEs were related to laboratory assessments, and no subjects in the esketamine group had a markedly-abnormal laboratory result. One subject in the esketamine group had an AE of alanine aminotransferase increased, with a change from 16 U/L at baseline to 126 U/L at Day 25 (upper end of range 34 U/L); that subject was taking a concomitant medication with elevated liver enzymes labeled as a reported potential adverse reaction. In the placebo group, one subject demonstrated a markedly-abnormal measurement for low phosphate, and one subject for high erythrocytes.

Hepatic Safety

With regard to hepatic safety, equal numbers of subjects between treatment groups in the phase 3 MDSI studies demonstrated an ALT >3xULN (3 per group) and an equal number demonstrated a markedly abnormally high ALT of >200 U/L (1 per group). In the Trial SUI2001 treatment phase, one subject in the esketamine group demonstrated an increase in ALT >3xULN (discussed above as a related AE), with no markedly-abnormal ALT results. Per the Applicant, the phase 2/3 MDSI study ALT elevations were primarily asymptomatic, transient,

and resolved spontaneously without worsening. No subjects in either group demonstrated an AST >3xULN or markedly abnormally high AST. No cases met the criteria for Hy's law.

According to the Applicant, in the ongoing open-label extension study TRD3008, overall, 43 of 1140 (3.8%) subjects experienced one or more treatment-emergent hepatic AEs. The most common (≥ 5 subjects) investigations-related AEs included: gamma-glutamyl transferase increased (11 (1.0%) subjects), ALT increased (10 (0.9%) subjects), AST increased (7 (0.6%) subjects), and hepatic enzyme increased (6 (0.5%) subjects). The most common (≥ 5 subjects) hepatobiliary disorders included: AEs of cholelithiasis (6 (0.5%) subjects) and hepatic steatosis (5 (0.4%) subjects). AEs of cholecystitis, non-alcoholic steatohepatitis and primary biliary cholangitis were experienced by one (0.1%) subject, each. No subjects in the induction phase and three subjects in the optimization/maintenance phase reported SAEs related to hepatic disorders (PT cholelithiasis). One subject in the induction phase and one subject in the optimization/maintenance phase reported AEs that led to withdrawal of study medication (PTs hepatic enzyme increased and ALT increased, respectively).

Clinical Reviewer's Comment: Overall, there does not appear to be a new clinical laboratory safety signal for esketamine, including with regard to hepatic safety.

Vital Signs

In the phase 3 MDSI studies, BP, heart rate, and respiratory rate were measured at screening and on dosing days predose and at 40 minutes, 60 minutes, and 90 minutes post-dose; temperature was measured predose only. Pulse oximetry was performed on dosing days every 15 minutes from predose to 90 minutes post-dose.

No SAEs were related to vital sign measurements in the phase 2/3 MDSI studies. AEs related to blood pressure and heart rate are discussed in each section below. In addition to those, in the phase 3 MDSI studies, one subject each (0.4%) had an AE of body temperature increased and weight increased in the placebo group only. In the Trial SUI2001 esketamine group only, two subjects (5.7%) had an AE of weight increased.

Blood Pressure

In the phase 3 MDSI studies, 34 subjects (15%) in the esketamine group had an AE of blood pressure increased, compared to 15 subjects (6.7%) in placebo. Two subjects (0.9%) had an AE of orthostatic hypotension in the esketamine group, compared to one subject (0.4%) in placebo. One subject (0.4%) per group had an AE of blood pressure decreased. In Trial SUI2001, two subjects (5.7%) in the esketamine group had an AE of blood pressure increased, compared to one subject (3.2%) in placebo. In the phase 3 MDSI studies esketamine group only, an AE of blood pressure increased caused two subjects (0.9%) to discontinue study drug (compared to one subject in the placebo group); caused four subjects (1.8%) to reduce or interrupt their

dose; and was considered a severe AE in five subjects (2.2%).

In the phase 2/3 MDSI studies, mean predose BP values were similar in all treatment groups on all dosing days; subjects were not to be dosed if SBP was >140 mmHg or DBP was >90 mmHg. In the double-blind treatment phase of the pooled phase 3 MDSI studies, the largest mean maximum SBP increase was 14.3 mmHg in the esketamine group (on Day 1) versus 5.1 mmHg in placebo (also on Day 1), for a placebo-subtracted difference of 9.2 mmHg. For DBP, the largest mean maximum DBP increase was 10 mmHg in the esketamine group (on Day 1) versus 4.4 mmHg in placebo (on Day 11) for a placebo-subtracted difference of 5.6 mmHg.

The TRD label information describes the mean placebo-subtracted BP increases at 40 minutes and at 90 minutes post-dose; for the pooled phase 3 MDSI studies, the mean placebo-subtracted increase in SBP was 9.7 mmHg at 40 minutes (compared to 7 to 9 mmHg for TRD) and 3.7 mmHg at 90 minutes post-dose (compared to 2 to 5 mmHg for TRD). For the pooled phase 3 MDSI studies, the mean placebo-subtracted increase in DBP was 6.5 mmHg at 40 minutes (compared to 4 to 6 mmHg for TRD) and 3.2 mmHg at 90 minutes post-dose (compared to 1 to 3 mmHg for TRD). The mean maximum SBP post-dose values ($\pm$ standard deviation) over all treatment-phase timepoints were 141 ± 16 mmHg in the esketamine group versus 132 ± 13 mmHg in placebo; for DBP, the values were 91 ± 9 mmHg in the esketamine group versus 86 ± 8 mmHg in placebo.

The Applicant reports that “on all dosing days, mean SBP and DBP values in all esketamine + SOC group increased from baseline at the 40-minute post-dose timepoint and subsequently returned close to predose values within 1.5 hours post-dose.” In the placebo group, mean BP values were generally stable across timepoints on treatment days. However, although that time course may have been true for the majority of esketamine subjects, it was not true for all. Depending on the treatment day, 54% to 63% of esketamine subjects recorded their maximum percent increase from predose baseline SBP at 40 minutes post-dose; 21% to 28% recorded theirs at 60 minutes; and 14% to 19% recorded theirs at 90 minutes. (In the placebo group, the largest percentage of subjects with the maximum percent increase from predose baseline also occurred at 40 minutes post-dose, but the difference in percentage of subjects with 40 minutes versus 60 minutes as the maximum increase was considerably smaller.) There was a trend for more subjects in the esketamine group to record their maximum percent SBP increase at 40 minutes post-dose earlier in the treatment phase (i.e., 59% to 63% of subjects on Days 1 to 11, versus 54% to 58% on Days 15 to 25).

The Applicant deemed abnormally high post-dose SBP as an increase of ≥ 20 mmHg to a value ≥ 180 mmHg, or low as a decrease of ≥ 20 mmHg to a value ≤ 90 mmHg. (Among subjects whose post-dose SBP was ≥ 180 mmHg, the change from baseline was far greater than 20 mmHg, ranging from 49 to 80 mmHg.) The Applicant deemed abnormally high post-dose DBP as an increase of ≥ 15 mmHg to a value ≥ 105 mmHg, or low as a decrease of ≥ 15 mmHg to a value ≤ 50 mmHg. I looked for post-dose SBP ≥ 180 mmHg or an increase ≥ 40 mmHg, and post-dose DBP

≥110 mmHg or an increase ≥25 mmHg (which is in line with the TRD label examination); Table 63 lists subjects meeting my criteria for potentially clinically significant increases.

Table 63. Subjects with Potentially Clinically Significant Abnormal Blood Pressures During the Treatment Phase in Pooled Studies SUI3001 and SUI3002

Blood Pressure Parameter	Placebo + SOC (N=225)	Esketamine + SOC (N=227)
Potentially Clinically Significant Change	n (%)	n (%)
Systolic Blood Pressure		
Post-dose value ≥180 mmHg	2 (0.9%)	5 (2.2%)
Post-dose increase ≥40 mmHg	2 (0.9%)	27 (11.9%)
Diastolic Blood Pressure		
Post-dose value ≥110 mmHg	3 (1.3%)	6 (2.6%)
Post-dose increase ≥25 mmHg	7 (3.1%)	28 (12.3%)

Source: Clinical Reviewer-created from Integrated Summary of Safety ADVS dataset

Abbreviation: SOC = standard of care

In the pooled phase 3 MDSI trials, 12 to 19% of esketamine-treated subjects and 1 to 4% of placebo-treated subjects experienced an increase of ≥40 mmHg in SBP or an increase of ≥25 mmHg in DBP in the first 90 minutes post-dose during the treatment phase. The percentage of subjects meeting Applicant criteria for abnormal decreases in SBP or DBP were at least twice as high in the placebo group compared to esketamine, and numerically low for esketamine (0.9% for SBP, 1.8% for DBP).

Clinical Reviewer's Comment: The numbers of subjects with potentially clinically significant post-dose BPs were generally similar in the phase 3 MDSI program compared to the TRD label information (for TRD subjects <65 years-old); a slightly higher percentage in MDSI had a ≥40 mmHg increase in SBP (12% versus 8% in TRD). Mean placebo-subtracted maximum BP increases from predose baseline were similar to the TRD program. There appears to be a subset of subjects for whom the post-dose BP peak occurs later than 40 minutes: roughly 2 to 3 out of 10 subjects at 60 minutes, and roughly 1 to 2 out of 10 subjects at 90 minutes. Per the original NDA review and the TRD label information, BP effects last for approximately 4 hours. However, with an overall relatively small mean maximum increase from baseline (given the recommendation to assess benefit/risk with administration if predose baseline BP is >140/90 mmHg), there does not appear to be a new or notably increased BP safety signal from the MDSI data. It appears likely that the 2-hour REMS monitoring requirement would continue to capture the large majority of peak BPs (i.e., if any should present symptomatically).

Heart Rate

In the phase 3 MDSI trials, eight subjects (3.5%) in the esketamine group had an AE of

tachycardia, compared to two subjects (0.9%) in placebo. In Trial SUI2001, one subject (2.6%) in the esketamine group had an AE of tachycardia.

In the pooled phase 3 MDSI trials, the mean predose heart rate across all treatment days was generally slightly higher in the esketamine group compared to placebo (76 versus 74 beats per minute (bpm)). The mean post-dose values at 40 minutes (which were generally the peak post-dose measurements for the esketamine group) across all treatment days demonstrated a 1 bpm increase with esketamine versus a -2 bpm decrease with placebo. At 90 minutes across all treatment days, the mean post-dose values demonstrated a -2 bpm decrease for both treatment groups.

The Applicant deemed clinically significant changes in heart rate as an increase of ≥ 15 bpm to a value ≥ 100 bpm, or a decrease of ≥ 15 bpm to a value ≤ 50 bpm. A greater percentage of subjects in the esketamine group met the criteria for increases in heart rate than in placebo (11.0 versus 7.6%). An equal number of subjects between treatment groups met the criteria for decreases, and was low overall (1.8%).

Clinical Reviewer's Comment: The AE rate for tachycardia was slightly higher in the phase 3 MDSI studies than the TRD label information (3.5% versus 2%). Overall, there does not appear to be any new or notably increased safety signal related to heart rate.

Respiratory Rate and Pulse Oximetry

There were no respiratory-depression-related or pulse-oximetry-related treatment-phase AEs in any of the phase 2/3 MDSI studies. In the phase 3 MDSI studies esketamine group only, four subjects (1.8%) reported dyspnea, and one subject (0.4%) each reported respiratory distress and respiratory rate increased. The subject (b) (6) who reported respiratory distress also reported AEs of anxiety and dizziness on the same treatment day (Day 15, fifth dose), and did not exhibit any clinically significant change in vital signs that day, including respiratory rate (range 16 to 18 breaths/minute).

In the phase 3 MDSI studies, mean post-dose respiratory rates at 40 minutes across all treatment days were nearly identical between treatment groups (with nearly-identical ranges), and demonstrated minimal mean change from predose baselines.

As noted by the Applicant, oxygen saturation levels $< 93\%$ for two or more consecutive assessments within the same visit were reported in isolated cases: four subjects (1.8%) in each treatment group in the pooled phase 3 MDSI studies, and one subject in the esketamine group only in Trial SUI2001. Per the Applicant, in all of those subjects, no clinical symptoms of compromised respiratory function were reported, other vital signs remained within the normal range, and the cases resolved spontaneously in the post-dose period.

Clinical Reviewer's Comment: Overall, there does not appear to be a safety signal related to respiratory depression or oxygen saturation; regarding the latter, equal numbers of subjects in each group experienced oxygen saturation levels <93% for two or more consecutive assessments within the same visit.

Electrocardiograms

In the phase 2/3 MDSI studies, 12-lead ECGs were performed at screening (baseline) and at 1 hour post-dose on Days 1, 8, and 25. No clinically significant effects of esketamine on ECGs were noted, including heart rate, PR duration, QRS duration, QTcB or QTcF interval, QT duration, and RR duration. One subject (0.4%) in each group had an AE of atrioventricular block first degree during the treatment phase; one subject (0.4%) in the placebo group had an AE of arrhythmia during the treatment phase.

QT

No new QT studies were submitted with this supplement. In the phase 2/3 MDSI studies, no subject had a QTcF interval >500 msec; in the phase 3 MDSI studies, one subject in the esketamine group had a QTcF interval >480 msec. That subject (b) (6) a 57-year-old Hungarian female, had a Day 25 measurement of 484 msec, a +23 msec increase from 461 msec baseline; she had no change from baseline on Day 1, and a -5 msec change from baseline on Day 8. She was taking concomitant escitalopram, alprazolam, and perindopril. An equal number of subjects in each group (27 subjects (12%)) had an increase in QTcF ≥ 30 msec, and an equal number of subjects in each group (4 subjects (1.8%)) increased by ≥ 30 msec to a QTcF value between 450 and 470 msec.

Clinical Reviewer's Comment: Overall, there does not appear to be a safety signal regarding ECG parameters in the MDSI data.

Immunogenicity

An AE of rash (as per Table 55 groupings) occurred in eight subjects (3.6%) in the placebo group compared to six subjects (2.6%) in the esketamine group during the phase 3 MDSI studies treatment phase; one subject (0.4%) in the esketamine group had an AE of urticaria. No subjects discontinued study drug for these AEs. There were no AEs of hypersensitivity during the treatment phase in either group.

Clinical Reviewer's Comment: There does not appear to be a safety signal for drug hypersensitivity based on the MDSI data.

7.5.5. Analysis of Submission-Specific Safety Issues

Currently-Labeled Submission-Specific Safety Issues

Sedation

Sedation is a known AE with esketamine administration. Risk of sedation is described in the current TRD label as a boxed warning, as a reason for the REMS 2-hour monitoring requirement, under warnings and precautions, and under adverse reactions. In the phase 3 MDSI studies treatment phase, sedation (as grouped by related PTs per Table 55) was reported as an AE in 66 subjects (29.1%) in the esketamine group compared to 27 subjects (12%) in placebo. In the esketamine group only, sedation led to study drug discontinuation in two subjects (0.9%) or dose reduction/interruption in eight subjects (3.5%). No SAEs were related to sedation.

In addition to AE reporting, sedation was measured using the MOAA/S scale every 15 minutes on dosing days from predose to 90 minutes post-dose, or longer if necessary. MOAA/S scoring ranges from 0 (no response after painful trapezius squeeze), 1 (responds only after painful trapezius squeeze), 2 (responds only after mild prodding or shaking), 3 (responds only after name is called loudly and/or repeated), 4 (lethargic response to name spoken in normal tone), to 5 (responds readily to name spoken in normal tone).

In the phase 3 MDSI trials, 108 subjects (47.6%) in the esketamine group had at least one post-dose MOAA/S score ≤ 4 (indicating the presence of sedation) across all timepoints and treatment days, compared to 40 subjects (17.8%) in placebo. In the phase 3 MDSI trials, MOAA/S scores ≤ 3 (indicating moderate or greater sedation) occurred in 34 subjects (15%) in the esketamine group, compared to 4 subjects (1.8%) in placebo. In Trial SUI2001, 22.9% of subjects in the esketamine group had a MOAA/S score ≤ 3 , compared to 9.7% of subjects in placebo. Per the Applicant, there were no clinically meaningful safety findings associated with the MOAA/S scores ≤ 3 (i.e., no symptoms of respiratory distress were observed, and vital signs including oxygen saturation remained within normal ranges). Of the 34 subjects in the phase 3 MDSI trials with at least one post-dose MOAA/S score ≤ 3 , half of the subjects experienced an event on Day 1, roughly a quarter of the subjects experienced an event on Day 4 and Day 8 each, and <10% experienced an event on each of the remaining dosing days (percentages do not add up to 100% because subjects may have had multiple scores ≤ 3 across all dosing days).

In the phase 3 MDSI studies, MOAA/S scores of ≤ 2 occurred in seven subjects (3.1%) in the esketamine group only; only one of those subjects (b) (6) had MOAA/S scores of 0 or 1 (including on six of eight dosing days). That subject, a 47-year-old Belgian male with a BMI of 25.5 kg/m² at baseline, was also taking sertraline, clomipramine, and quetiapine (titrated to BID) as antidepressant plus augmentation therapy during the treatment phase, as well as lorazepam. His esketamine dose was reduced to 56 mg after the second dose. His MOAA/S

scores rebounded after each drop, and his treatment with esketamine was not interrupted. Of the other six subjects with MOAA/S scores of 2, all occurrences happened on one dosing day only:

- On Day 1, three subjects had scores of 2. Subject (b) (6) had five scores of 2, at 50 minutes, 60 minutes, 65 minutes, 70 minutes, and 75 minutes post-dose; that subject withdrew for an AE of dissociation after one dose. Subject (b) (6) had two scores of 2, at 45 minutes and 60 minutes post-dose, and had two scores of 3 also on Day 1 only. Subject (b) (6) had one score of 2 at 15 minutes post-dose, and had scores of 3 on Days 1 and 4; that subject withdrew for lack of efficacy after three doses.
- On Day 11 Subject (b) (6) had a score of 2 at 30 minutes post-dose; his only score of 3 also occurred on Day 11.
- On Day 25 two subjects had scores of 2. Subject (b) (6) had a score of 2 at 30 minutes post-dose and had no other scores <4. Subject (b) (6) had two scores of 2, at 60 minutes post-dose and 70 minutes post-dose. The investigator reportedly interpreted the MOAA/S score of 2 as a symptom of dissociation, though that subject also had scores of 3 on Days 4, 8, 15, and 25.

In Trial SUI2001, one subject in each treatment group had a MOAA/S score of 2 during the treatment phase, neither of which had respiratory depression or required medical intervention.

Generally, MOAA/S scores demonstrated onset of sedation around 15 minutes post-dose, peaking at 30 to 45 minutes post-dose, and resolving by 60 to 90 minutes post-dose. The large majority of subjects' MOAA/S scores returned to 5 by 90 minutes post-dose in the phase 3 MDSI trials. In the esketamine group, 14 subjects (6.2%) had scores of 4 at 90 minutes, compared to 4 subjects (1.8%) in placebo. Among the 14 subjects in the esketamine group, six subjects (2.6%) had scores of 4 at 90 minutes on multiple dosing days (range: 2 to 4 dosing days); occurrences happened on all dosing days (except Day 11), with the highest number on Day 1 and trending downward over the treatment period. Two subjects (0.9%) in only the esketamine group had scores of 3 at 90 minutes, both on Day 1: Subject (b) (6) had no further MOAA/S scores collected after 90 minutes, and withdrew for an AE of dissociation after one dose; Subject (b) (6) increased to a score of 5 at 2 hours 15 minutes post-dose. Subject (b) (6) in the esketamine group (as discussed above with multiple scores of 0 and 1 on six of eight dosing days) had a score of 0 at 90 minutes, with no further MOAA/S scores collected that day; the CRF narrative notes that vital signs at 90 minutes were within normal limits and no post-dose treatment was given.

I examined the phase 3 MDSI data for subjects who demonstrated MOAA/S score fluctuation (i.e., subjects whose scores dropped to ≤ 3 , demonstrated interim improvement, then dropped to ≤ 3 again). Five subjects (2.2%) in the esketamine group met that criteria, including Subject

(b) (6) (as discussed above with multiple scores of 0 and 1 on six of eight dosing days). Of the other four subjects with MOAA/S score fluctuations to ≤ 3 after interim improvement, all occurrences happened on one dosing day only: in two subjects on Day 4 (b) (6) and (b) (6), one subject on Day 15 (b) (6), and one subject on Day 25 (Subject (b) (6) as discussed above, on that day the investigator reportedly interpreted a MOAA/S score of 2 as a symptom of dissociation, though unclear if the fluctuation was also interpreted as a symptom of dissociation).

Clinical Reviewer's Comment: Overall, there does not appear to be a new or worsened safety signal for sedation in the MDSI data. Data is limited for subjects receiving MOAA/S scores ≤ 2 ; other than Subject (b) (6) with scores of 0 and 1 on a total of six of eight dosing days, all subjects scored 2 as single-day events with no apparent trend, and mostly with their other-lowest-scores of 3 on the same day as scores of 2. The subject with scores of 0 and 1 was also taking potentially sedating concomitant medications (e.g., quetiapine and lorazepam); a significant percentage of subjects in the studies received concomitant benzodiazepines or other potentially sedating medications like quetiapine (although per-protocol they were not to take benzodiazepines within 8 hours of dosing on Day 1 or within 8 hours on subsequent dosing days). Therefore, it is difficult to draw any correlational inferences for that subject or the other small numbers of subjects with scores ≤ 2 , fluctuation to scores ≤ 3 after interim improvement, or scores of ≤ 4 at 90 minutes post-dose. The REMS 2-hour minimum monitoring appears adequate given the time course of the majority of subjects' sedation, and the REMS recommends assessment at 2 hours to determine if patients are clinically stable and ready to leave the healthcare setting.

Dissociation

Dissociation is a known AE with esketamine administration. Risk of dissociation is described in the current TRD label as a boxed warning, as a reason for the REMS 2-hour monitoring requirement, under warnings and precautions, and under adverse reactions. In the phase 3 MDSI studies treatment phase, dissociation (as grouped by related PTs per Table 55) was reported as an AE in 108 subjects (47.6%) in the esketamine group compared to 30 subjects (13.3%) in placebo. In the esketamine group only, dissociation led to study drug discontinuation in six subjects (2.6%) or dose reduction/interruption in 13 subjects (5.7%), and was considered severe in 11 subjects (4.8%).

Depersonalization/derealization disorder (a subterm of the Table 55 dissociation grouping) was considered an SAE in one subject (0.4%) in the esketamine group only. That subject (b) (6) a 34-year-old female in the United States, had a history of anorexia, insomnia, physical abuse, fibromyalgia, interstitial cystitis with chronic pelvic and back pain, ECT and TMS treatment, and numerous trials of antidepressants, antipsychotics, and mood stabilizers. She had been discharged from the initial hospitalization on Day 16 after five inpatient esketamine doses. On

Day 21 post-dose, the SAE and a nonserious AE of dissociation were reported, and the subject reportedly “got confused about which thoughts were real; she was disorganized. She stumbled and was unable to take care of herself. Symptoms were still present at 3 hours post-dose” and she was hospitalized for further monitoring. A urine drug screen positive for methadone was considered a false positive by the investigator, as the subject had taken low-dose chlorpromazine on Day 20 (she was also taking vortioxetine, asenapine, zolpidem, and gabapentin). She had recovered almost fully several hours later, and was ready for discharge the next morning.

In addition to AE reporting, dissociation was measured using the CADSS on dosing days predose and at 40 minutes and 90 minutes post-dose; if any CADSS items scored zero at 40 minutes, they were not repeated at 90 minutes and zero was carried forward. The CADSS consists of 23 subjective items, divided into three components: depersonalization (seven questions), derealization (13 questions), and amnesia (three questions). Responses are coded on a 5-point scale, from 0 (not at all), 1 (mild), 2 (moderate), 3 (severe), to 4 (extreme). The maximum score is 92, and a score between 0 and 4 is considered in the normal range.

Clinical Reviewer’s Comment: Carrying forward CADSS scores of zero to 90 minutes if an item scored zero at 40 minutes appears to potentially miss later-onset symptoms, if they should occur, although the Applicant had noted that 40 minutes corresponded with the time of peak plasma concentrations in the TRD submission, and did not carry forward observations in the TRD studies. Regarding the subject with a dissociation-related SAE, of note, her CADSS total scores predose and 90 minutes post-dose were both 0; her 40-minute post-dose score was 6. One analysis of CADSS scores in the literature suggested the CADSS only partially captures the acute effects of IV ketamine administration (van Schalkwyk et al. 2018), so it is possible that CADSS scores underestimate the extent of dissociative symptoms related to (es)ketamine.

In the phase 3 MDSI trials, 191 subjects (84.1%) in the esketamine group experienced post-dose dissociative symptoms at at least one timepoint across all dosing days, as measured by a CADSS total score >4 (and change from baseline >0), compared to 36 subjects (16%) in placebo. The mean maximum post-dose CADSS total score across all timepoints and dosing days was 17.1 ± 14.0 (SD) for the esketamine group (range: 0 to 78), compared to 2.8 ± 5.3 (SD) for placebo (range: 0 to 33).

Based upon the changes observed in mean CADSS total scores over time on each dosing day, dissociative effects appear to peak by 40 minutes post-dose and typically resolve by 90 minutes post-dose. The mean 40-minute post-dose CADSS total score across all dosing days was 7.3 ± 1.0 (SD) for the esketamine group (range: 0 to 78), compared to 1.0 ± 3.0 (SD) for placebo (range: 0 to 33). The mean 90-minute post-dose CADSS total score across all dosing days was 1.1 ± 3.2 (SD) for the esketamine group (range: 0 to 37), compared to 0.5 ± 2.1 (SD) for placebo (range: 0 to 31). A proportion of subjects still had at least one CADSS total score >4 at 90

minutes post-dose across all dosing days: 47 subjects (20.1%) in the esketamine group, compared to 12 subjects (5.3%) in placebo. Roughly two-thirds of those subjects had 90-minute scores >4 on 1 to 2 dosing days, while the remaining third had 90-minute scores >4 on ≥ 3 dosing days.

However, many of the 90-minute CADSS scores were not far above 4: across all dosing days, 39 subjects (17.1%) in the esketamine group and 11 subjects (4.9%) in placebo had at least one score ≥ 5 and ≤ 10 ; 19 subjects (8.4%) in the esketamine group and 5 subjects (2.2%) in placebo had at least one score >10 and ≤ 20 ; and 5 subjects (2.2%) in the esketamine group and 1 subject (0.4%) in placebo had at least one score >20 at 90 minutes post-dose. Subject (b) (6) in the esketamine group, a 55-year-old white Bulgarian male, had 90-minute post-dose scores ranging from 29 to 31 on all dosing days, with 40-minute scores ranging from 44 to 52; except Day 1, when his 40-minute score was 9 and his 90-minute score was 0. All of his predose scores were 0. The Applicant did not provide the CRF or a narrative for this subject.

As noted in the TRD program, attenuation appeared to occur with repeated treatment: for subjects in the esketamine group, the peak mean CADSS total score at 40 minutes post-dose decreased with consecutive doses: from 14.3 ± 12.6 (SD) on Day 1, to 8.2 ± 9.9 (SD) on Day 4, to 7.4 ± 9.9 (SD) on Day 8, to 6.1 ± 8.5 (SD) on Day 11. After that, the peak mean 40-minute score appeared to plateau around 5.0 ± 6.8 (SD) to 5.5 ± 8.8 (SD) on remaining Days 15, 18, 22, and 25. The proportion of subjects in the esketamine group with 90-minute scores >4 was higher on Day 1 (31 subjects (13.7%)) compared to Day 25 (8 subjects (3.5%)).

Clinical Reviewer's Comment: Overall, there does not appear to be a new or worsened safety signal for dissociation in the MDSI data. It continues to appear that a subset of subjects are prone to more severe and/or longer-lasting dissociation. The REMS 2-hour minimum monitoring appears adequate given the CADSS score improvement of the majority of subjects at 90 minutes post-dose, and the REMS recommends assessment at 2 hours to determine if patients are clinically stable and ready to leave the healthcare setting.

Cognitive Impairment

Risk of cognitive impairment is described in the current TRD label under warnings and precautions, as both a short-term impairment observed at 40 minutes post-dose that resolved at 2 hours post-dose in a study in healthy volunteers, and as a long-term risk reported with repeated ketamine misuse or abuse. Cognitive function was not formally assessed in the MDSI studies. Potentially related AEs were reported, with confusional state, disturbance in attention, and mental impairment grouped as per Table 55 as mental impairment, which occurred in nine subjects (4%) during the phase 3 studies treatment phase in the esketamine group only.

Clinical Reviewer's Comment: It is difficult to draw any conclusions from the AEs

potentially related to cognitive impairment, because they are somewhat vague and/or appear to possibly overlap with dissociative symptoms.

At the time of the interim database lock, cognitive data was available for 1,131 subjects in the ongoing long-term open-label study TRD3008, which evaluated subjects' cognition using a computerized cognitive battery. The interim CSR presented data for changes from baseline through Week 76, at which point sample sizes remained relatively large (e.g., 154 subjects provided data for the test of psychomotor function). Group mean performance on all tests, including psychomotor function, attention, visual learning, working memory, executive function, verbal learning, delayed verbal memory, and recognition memory, demonstrated either an improvement or stability from baseline. Upon examination of age subgroups, results were the same for subjects <65 years-old. In subjects ≥65 years-old (measured through Week 64, the latest timepoint with a reliable sample size), results were the same for all tests, except psychomotor function and attention (the tests of simple and choice reaction time), which demonstrated a decline in performance from baseline to Week 64.

Four of the phase 3 TRD studies had found no significant negative effect in the esketamine treatment group using the computerized cognitive battery and the Hopkins Verbal Learning Test-Revised. However, in the long-term, open-label Study TRD3004, a similar pattern with subjects ≥65 years-old was evident as demonstrated in Study TRD3008, although there were several complicating factors: a substantial decrease in the number of subjects ≥65 years-old between Day 28 and Week 44 (from 122 to 29 subjects); high intraindividual variability on the tests of psychomotor function and attention among subjects ≥65 years-old; and some improvement between Week 44 and Week 52 (study completion) on the tests of reaction time. The review team had recommended completion of 3-year TRD3008 as a PMR to further examine the issue.

Clinical Reviewer's Comment: Although the MDSI program examined a 4-week treatment phase, proposed labeling indicates that subjects may possibly continue on esketamine (especially if they have TRD), so effects with longer-term administration bear consideration. The longer-term cognitive battery results from study TRD3008 are reassuring for subjects <65 years-old, and for most domains with subjects ≥65 years-old. Without a control group, it is difficult to draw any conclusions about the decline from baseline in performance on tests of psychomotor function and attention (via simple and choice reaction time) in subjects ≥65 years-old. It does appear to replicate the findings from TRD3004, though for that study the Applicant had noted that broader impairments in attention were not evident, given that performance on tests of more complex cognitive domains was unaffected, and the TRD3004 findings were complicated by several factors. Greater detail will be available when the 3-year PMR Study TRD3008 is completed.

Ulcerative or Interstitial Cystitis

Cases of ulcerative or interstitial cystitis are described in the current TRD label under warnings and precautions with long-term off-label use or misuse/abuse of ketamine. There was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in the TRD studies in esketamine subjects compared to placebo, though no cases of interstitial cystitis were observed, including through 1 year. In the phase 3 MDSI studies treatment phase, there was a higher rate of potentially cystitis-related AEs (i.e., related to lower urinary tract symptoms: pollakiuria, dysuria, and micturition urgency) in the esketamine group (7 subjects (3.1%)) compared to placebo (2 subjects (0.9%)). There were no SAEs, discontinuations, or severe AEs related to lower urinary tract symptoms.

The interim CSR for ongoing open-label extension Study TRD3008 reported that 44 subjects (3.9%) of esketamine-treated subjects experienced AEs related to lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, cystitis noninfective), and 8 subjects (0.7%) reported cystitis. All AEs of cystitis were reported during the optimization/maintenance phase, none during induction, and were classified as mild or moderate. One SAE of cystitis occurred in Subject (b) (6) (reported term: chronic cystitis) that resulted in a later dose reduction. That subject, a 63-year-old U.S. female, had a past medical history of urinary tract infections (four times per year in the previous 4 years), abnormal pap smear with low grade squamous intraepithelial lesion, and left breast malignant neoplasm. The SAE occurred on Day 360 as confirmed by cystoscopy and biopsy, after receiving esketamine through Day 134 at 84 mg, at 70 mg from Day 135 through Day 147, at 84 mg through Day 360, and reduced to 56 mg on Day 417; the subject's treatment with esketamine was ongoing at the time of data lock. One AE during the induction phase occurred in a subject who had an unrelated SAE of urinary bladder polyp on Day 2.

Trial SUI2001 utilized the BPIC-SS, a patient-reported outcome measure to evaluate new treatments for cystitis or bladder-related symptoms; a total score >18 has demonstrated differentiation between healthy controls and overactive bladder. No subjects in either group demonstrated a post-dose score >18 during the treatment phase.

Clinical Reviewer's Comment: Overall, potentially cystitis-related AEs were reported at similar rates in the original TRD data, the phase 3 MDSI studies, and the interim CSR for ongoing study TRD3008. Cystitis AEs were reported in TRD3008 at <1% frequency; the one SAE sounds confounded by urinary tract infection history. Greater detail will be available when the 3-year PMR TRD3008 is completed.

Nausea and Vomiting

Nausea and vomiting are known AEs with esketamine administration. Risks of nausea and vomiting are described in the current TRD label under adverse reactions. In the phase 3 MDSI

studies, nausea was reported as an AE in 60 subjects (26.4%) in the esketamine group compared to 32 subjects (14.2%) in placebo. In the esketamine group only, nausea led to study drug discontinuation in 2 subjects (0.9%) or dose reduction/interruption in 11 subjects (4.8%), and was considered severe in 5 subjects (2.2%). Vomiting was reported as an AE in 26 subjects (11.5%) in the esketamine group compared to 12 subjects (5.3%) in placebo. In the esketamine group only, vomiting led to study drug discontinuation in 1 subject (0.4%) or dose reduction/interruption in 5 subjects (2.2%), and was considered severe in 2 subjects (0.9%). No SAEs were related to nausea or vomiting.

The majority of AEs occurred on dosing days (in the esketamine group, 89.1% for nausea and 80% for vomiting), and resolved the same day (94.4% for nausea and 100% for vomiting). Rescue medication was required for treatment of AEs of nausea and vomiting in 4% and 0.4%, respectively, of esketamine subjects. Attenuation appeared to occur with repeated treatment: the number of AE occurrences decreased greatly over the first few dosing days (for nausea, 39 on Day 1, to 19 on Day 4, to 6 on Day 8; for vomiting, 15 on Day 1, to 7 on Day 4, to 0 on Day 8) and plateaued (or tapered off entirely for vomiting).

Clinical Reviewer's Comment: Overall, there does not appear to be a new or worsened signal for nausea and vomiting in the MDSI data. They appear to attenuate with repeated administration, fairly markedly after generally three doses.

Currently-Unlabeled Submission-Specific Safety Issues

Events Potentially Related to Suicidal Ideation and Behavior

Suicidal ideation and behavior are described in the current TRD labeling only as a class risk of antidepressants in adolescents and young adults—as a boxed warning and in warnings and precautions. Table 64 lists AEs potentially related to suicidal ideation and behavior during the treatment phase in the pooled phase 3 MDSI studies; as with other AE tables, I considered the treatment phase to extend through and include Day 27, within 2 days of the last dose of study drug. Table 65 lists the results during the follow-up phase.

Table 64. Adverse Events Potentially Related to Suicidal Ideation and Behavior During the Treatment Phase in Pooled Trials SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)		Esketamine + SOC (N=227) n (%)	
	AE*	SAE	AE*	SAE
Psychiatric disorders				
Suicidal ideation	9 (4.0%)	4 (1.8%)	8 (3.5%)	2 (0.9%)
Intentional self-injury	4 (1.8%)	0	7 (3.1%)	0
Suicide attempt	3 (1.3%)	3 (1.3%)	4 (1.8%)	4 (1.8%)
Depression suicidal	2 (0.9%)	1 (0.4%)	2 (0.9%)	2 (0.9%)
Completed suicide	0	0	1 (0.4%)	1 (0.4%)
Investigations				
Intentional overdose	0	0	1 (0.4%)	0

Source: Adapted from Integrated Summary of Safety Table 18, p. 68, and ADAE dataset

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SOC = standard of care

* Adverse events include serious adverse events

Table 65. Adverse Events Potentially Related to Suicidal Ideation and Behavior During the Follow-Up Phase in Pooled Trials SUI3001 and SUI3002

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=185) n (%)		Esketamine + SOC (N=190) n (%)	
	AE*	SAE	AE*	SAE
Psychiatric disorders				
Suicidal ideation	12 (6.5%)	6 (3.2%)	10 (5.3%)	5 (2.6%)
Suicide attempt	3 (1.6%)	3 (1.6%)	7 (3.7%)	7 (3.7%)
Depression suicidal	5 (2.7%)	5 (2.7%)	5 (2.6%)	5 (2.6%)
Intentional self-injury	2 (1.1%)	0	3 (1.6%)	0

Source: Adapted from Integrated Summary of Safety Table 19, p. 69, and ADAE dataset

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SOC = standard of care

* Adverse events include serious adverse events

During the treatment phase, one subject (0.4%) each discontinued esketamine because of an AE of depression suicidal or suicidal ideation; one subject (0.4%) in each treatment group reduced or interrupted study drug dose because of an AE of suicide attempt; and three subjects (1.3%) in the esketamine group and two subjects (0.9%) in placebo experienced a severe AE of suicide attempt, and one subject (0.4%) in the esketamine group and three subjects (1.3%) in placebo experienced a severe AE of suicidal ideation.

During the treatment phase in Trial SUI2001, three subjects (8.6%) in the esketamine group reported AEs potentially related to suicidal ideation and behavior: suicidal ideation (two

subjects, which were both SAEs) and self-injurious behavior (one subject). One placebo subject who discontinued reported suicidal ideation. During the follow-up phase, two subjects (7.4%) in the esketamine group reported one potentially related AE each, suicidal ideation (an SAE) and intentional self-injury. Five subjects (22.7%) in placebo reported suicide attempt (three subjects, SAEs), suicidal ideation (one subject, an SAE), and self-injurious ideation (one subject).

The Applicant notes that across all completed and ongoing studies of esketamine in both TRD and MDSI, four completed suicides were reported in subjects receiving esketamine (two in completed TRD studies, one in the ongoing open-labeled Study TRD3008, and one in the phase 3 MDSI studies). Based upon the combined cumulative exposure across indications (1827.8 patient-years), the Applicant calculates an incidence of 0.22 completed suicides per 100 patient-years of exposure across all completed and ongoing studies of esketamine. The Applicant notes that is comparable to the rate reported in a meta-analysis of studies in patients with MDD (who were treated with antidepressants; also 0.22; Braun et al. 2016), and lower than the rate reported in a meta-analysis of patients with TRD receiving various treatments (ECT, VNS, DBS, and one ketamine study; Bergfeld et al. 2018).

Clinical Reviewer's Comment: Generally, rates of AEs potentially related to suicidal ideation and behavior were similar between treatment groups; the exceptions of the follow-up-phase higher number of suicide attempts and treatment-phase intentional self-injury were discussed previously regarding SAEs and common AEs, respectively. As noted, the follow-up-phase suicide attempts in the esketamine group were reported on Days 29, 30, 36, 49, 60, 64, and 86 (and the completed suicide occurred on Day 27). In the placebo group, they were reported on Days 28, 37, and 39. One might be tempted to conjecture about a potential withdrawal effect from esketamine predisposing to suicide attempt, but the fact that the placebo group attempts were also relatively early in the follow-up phase doesn't support that theory (also, the groups were roughly equal regarding suicidal ideation). (The Applicant's Kaplan-Meier hazard ratio of 1.28 does demonstrate the impact of the slightly shorter time interval to the completed suicide and first three suicide attempts in the esketamine group.) The suicide attempts may, however, signal a need for caution while discontinuing treatment in this population. The Applicant's literature comparisons offer some reassurance. Those meta-analyses examined many different antidepressants or other types of treatment, rather than just one treatment, which is less supportive; but the TRD meta-analysis excluded studies where subjects had a history of attempted suicide, which makes for a lower-risk group than the esketamine studies.

Per the Applicant, for the pooled phase 3 MDSI studies, responses from patient-reported modules of the SIBAT were mapped to corresponding categories of the Columbia Classification Algorithm for Suicide Assessment (C-CASA) 2012 Plus (an extended version of C-CASA 2012), including overall categories of suicidal ideation, suicidal behavior, self-injurious behavior, and no suicidal ideation or behavior/not enough information. (The overall categories are divided

further (e.g., suicidal behavior includes “Completed Suicide,” “Suicide Attempt,” “Interrupted Suicide Attempt,” “Aborted Suicide Attempt,” and “Preparatory acts toward imminent suicidal behavior”).)

At baseline, the data for most subjects were mapped to the C-CASA 2012 Plus category “Suicide Attempt,” “Aborted Suicide Attempt,” or “Interrupted Suicide Attempt” (76.1% of subjects in the esketamine group versus 75.1% of subjects in placebo). Based on the C-CASA mapping, all post-baseline “Suicide Attempts” were cross-referenced with AE reporting of suicide attempts and queried if an event was not reported as an AE. According to the Applicant, several self-reported “Suicide Attempts” from the SIBAT C-CASA mapping were confirmed not to be suicide attempts per the investigator.

Per the Applicant, in both treatment groups, the majority of subjects’ most severe postbaseline C-CASA severity category during the double-blind treatment phase was suicidal ideation (66.4% of subjects in the esketamine group versus 69.3% of subjects in placebo). Of the subjects with a baseline severity category of suicidal ideation, one of 21 esketamine subjects versus one of 28 placebo subjects had a most severe postbaseline severity category of suicidal behavior. Of the subjects with a baseline severity category of suicidal behavior, 36 of 189 (19%) subjects in the esketamine group and 38 of 190 (20%) subjects in placebo had a most severe postbaseline severity that remained in the suicidal behavior category. Results were generally similar for subjects ages 18 to 24 years-old.

Per the Applicant, in both treatment groups, the majority of subjects’ most severe postbaseline C-CASA severity category during the follow-up treatment phase was suicidal ideation (51.1% of subjects in the esketamine group versus 56.2% of subjects in placebo). Of the subjects with a baseline severity category of suicidal ideation, none of 20 esketamine subjects versus three of 22 placebo subjects had a most severe postbaseline severity category of suicidal behavior. Of the subjects with a baseline severity category of suicidal behavior, 40 of 168 (23.8%) subjects in the esketamine group and 30 of 163 (18.4%) subjects in placebo had a most severe postbaseline severity that remained in the suicidal behavior category. Results were generally similar for subjects ages 18 to 24 years-old.

Clinical Reviewer’s Comment: The C-CASA data do not appear to demonstrate any notable signal for worsening suicidal ideation/behavior between treatment groups in either the double-blind or follow-up treatment phases.

Psychotomimetic Effects

Racemic ketamine is known to potentially cause temporary psychotomimetic effects (Lahti et al. 2001), although it is unclear if or how that might translate into inducing any more-than-temporary symptoms. Trial SUI2001 utilized the BPRS+ as a 4-item subscale to assess treatment-emergent psychotic symptoms (suspiciousness, hallucinations, unusual thought

content, and conceptual disorganization), measured predose and post-dose at 40 minutes, 2 hours, and 4 hours. Scoring ranges from 0 (not assessed), 1 (not present), 2 (very mild), 3 (mild), 4 (moderate), 5 (moderately severe), 6 (severe), to 7 (extremely severe), with a high score of 28. During the treatment phase, a greater number of subjects in the esketamine group (22 subjects (62.9%)) demonstrated an increase in total BPRS score at any time than placebo (6 subjects (19.4%)). A greater number of subjects in the esketamine group (14 subjects (40%)) demonstrated a BPRS total score ≥ 3 at any time than placebo (no subjects). Symptoms peaked at 40 minutes post-dose (Day 1 esketamine mean 1.8 ± 2.8 (SD) versus placebo mean 0.1 ± 0.3 (SD)) and resolved by 2 hours post-dose; maximal increases were noted on Day 1 and Day 4 of the treatment phase (e.g., Day 4 post-dose 40 minute esketamine mean 1.4 ± 2 (SD), thereafter post-dose 40 minute mean range 0.7 to 1).

One subject (b) (6) in the phase 3 MDSI trials and one subject (b) (6) in ongoing Trial SUI2002 in the esketamine group experienced an SAE of psychosis during treatment phase, both described in Section 7.5.4. Additionally, one subject (b) (6) in the Trial SUI2001 esketamine group experienced moderate AEs of psychotic disorder and paranoia (as well as an SAE of agitation causing prolonged hospitalization and discontinuation). That subject, a 19 year-old unreported-race male in the United States, had a history of depressive moods, mild cannabis use disorder, nicotine use, and agitation. Concomitant medications included bupropion and quetiapine. He received one dose of esketamine on Day 1; on Day 3, he demonstrated increased agitation, threatening to leave, and threatening to harm himself or other people. He was placed on an involuntary hold, transferred to a unit with a higher level of care, and received haloperidol and lorazepam. Esketamine treatment was discontinued and the subject was withdrawn from the study. The psychotic disorder and paranoia AEs reportedly lasted 2 days and resolved. An AE of (rule out) bipolar disorder was reported, but noted as resolved after 3 days. However, of note, lithium was started and bupropion and quetiapine were discontinued.

As of the interim CSR cutoff date of December 31, 2018, no AEs of psychosis were reported in the ongoing open-label study TRD3008 (and none in the 120-day safety update with cutoff of October 2, 2019). Including the induction and optimization/maintenance phases, nine subjects (0.8%) reported an AE of hallucination visual, six subjects (0.5%) reported an AE of hallucination, three subjects (0.3%) reported an AE of paranoia, two subjects (0.2%) reported an AE of hallucination auditory, and one subject (0.1%) each reported AEs of delusion, hypnopompic hallucination, somatic hallucination, and suspiciousness. One subject (0.1%) each discontinued study drug during the optimization/maintenance phase for AEs of hallucination and paranoia.

Clinical Reviewer's Comment: One potential difficulty with capturing psychosis (whether with related AEs or by BPRS+) is the overlap with dissociative symptoms; i.e., hallucinations are considered to be in the dissociation PT grouping for the MDSI studies, as they were for the original TRD submission. For example, for subjects scoring total

BPRS scores ≥ 4 in Trial SUI2001, they also generally had elevated CADSS scores at 40 minutes post-dose.

However, as noted previously regarding the subjects with SAEs of psychotic disorder in the phase 3 MDSI studies and ongoing study SUI2002, and for the subject in SUI2001, the subjects' ages and MDD are consistent with the potential for psychotic symptoms, which confounds any inference of drug-induced causality (additionally, the SUI2001 subject, also given a rule-out bipolar disorder AE, is confounded by a potential cannabis use disorder). As previously noted in the literature, an outpatient sample estimated an incidence of psychotic depression of 5.3% among depressed patients (Gaudiano et al. 2011), and an inpatient sample estimated the incidence as high as 25% (Coryell et al. 1984; though the latter is an older sample).

The minimal signal for psychosis in ongoing open-label long-term study TRD3008 is reassuring for lack of a long-term effect, though it is possible that any potential effect may occur early in predisposed individuals. In the three cases from the phase 2/3 MDSI studies, the subjects appeared to experience an emergence of psychotic or bipolar illness, though a temporary effect is possible. Given the overall low incidence in the MDSI phase 2/3 studies and background confounding, continued monitoring in the postmarket setting will observe for any further evidence of a signal.

Hypomania or Mania

The Applicant notes that the overall risk of emergence of manic symptoms has been estimated as 3.4% per year of treatment with the use of oral antidepressants (Baldessarini et al. 2013), which may be related to undiagnosed bipolar disorder. Across the phase 2/3 MDSI studies, no AEs of mania or hypomania were reported. As discussed above, in Trial SUI2001 one subject had an AE of (rule-out) bipolar disorder; although the AE was reportedly resolved, the subject's bupropion was discontinued and replaced with lithium. As reported in the 120-day safety update, in the ongoing blinded pediatric study SUI2002, Subject (b) (6) experienced an SAE of bipolar disorder. The subject, a 15-year-old white female with a history of MDD with "irritability at baseline" started escitalopram and blinded study drug; on Day 26, following her last study drug administration, the SAE of bipolar disorder was reported. She was re-admitted to the hospital after a suicide attempt on the same day in the context of a mixed mood state including irritability, excitation, and aggression after an argument with her mother. Escitalopram was discontinued, and she was treated with risperidone and valproate. Per the Applicant's response to an IR regarding suicide attempts, post-enrollment, previous records were found that indicated a suspected but unconfirmed bipolar diagnosis; the subject had a second suicide attempt following a sertraline retrial late in the follow-up phase.

In the ongoing, open-label extension study TRD3008, an AE of mania was reported in three subjects (0.3%), including one SAE, all of which led to discontinuation of study drug; and an AE

of hypomania was reported in two subjects (0.2%), one of which led to discontinuation of study drug. An AE of bipolar disorder was reported in one subject (0.1%).

During the phase 3 MDSI studies treatment phase, euphoric mood occurred in the esketamine group at $\geq 5\%$ and more than twice the rate of placebo (i.e., in 17 subjects (7.5%) versus one subject (0.4%)). In the 17 subjects, it occurred once in approximately half, two to three times in another 40%, and five and seven times in one subject each. The events were considered mild in 14 subjects and moderate in three. All events occurred on dosing days, with a mean duration of 2.4 ± 7.3 hours and median of 0.9 hours; two outliers reported durations of 42.8 and 16.6 hours. (Subject (b) (6) with the duration of 42.8 hours on Day 1, later withdrew for lack of efficacy after 3 doses, and experience the SAE of psychotic disorder as described previously.) All events resolved and no doses were changed as a result.

Clinical Reviewer's Comment: Overall, there does not appear to be a notable safety signal for hypomania or mania (i.e., two bipolar disorder AEs in the phase 2/3 MDSI studies, and minimal reports in TRD3008 (<1%)), especially given the literature background rate estimate. The AEs of euphoric mood in the phase 3 MDSI studies occurred on dosing days, were mainly mild and some moderate, and resolved same-day in almost all cases (all if excluding Subject (b) (6) with later onset of psychotic disorder).

7.5.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

See Section 7.5.5 Analysis of Submission-Specific Safety Issues regarding use of the MOAA/S, CADSS, BPIC-SS, SIBAT, and BPRS+.

7.5.7. Safety Analyses by Demographic Subgroups

In the phase 3 MDSI studies esketamine group, the majority of subjects were female (59.5%). In the esketamine group, female subjects reported a higher rate of frequently reported AEs ($\geq 10\%$ in both subgroups, as per Table 55 groupings, and greater than placebo overall) during the treatment phase than male subjects for the AEs dissociation (52.5% versus 40.2%), dizziness (48.9% versus 40.2%), sedation (32.5% versus 23.9%), nausea (31.1% versus 19.6%), dysgeusia (21.5% versus 18.5%), and hypoesthesia (14.8% versus 10.9%). Male subjects reported a higher rate than female subjects of the AE blood pressure increased (21.7% versus 10.4%).

Clinical Reviewer's Comment: Most AE frequency differences between sexes were not notable. Dissociation and nausea were reported in females >10% more than males, and blood pressure increased was reported in males >10% more than females; however, for all three AEs the difference was <15%, so it is unclear whether the differences in frequency have any clinical significance. In the U.S., hypertension affects men and women nearly equally (Benjamin et al. 2017), although globally in high-income

countries, men have a higher prevalence than women (Mills et al. 2017). It is unclear why women may have experienced higher rates of dissociation and nausea.

In the phase 3 MDSI studies esketamine group, 81 subjects (35.7%) were aged 18 to 34 years, 104 subjects (45.8%) were aged 35 to 54 years, and 42 subjects (18.5%) were aged 55 to 64 years. In the esketamine group, the 18-to-34 group reported a higher rate of frequently reported AEs ($\geq 10\%$ in all subgroups, as per Table 55 groupings, and greater than placebo overall) during the treatment phase than the 35-to-54 and 55-to-64 groups for the AEs nausea (30.9% versus 26.9% and 16.7%, respectively) and hypoesthesia (16% versus 11.5% and 11.9%, respectively). The 35-to-54 group reported a higher rate than the 18-to-34 and 55-to-64 groups for the AE dissociation (52.9% versus 46.9% and 35.7%, respectively). The 55-to-64 group reported a higher rate than the 18-to-34 and 35-to-54 groups for the AEs dizziness (52.4% versus 45.7% and 42.3%, respectively), dysgeusia (40.5% versus 23.5% and 14.4%, respectively), sedation (38.1% versus 21% and 31.7%, respectively), and anxiety (16.7% versus 11.1% and 15.4%, respectively).

Clinical Reviewer's Comment: Most AE frequency differences between age groups were not notable, and the smaller size of the 55-to-64 year-old group may limit the utility of any comparisons. The 18-to-34 year-old group reported >10% more frequent nausea than the 55-to-64 year-old group. The 35-to-54 year-old group reported >10% more frequent dissociation than the 55-to-64 year-old group. The 55-to-64 year-old group reported >10% more frequent dysgeusia than both of the other groups, >10% more frequent sedation than the 18-to-34 year-old group, and >10% more frequent dizziness than the 35-to-54 year-old group. One possibility is that older subjects may have been more prone to having concomitant medical conditions and medications with the potential for greater sedation than younger subjects.

In the phase 3 MDSI trials esketamine group, 169 subjects (74.4%) were white, 29 subjects (12.8%) were Asian, 17 subjects (7.5%) were "other," and 12 subjects (5.3%) were black. Given the large imbalance in group sizes, it is not informative to compare AE incidences between groups.

7.5.8. Specific Safety Studies/Clinical Trials

No new specific safety studies were submitted with this supplement.

7.5.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity or tumor development studies were submitted with this

supplement.

Human Reproduction and Pregnancy

Per the Applicant, 11 pregnancies were reported in subjects across all TRD and MDSI studies as of the cutoff date of April 20, 2019, with esketamine, placebo, or blinded study drug: eight in phase 3 studies, two in phase 2 studies, and one in a phase 1 study. Additionally, four pregnancies were reported in partners of male subjects who received esketamine in phase 3 studies as of April 20, 2019.

From the TRD submission, the cases of subjects receiving esketamine resulted in two ectopic pregnancies, two spontaneous abortions, one blighted ovum leading to elective abortion, one elective abortion, and one ongoing pregnancy with a reportedly normal fetus at the time of submission. The still-blinded subject withdrew from treatment and the pregnancy outcome was unknown. The Applicant assessed the non-elective-abortion cases as not related to study drug: in both of the ectopic pregnancies, the subjects had previously had sterilization procedures. In both of the spontaneous abortions, the subjects were of advanced maternal age, had had previous spontaneous abortions, and were obese. In the case of blighted ovum (a phase 1 study), the subject was of advanced maternal age, and had received IN esketamine on one day during Period 3 and IV esketamine on one day during Period 4.

From the MDSI submission, the two cases of subjects receiving esketamine (in Study TRD3008) resulted in a spontaneous abortion and an elective abortion. (One placebo subject (in Study SUI3001 (b) (6) In the case of spontaneous abortion (that the Applicant assessed as not related to study drug), the subject (b) (6) had a risk factor of advanced maternal age and weighed 267 lbs. She had been receiving esketamine 84 mg twice weekly along with an oral contraceptive and sertraline. The most recent dose of esketamine was approximately 3 weeks after the subject's last menstrual period and approximately two weeks before her confirmed pregnancy. Esketamine was withdrawn. The spontaneous abortion AE was reported on April 2, 2019, approximately 1 week after her positive urine pregnancy test.

Of the four reported cases of pregnancies in partners in male subjects, two resulted in normal pregnancy and delivery and two had no outcome information available.

Clinical Reviewer's Comment: Given the background rate of spontaneous abortions and the risk factors detailed by the Applicant in those cases, overall, there does not appear to be a safety signal for spontaneous abortion; the cases of ectopic pregnancy appear likely related to the subjects' previous sterilization procedures.

Pediatrics and Assessment of Effects on Growth

The Applicant submitted CRFs for ongoing pediatric Study SUI2002, but did not submit an interim CSR or datasets for analysis.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Per the Applicant, there have been no reported overdose cases with esketamine in any of the clinical studies. The Applicant's comprehensive evaluation of abuse potential was reviewed with the TRD application. In the phase 3 MDSI studies, the Applicant examined AEs suggestive of abuse potential and reported a higher treatment-phase occurrence in the esketamine group than placebo for the most common AEs suggestive of abuse potential (ungrouped) like dizziness, dissociation, somnolence, euphoric mood, hallucination visual, and feeling drunk. Per the Applicant, most AEs suggestive of abuse potential occurred on intranasal dosing days and resolved same-day. Most were mild to moderate; 4.8% of subjects in the esketamine group reported severe AEs suggestive of abuse potential, compared to 0.4% in placebo. In both groups, the number of AEs suggestive of abuse potential was generally highest on Day 1 and decreased for subsequent dosing days.

Per the Applicant the long-term phase 3 studies TRD3003 and TRD3004 did not present evidence suggestive of a distinct withdrawal syndrome; the TRD review noted that withdrawal effects were unlikely given that dosing pre-randomization was infrequent (weekly or every 2 weeks).

Clinical Reviewer's Comment: As noted in the TRD review, because esketamine is administered under clinical supervision and distributed to certified prescribers as per the REMS program, the risk of overdose and abuse/misuse is less likely.

7.5.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

DPV completed a postmarket drug safety surveillance summary on March 24, 2020 utilizing product labeling, top reported PTs in FAERS, disproportionality analysis of FAERS data using Empirica Signal, published medical literature, the Applicant's periodic safety reports and responses to subsequent IRs, and the 6-month REMS Assessment Report to detect new safety signals reported with the use of esketamine. DPV focused on 1) unlabeled AEs with the potential for serious outcomes, 2) labeled AEs with unexpected characteristics, such as an increase in severity, and 3) other important safety findings that may indicate a new safety signal.

Of labeled AEs with unexpected characteristics, the Applicant had identified 10 SAEs of sedation- or dissociation-related SAEs, including several that occurred outside the 2-hour

monitoring period. One case (previously mentioned in Section 7.5.4) involved PTs including altered visual depth perception (occurring sometime in the first 24 hours after dosing and lasting approximately 4 days), feeling drunk, and road traffic accident. That case (b) (6) involved a 47-year-old woman in the 1 to 3 days after esketamine treatment (unclear on which day the accident occurred). The patient “wrecked her car” in her driveway by hitting her all-terrain vehicle (ATV). The report stated that the patient began feeling drunk the day after her esketamine dose; she “felt fine” but her depth perception was off, “ran into walls,” had trouble typing, and finally hit her ATV with her car in her driveway. These symptoms completely resolved within 2 days of the event. DPV identified one new safety signal that was also a labeled AE with unexpected characteristics: blood pressure increased lasting beyond the 2-hour monitoring period. There were four cases of blood pressure increased or hypertension among the Applicant-identified SAEs lasting beyond the 2-hour monitoring period or had unknown duration. Two of those cases reported an outcome of resolved/resolving, one reported an outcome of not resolved, and the last reported an unknown outcome.

Clinical Reviewer’s Comment: Current labeling indicates that patients should be monitored for at least 2 hours regarding the risks of sedation, dissociation, and increase in blood pressure, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. It appears there have been a small number of postmarketing cases in which SAEs occurred after the 2-hour monitoring period (although difficult to say when exactly from “≤1 day” or unknown latency to events). DPV will closely monitor other sedation- or dissociation-related SAEs that occur or persist outside of the 2-hour monitoring period, and has opened a Newly Identified Safety Signal to perform a separate review of hypertension and esketamine, focusing on cases lasting beyond the 2-hour window or with progression to a hypertensive urgency or emergency resulting in escalation of care or end organ damage.

Of unlabeled AEs with the potential for serious outcomes (including serotonin syndrome, acute kidney injury, anaphylactic reaction, seizure, cerebrovascular accident, blindness, drug-induced liver injury), most involved one or two cases only with confounding or insufficient information. DPV’s summary identified six unique cases with the PT completed suicide:

...one of which lacked sufficient details for assessment such as timing of esketamine administration relative to the suicide. One additional case indicated that the patient never received esketamine prior to the suicide. The remaining four cases described patients with severe underlying disease (treatment resistant depression, in one case failing more than 35 sessions of electroconvulsive therapy) who received two or more doses of esketamine and then committed suicide at varying time periods after the last dose prior to the event. In addition to severity of illness and high background rate of death by suicide in this patient population, another confounding factor for case

assessment is the presence of other antidepressants which are labeled for increased risk of suicide.

I reviewed the quarterly PADERs since initial approval March 2019 and the 6- and 12-month REMS Assessment Reports, including cases of completed suicide, death not otherwise specified, and suicide attempts, and obtained further case details from DPV's FAERS search and an IR response from the Applicant.

I identified 10 completed suicide cases (including the five cases identified by DPV in which the subject had received esketamine). One of the DPV-identified cases had reportedly concealed active heroin and marijuana use from his clinicians, and another had an acute stressor prior to the event (eviction from uncle's house). In the additional five cases of completed suicide, one subject with TRD lacked a personal history of attempts but had a strong family history of suicides (father, several paternal male relatives). Another case also had a strong family history of suicides (by brother and sister in their 40s) and a history of brain surgery and seizures. In a third case in Switzerland, the treating clinician was reportedly unaware the subject had previously discussed suicidal intent with a private psychiatrist and was in contact with an organization to provide passive suicide assistance in a palliative setting. Another case had an acute stressor and a history of MDD with catatonia. Two of the 10 cases lacked a significant amount of detail. The three cases of death not otherwise specified lacked detail. In a case of death due to road traffic accident, the 22-year-old male was hit by an automobile on his bike, but it was reported that it was not a suicide, and that the patient was doing well on esketamine.

Clinical Reviewer's Comment: Overall, I agree with DPV's assessment that the cases of completed suicide are confounded by severity of illness, a high background rate of suicide in this population, presence of other antidepressants, as well as various other factors (e.g., strong family history of suicide, acute stressors, prior planning before starting esketamine). DPV will continue to closely monitor this signal for esketamine.

I identified 15 cases of suicide attempts. Five cases lacked detail; seven cases involved acute stressors; three cases involved longer-term esketamine treatment (i.e., >1.5 years); in three cases, subjects continued esketamine treatment after their attempts. One subject was diagnosed with bipolar disorder and appeared to be activated by antidepressants in general.

Clinical Reviewer's Comment: Similar to cases of completed suicides, the cases of suicide attempts are confounded by severity of illness, a high background rate of suicide (attempts) in this population, presence of other antidepressants, and acute stressors. The cases in which attempts occurred during longer-term treatment make it difficult to draw any conclusions about a causal effect, and the cases in which treatment was continued post-attempt do not make a compelling argument for causality. DPV should monitor this signal along with completed suicides for esketamine.

Expectations on Safety in the Postmarket Setting

The current REMS appears adequate to address the risk of serious adverse outcomes from sedation, dissociation, and elevated blood pressure. The healthcare setting administration also allows for minimization of the risks of abuse and diversion. The Applicant is conducting a 3-year ongoing open-label Study TRD3008 to better characterize the risks of cognitive impairment and ulcerative or interstitial cystitis.

7.5.11. Integrated Assessment of Safety

The Applicant submitted sufficient information to adequately assess esketamine's safety profile. No new safety concerns appeared to emerge from the MDSI study data. The current labeling and REMS address the major AEs (i.e., sedation, dissociation, and risks of abuse and misuse, as well as increased blood pressure). Long-term risks of cognitive impairment and ulcerative or interstitial cystitis will be addressed with fulfillment of the TRD PMR with the completion of the ongoing, open-label, long-term Study TRD3008. Ongoing REMS data collection and pharmacovigilance will continue to monitor for longer-term safety issues.

7.6. Statistical Issues

See details under specific studies.

7.7. Conclusions and Recommendations

As previously noted, the two phase 3 Trials SUI3001 and SUI3002 (and supportive phase 2 Trial SUI2001) presented by the Applicant meet the statutory standard for substantial evidence of effectiveness for esketamine plus standard of care with regard to the primary efficacy endpoint, change from baseline to 24 hours (Day 2) on the MADRS total score. In the context of the rapid time to onset of benefit than other antidepressants for this severely ill population, the LS means MADRS total score treatment differences demonstrated in the studies, with supportive information regarding the durability and persistence of effect, are clinically meaningful for esketamine's intended use: as means to provide more rapid relief for patients while awaiting onset of benefit of other antidepressants. The MDSI program studies did not demonstrate evidence of effectiveness regarding the key secondary endpoint (CGI-SS-R change from baseline to 24 hours (Day 2)). Regarding safety, the Applicant submitted sufficient information to adequately assess esketamine's safety profile, and no new safety concerns appeared to emerge from the MDSI study data. The current labeling and REMS address the major AEs (i.e., sedation, dissociation, and risks of abuse and misuse, as well as increased blood pressure). Given these results, the review team recommends approval of this efficacy supplement for the indication and with the limitations of use previously described.

8 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not convened for this submission.

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9 Pediatrics

An agreed initial Pediatric Study Plan (iPSP) was issued on January 13, 2017 for:

- A partial waiver for conducting pediatric studies with intranasal esketamine in neonates, infants and children (aged 0 to <9) for the treatment of MDD in subjects who are assessed to be at imminent risk for suicide. This partial waiver request is based upon the statutory grounds as stated in 21 CFR 314.55(c)(3): “Necessary studies are impossible or highly impracticable because, for example, the number of such patients is so small or geographically dispersed.”
- A deferral for intranasal esketamine as a treatment for MDD in children and adolescent subjects 9 to < 18 years of age who are assessed to be at imminent risk for suicide. The statutory basis for this deferral request and as outlined in 21 CFR 314.55(b), is that “the drug is ready for approval in adults before studies in pediatric patients are complete.”

A Pediatric Written Request (PWR) was issued on August 2, 2017, amended January 8, 2018, under IND 129516 for the following required studies:

- Nonclinical juvenile rat neurotoxicity assessment study: Prior to enrolling children ages 9 to < 12 years of age into clinical trials, Applicant must conduct a neurotoxicity assessment study in juvenile animals in order to examine the excitotoxic and apoptotic potential of esketamine treatment on the adolescent brain
- Study 1 (SUI2002): Dose-finding/efficacy and safety study (ages 9 years to less than 18 years). Applicant must conduct a randomized, double-blind, double-dummy, parallel group, multi-dose study of intranasal esketamine versus oral midazolam for 4 weeks in children 9 to less than 18 years of age with major depressive disorder and suicidal ideation. The Applicant is currently conducting this study.
- Study 2 (SUI3003): Efficacy and safety study (ages 9 years to less than 18 years). Applicant must conduct a randomized, double-blind, double-dummy, parallel group study of intranasal esketamine versus oral midazolam for 4 weeks in children 9 to less than 18 years of age with major depressive disorder and suicidal ideation.
- Additionally, the Applicant plans to conduct a phase 3 open-label safety study (SUI3004).

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing information

The table below summarizes significant changes to the proposed prescribing information made by the Agency. This labeling was under negotiation at the time of completion of this review. The remainder of this section will only focus on high-level issues.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Highlights		
Boxed Warning	See comments below in FPI Boxed Warning for more information.	
Indications and Usage	See comments below in FPI Indications and Usage for more information.	
Dosage and Administration	See comments below in FPI Dosage and Administration for more information.	
Warnings and Precautions	See comments below in FPI Warnings and Precautions for more information.	
Adverse Reactions	See comments below in FPI Adverse Reactions for more information.	
Use in Specific Populations	See comments below in FPI Use in Specific Population for more information.	
Full Prescribing Information		
Boxed Warning		
1. Indications and Usage	Applicant proposed treatment of “rapid reduction of depressive symptoms in adult patients with” MDD “who have active suicidal ideation with intent.” Applicant proposed Limitations of Use (LOU) of (b) (4) Use of SPRAVATO does not preclude the need for hospitalization, if clinically warranted.”	Removed “rapid” given adequate description in Section 14 of time course of response, and use of a non-scientificallly-valid, not-easily-recognizably-defined term for health care providers, as per guidance. Modified to treatment of “depressive symptoms in adults with” MDD “with acute suicidal ideation or behavior.” Modified LOU to “the effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if

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NDA 211243 S004

Spravato (esketamine) nasal spray

		clinically warranted, even in patients experience improvement after an initial dose of SPRAVATO,” to note program failure on CGI-SS-R secondary endpoint and note that standard of care included a clinically warranted inpatient psychiatric admission.
2. Dosage and Administration	Applicant rewrote instructions for missed treatment sessions to same effect.	
4. Contraindications		
5. Warnings and Precautions	Applicant revise (b) (4) (b) (4)	(b) (4) Modified W&P data to include MDSI data regarding sedation, dissociation, and increase in blood pressure.
6. Adverse Reactions	Applicant added paragraph describing MDSI program AE data.	Added separate section describing MDSI data exposure, reasons for discontinuation, most common AEs including separate table; modified AE-of-interest paragraphs (i.e., sedation, dissociation, increase in blood pressure, nausea and vomiting) to include MDSI data.
7. Drug Interactions		
8. Use in Specific Populations		
9. Drug Abuse and Dependence		
10. Overdosage		
11. Description		
12. Clinical Pharmacology		
13. Nonclinical Toxicology		
14. Clinical Studies	Applicant added paragraph, table (b) (4) and graph describing MDSI data, including effects on suicidality.	Revised additions: table (b) (4) (b) (4) effects on suicidality revised to accurately reflect failure on secondary endpoint and remove subpopulation analysis.
16. How Supplied/ Storage and Handling		
17. Patient Counseling	Applicant added information	Revisions made to align with

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Spravato (esketamine) nasal spray

	regarding MDSI studies.	revisions in above sections.
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Other Prescription Drug Labeling

Not applicable.

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11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant has submitted a proposal for modifications to the existing REMS which is under negotiation and discussion with our review team. The Applicant proposes modifications for

(b) (4) Please refer to the DRM review for more details; briefly, DRM does not find the proposed REMS modification acceptable. In particular, DRM does not believe (b) (4)

(b) (4) hospitals with on-site pharmacies and emergency departments generally have policies and procedures in place to provide informed consent to patients that undergo treatments and are required to document these procedures. DRM recommends that as part of certification hospitals agree that policies and procedures are in place to ensure that staff is trained and patients are monitored.

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12 Postmarketing Requirements and Commitment

The review team does not recommend any PMRs or PMCs. Long-term data regarding the risks of ulcerative or interstitial cystitis and cognitive impairment are being collected under the PMR for the TRD application with ongoing, long-term open-label Study TRD3008. The Applicant has collected data on longer-term administration under the TRD program.

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13 Additional OCP Division Director Comments

None.

14 Additional OB Division Director Comments

None.

15 Additional Clinical Division Director Comments

I have reviewed the above information, made edits as appropriate, and concur with the conclusions reached by the review team.

16 Office Director (or designated signatory authority) Comments

The designated signatory authority for this efficacy supplement is Director of the Division of Psychiatry, Tiffany R. Fachione, MD.

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17 Appendices

17.1. References

American Psychiatric Association, 2010, Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition, Arlington (VA): American Psychiatric Association.

American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Arlington (VA): American Psychiatric Association.

Baldessarini RJ, Faedda GL, Offidani E, Vazquez GH, Marangoni C, Serra G, and Tondo L, 2013, Antidepressant-Associated Mood-Switching and Transition from Unipolar Major Depression to Bipolar Disorder: A Review, *J Affect Disord*, 148(1):129-135.

Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, and Muntner P, 2017, Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association, *Circulation*, 135(10):e146-e603.

Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, and Denys D, 2018, Treatment-Resistant Depression and Suicidality, *J Affect Disord*, 235:362-367.

Blair-West GW, Cantor CH, Mellsop GW, and Eyeson-Annan ML, 1999, Lifetime Suicide Risk in Major Depression: Sex and Age Determinants, *J Affect Disord*, 55(2):171-178.

Braun C, Bschor T, Franklin J, and Baethge C, 2016, Suicides and Suicide Attempts During Long-Term Treatment With Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients With Major Depressive Disorder, *Psychother Psychosom*, 85(3):171-179.

Brown GK, Beck AT, Steer RA, and Grisham JR, 2000, Risk Factors for Suicide in Psychiatric Outpatients: A 20-Year Prospective Study, *J Consult Clin Psychol*, 68(3):371-377.

Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, and Carvalho AF, 2017, Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review with Network Meta-Analysis, *JAMA Psychiatry*, 74(2):143-152.

Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, Cheng CM, and Su TP, 2018, Rapid Inflammation Modulation and Antidepressant Efficacy of a Low-Dose Ketamine Infusion in Treatment-Resistant Depression: A Randomized, Double-Blind Control Study, *Psychiatry Res*, 269:207-211.

Cipriani A, Hawton K, Stockton S, and Geddes JR, 2013, Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis, *BMJ*, 346:f3646.

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JP, and Geddes JR, 2018, Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults With Major Depressive Disorder: A Systematic Review and Network Meta-Analysis, *Lancet*, 391(10128):1357-1366.

Coryell W, Pfuhl B, and Zimmerman M, 1984, The Clinical and Neuroendocrine Features of Psychotic Depression, *J Nerv Ment Dis*, 172(9):521-528.

Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, and Fawcett J, 2010, Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-Analysis, *JAMA*, 303(1):47-53.

Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeugh-Geiss A, Krebs EE, Moore CG, Morgan L, and Lohr KN, 2008, Comparative Benefits and Harms of Second-Generation Antidepressants: Background Paper for the American College of Physicians, *Ann Intern Med*, 149(10):734-750.

Gaudiano BA, Dalrymple K, and Zimmerman M, 2009, Prevalence and Clinical Characteristics of Psychotic Versus Nonpsychotic Major Depression in a General Psychiatric Outpatient Clinic, *Depress Anxiety*, 26(1):54-64.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018, Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017, *Lancet*, 392:1789-1858.

Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, Oquendo MA, and Mann JJ, 2018, Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial, *Am J Psychiatry*, 175(4):327-335.

Guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2018)

Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, and Grant BF, 2018, Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States, *JAMA Psychiatry*, 75(4):336-346.

Herrmann N, Black SE, Lawrence J, Szekely C, and Szalai JP, 1998, The Sunnybrook Stroke Study: A Prospective Study of Depressive Symptoms and Functional Outcome, *Stroke*, 29(3):618-624.

Holma KM, Melartin TK, Haukka J, Holma IA, Sokero TP, and Isometsa ET, 2010, Incidence and Predictors of Suicide Attempts in DSM-IV Major Depressive Disorder: A Five-Year Prospective Study, *Am J Psychiatry*, 167(7):801-808.

Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, Biggs MM, O'Connor K, Rasmussen K, Litle M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, and Kellner CH, 2004, Speed of Response and Remission in Major Depressive Disorder with Acute Electroconvulsive Therapy (ECT): A Consortium for Research in ECT (CORE) Report, *J Clin Psychiatry*. 2004;65(4):485-491.

Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, Mueller M, Bernstein H, Rasmussen K, O'Connor K, Smith G, Rush AJ, Biggs M, McClintock S, Bailine S, and Malur C, 2005, Relief of Expressed Suicidal Intent by ECT: A Consortium for Research in ECT Study, *Am J Psychiatry*, 162(5):977-982.

Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, McClintock SM, Tobias KG, Martino C, Mueller M, Bailine SH, Fink M, and Petrides G, 2010, Bifrontal, Bitemporal and Right Unilateral Electrode Placement in ECT: Randomized Trial, *Br J Psychiatry*, 196(3):226-234.

Lahti AC, Weiler MA, Michaelidis T, Parwani A, and Tamminga CA, 2001, Effects of Ketamine in Normal and Schizophrenic Volunteers, *Neuropsychopharmacol*, 25:455-467.

Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, and Murrough JW, 2014, A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder, *Biol Psychiatry*, 76(12):970-976.

Leon AC, 2007, The Revised Warning for Antidepressants and Suicidality: Unveiling the Black Box of Statistical Analyses, *Am J Psychiatry*, 164(12):1786-1789.

Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB, Simon G, Ahmedani BK, Clarke G, Hunkele EM, Waitzfelder B, Owen-Smith A, Raebel MA, Rossom R, Coleman KJ, Copeland LA, and Soumerai SB, 2014, Changes in Antidepressant Use by Young People and Suicidal Behavior After FDA Warnings and Media Coverage: Quasi-Experimental Study, *BMJ*, 348:g3596.

Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S, for the International Suicide Prevention Trial Study Group, 2003, Clozapine Treatment for Suicidality in Schizophrenia: International Suicide Prevention Trial (InterSePT), *Arch Gen Psychiatry*, 60(1):82-91.

Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, and He J, 2017, Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries, *Circulation*, 134(6):441-450.

Nugent AC, Ballard ED, Gould TD, Park LT, Moaddel R, Brutsche NE, and Zarate Jr CA, 2019, Ketamine Has Distinct Electrophysiological and Behavioral Effects in Depressed and Healthy Subjects, *Mol Psychiatry*, 24(7):1040-1052.

Olney JW, Labruyere J, and Price MT, 1989, Pathological Changes Induced in Cerebrocortical Neurons by Phencyclidine and Related Drugs, *Science*, 244(4910):1360-1362.

Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, Soleimani L, Charney DS, Foulkes AL, and Mathew SJ, 2014, Effects of Ketamine on Explicit and Implicit Suicidal Cognition: A Randomized Controlled Trial in Treatment-Resistant Depression, *Depress Anxiety*, 31(4):335-343.

Riedel M, Möller HJ, Obermeier M, Schennach-Wolff R, Bauer M, Adli M, Kronmüller K, Nickel T, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, and Seemüller F, 2010, Response and Remission Criteria in Major Depression – A Validation of Current Practice, *J Psychiatr Res*, 44(15):1063-1068.

Rosenkranz, G. K. (2010). A note of the Hodges-Lehmann estimator. *Pharmaceutical Statistics*, 9, 162-167. doi:10.1002/pst.387

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, and Fava M, 2006, Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report, *Am J Psychiatry*, 163(11):1905-1917.

Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, and Nemeroff CB for the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments, 2017, A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders, *JAMA Psychiatry*, 74(4):399-405.

Sokero TP, Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, and Isometsa ET, 2003, Suicidal Ideation and Attempts Among Psychiatric Patients with Major Depressive Disorder, *J Clin Psychiatry*, 64:1094-1100.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2018, Key Substance Use and Mental Health Indicators in the United States: Results From the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53), Rockville (MD): Center for Behavioral Health Statistics and Quality, SAMHSA, accessed June 1, 2020, <https://www.samhsa.gov/data/>.

Taylor MJ, Freemantle N, Geddes JR, and Bhagwagar Z, 2006, Early Onset of Selective Serotonin Reuptake Inhibitor Antidepressant Action: Systematic Review and Meta-Analysis, *Arch Gen Psychiatry*, 63(11):1217-1223.

van Schalkwyk GI, Wilkinson ST, Davidson L, Silverman WK, and Sanacora G, 2018, Acute Psychoactive Effects of Intravenous Ketamine During Treatment of Mood Disorders: Analysis of the Clinician Administered Dissociative States Scale, *J Affect Disord*, 227:11-16.

Walker ER, McGee RE, and Druss BG, 2015, Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-Analysis, *JAMA Psychiatry*, 72:334-341.

Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, Sos P, Wang G, Zarate CA Jr, and Sanacora G, 2018, The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis, *Am J Psychiatry*, 175(2):150-158.

Williams JW Jr, Mulrow CD, Chiquette E, Noël PH, Aguilar C, and Cornell J, 2000, A Systematic Review of Newer Pharmacotherapies for Depression in Adults: Evidence Report Summary, *Ann Intern Med*, 132(9):743-756.

Zimmerman M, Posternak MA, and Chelminski I, 2004, Defining Remission on the Montgomery-Åsberg Depression Rating Scale, *J Clin Psychiatry*, 65(2):163-168.

Zimmerman M, Posternak MA, and Chelminski I, 2004, Implications of Using Different Cut-Offs on Symptoms Severity Scales to Define Remission from Depression, *Int Clin Psychopharmacol*, 19(4):215-220.

Zisook S, Lesser IM, Lebowitz B, Rush AJ, Kallenberg G, Wisniewski SR, Nierenberg AA, Fava M, Luther JF, Morris DW, and Trivedi MH, 2011, Effect of Antidepressant Medication Treatment on Suicidal Ideation and Behavior in a Randomized Trial: An Exploratory Report from the Combining Medications to Enhance Depression Outcomes Study, *J Clin Psychiatry*, 72(10):1322-1332.

17.2. Financial Disclosure**Covered Clinical Study (Name and/or Number): SUI3001, SUI3002, SUI2001**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>See table below:</u>		
Study Number	Number of Principal Investigators	Number of Sub-Investigators
54135419SUI3001	58	287
54135419SUI3002	63	341
ESKETINSUI2001	15	88
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1 (SUI3002), 1 (SUI2001 – noted payment but below reporting threshold)</u>		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant) – N/A

One primary investigator provided a financial disclosure (b) (6) who participated in Tria (b) (6) reported receiving \$80,000 (b) (6)

(b) (6) The Applicant assessed the risk of bias due to the above referenced potential conflict of interest as low and considered it acceptable to allow the site to participate.

One sub-investigator reported a financial disclosure (b) (6) who participated in Tria (b) (6) reported receiving \$17,709 from Johnson & Johnson (b) (6). The Applicant noted this was below the reporting threshold.

Clinical Reviewer's Comment (b) (6)

(b) (6) any potential bias from conflict of interest is unlikely to affect the overall study results in a substantial manner. The (b) (6) disclosure was below the reporting threshold per the Applicant (b) (6) any potential bias from conflict of interest is unlikely to affect the overall study results in a substantial manner.

17.3. Nonclinical Pharmacology/Toxicology

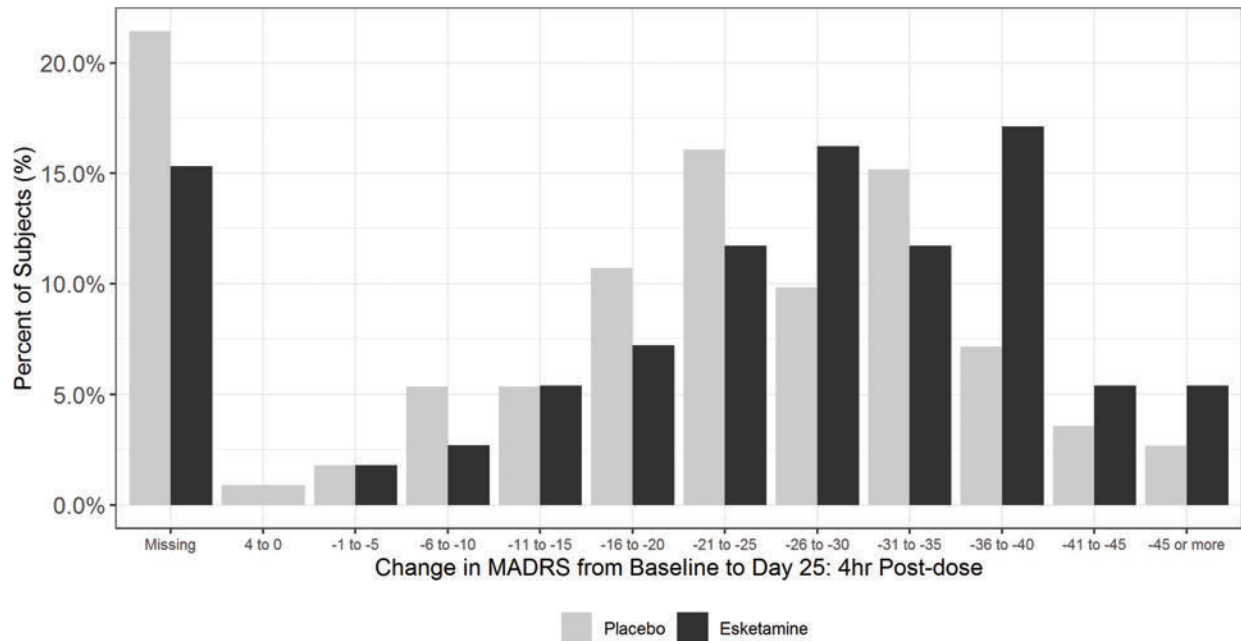
Not applicable for this submission

17.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable for this submission

17.5. Additional Clinical Outcome Assessment Analyses

Figure 23. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 25 Days Post-dose (SUI3001: FAS)

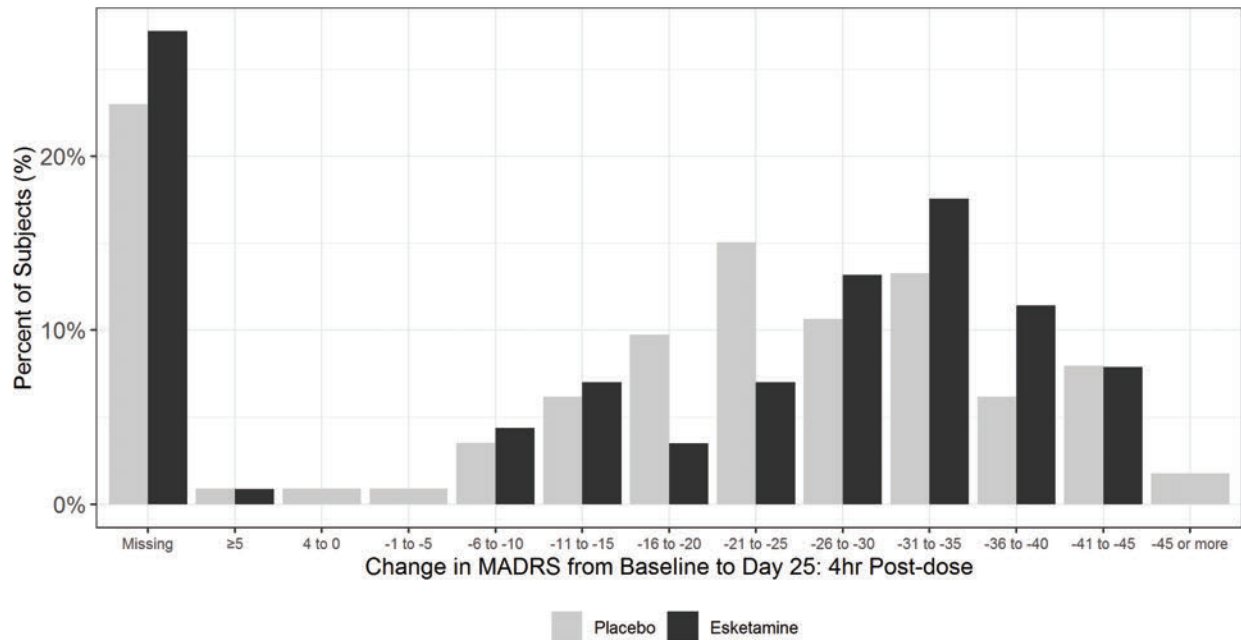


Study SUI3001

Source: Statistical Reviewer; SUI3001 FAS; dataset: admadr.

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Figure 24. Percentage of Subjects with Specified Magnitude of Change in MADRS Total Score at 25 Days Post-dose (SUI3002: FAS)



Study SUI3002

Source: Statistical Reviewer; SUI3002 FAS; dataset: admadr.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s004

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: 211243 S-004

Name of Drug: Spravato (esketamine) nasal spray

Applicant: Janssen Pharmaceuticals, Inc.

Indication: depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Pending Supplements:

NDA	Supplement	Dated	Provides for	Status
211243	S-003	August 14, 2019	PAS - revisions to section 13.1 (Nonclinical Toxicology - Carcinogenesis, Mutagenesis, Impairment of Fertility) of the Prescribing Information.	Approved February 11, 2020
211243	S-004	October 2, 2019	PAS – efficacy supplement to update labeling to reflect the safety and efficacy results from proposed new indication.	Pending

BACKGROUND

- The last approved labeling, for comparison purposes, was the labeling attached to the 2/11/2020 Agency approval letter.
- The clinical reviews have been completed and changes to labeling were proposed to the sponsor via email on 07/01/2020. Labeling agreement was reached via email on 07/31/2020.
- S-004 provides for the following changes: 1) modifications to the approved risk evaluation and mitigation strategy (REMS) and 2) a new indication for depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

REVIEW

0211243/S-004

Reviewed by Team:

CDTL: Bernard Fischer, MD; Clinical: Paul Bossie, MD; Biometric: Andrew Potter, PhD;
OPDP: Domenic Dalessandro; PLT: Shawna Hutchins, MPH, BSN, RN; DRM: Somya Dunn, MD;
ADL: Kim Updegraff,

- Proposed language to address the addition of safety and efficacy data for depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior was added to the Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5), Adverse Reactions (6), and Clinical Studies (14) sections.
- The existing Medication Guide was updated to reflect the changes in PI.

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/s/

SHIN-YE CHANG
07/31/2020 04:07:27 PM

PAUL A DAVID
07/31/2020 04:27:50 PM

07.10.2020 Clinical Inspection Summary (CIS)

Clinical Inspection Summary

Date	07/09/2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shin-Ye Sandy Chang, Pharm.D., Regulatory Project Manager Paul Bossie, M.D., Clinical Reviewer Bernard Fischer, M.D., Clinical Team Leader
NDA #	211243-S004
Applicant	Janssen Pharmaceuticals, Inc
Drug	Esketamine
NME	No
Therapeutic Classification	Antidepressant
Proposed Indication	Treatment of Major Depressive Disorder (MDD)
Consultation Request Date	11/15/2019
Initial Summary Goal Date	06/10/2020
Updated Summary Goal Date	07/10/2020
Action Goal Date	07/31/2020
PDUFA Date	08/02/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from two clinical trials, Study Protocols 54135419SUI3001 and 54135419SUI3002, were submitted to the Agency in support of a supplemental New Drug Application (NDA 211243-S004) for esketamine for the treatment of patients with major depressive disorders (MDD).

The clinical investigator sites of Drs. Barker, Litman, Kruger, Quarantini and Yadalam were inspected in support of this supplemental New Drug Application (NDA 211243-S004). Based on the results of these inspections, the conduct of the above studies was adequate, and the clinical data generated from Drs. Barker, Litman, Kruger, Quarantini and Yadalam sites appear to be reliable in support of this sNDA.

II. BACKGROUND

Janssen Pharmaceuticals, Inc submitted this supplemental NDA 211243-S004 to support the use of esketamine for the rapid reduction of symptoms of Major Depressive Disorder (MDD) in specific populations. Clinical inspections were conducted for the following protocols:

Protocol 54135419SUI3001

Title: "A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects

Assessed to be at Imminent Risk for Suicide”

The primary study objective was to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of MDD, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.

The primary efficacy endpoint was the change from baseline (Day 1, pre-dose) to 24 hours post first dose in depressive symptoms, as measured by the Montgomery Asberg Depression Rating Scale (MADRS) total score.

The key secondary efficacy endpoint was the change in clinical global impression-severity of suicidality-revised (CGI-SS-R) from Baseline to 24 hours post first dose.

Protocol 54135419SUI3002

Title: “A Randomized, Double-blind, Multicenter, Active-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”

The design of Protocol 54135419SUI3002 was identical to Protocol 54135419SUI3001.

Rationale for Site Selection

These Clinical Investigator (CI) sites were selected for inspection mainly due to large enrollment and inspection history.

III. RESULTS

1. James Barker, M.D

Site # US10008
24 2nd Avenue, NE
Hickory, NC 28601
Inspection dates: 16-18 March 2020

At this site for Protocol 54135419SUI3001, 8 subjects were screened and 7 were enrolled, all of whom completed the study. The study records for all 7 subjects enrolled were reviewed including, but not limited to, informed consent; inclusion/exclusion criteria; randomization, blinding, dosing, and study drug administration; the primary and key secondary efficacy endpoints; adverse event reporting; and protocol compliance. The study monitoring, ethics committee approval and communications, financial disclosures, FDA 1572s, study staff background and training were also reviewed during the inspection.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. Robert Litman, M.D.

Site # US10014
9605 Medical Center Drive, Suite 170
Rockville, MD 20850

Inspection dates: 10-14 and 18-20 February 2020

At this site for Protocol 54135419SUI3001, 29 subjects were screened, 22 were enrolled, and 10 subjects completed the study. Twelve subjects were discontinued. Subject (b) (6) (esketaamine group) committed suicide on Day 25. Subject (b) (6) (esketaamine group) experienced increased suicidal ideation and attempted suicide on Day 28. Subject (b) (6) (esketaamine group) withdrew consent after experiencing hallucinations on Day 1. Subject (b) (6) (placebo group) withdrew consent due to increased suicidal ideation on Day 18. The death and all adverse events mentioned above were reported to FDA. Five other subjects withdrew consent due to reasons reportedly not related to study or other unknown reasons. Three subjects were lost to follow-up.

All 22 enrolled subjects' records were reviewed. These records included, but were not limited to, Independent Review Board (IRB) approvals, training records, delegation of authority logs, financial disclosures, drug accountability, informed consent forms, study eligibility criteria, medical histories, physical examinations, progress notes, concomitant medications, the primary and the key secondary efficacy endpoint data, adverse events, and protocol deviations.

The primary and the key secondary efficacy endpoint data were verifiable.

However, there were some observations at Dr. Litman's site. Specifically:

- For Subject (b) (6) (esketaamine group), Dr. Litman decreased the subject's dose of bupropion XL from 300mg daily to 150mg daily at Day 22, reportedly due to bupropion's side effects of tremors and dry mouth, without consulting with the sponsor's medical monitor in advance as required by the protocol.

Reviewer's comment: Dr. Litman responded that at the time of the dose change, the subject was experiencing adverse events, and he made the decision to reduce the dose of bupropion XL from 300mg to 150mg daily in the best interest of the patient. The sponsor stated that this dose decrease was in alignment with standard of care practice. This change would not be expected to have an impact on the results of the clinical study because the primary and key secondary efficacy data involve change from baseline (Day 1, pre-dose) to 24 hours post first dose for two different scales. Of note, this protocol deviation was not reported to FDA as it was not deemed as a major protocol deviation by the sponsor.

- Two subjects had high blood pressure (BP) for which the protocol was not followed:
 - Subject (b) (6) (esketaamine group): at screening, the subject had a BP of 130/91. Protocol amendment 3 stated that "an abnormal blood pressure value at screening can be repeated once after 5 minutes of relaxation for subject eligibility." However, there was no repeat BP taken at that time. At post-dose Day 1 (40 minutes following dose), this subject had a BP of 188/127. At 1-hour post dose, the BP had dropped to 153/105 mmHg, at 90 minutes post-dose it was 141/108 mmHg, and by the end of the day it was 133/99. Protocol Amendment 3 stated "at any post-dose timepoint on any dosing day, if diastolic BP $\geq$ 120 mmHg, subject must discontinue from further dosing. Subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment." However, the site continued dosing the subject once every few days according to schedule and did not refer the subject for medical follow-up.

Reviewer's comment: The safety of this subject was compromised as the transient but rather high blood pressures following the first dose of esketamine did not lead to discontinuation and medical follow-up as required by protocol. However, the BP elevations following the subsequent esketamine doses were much less. Also, there is no evidence this subject experienced any actual harm.

- Subje (b) (6) (esketamine group): at post-dose Day 22, this subject had a BP of 159/111 mmHg. Protocol Amendment 2 stated “at any post-dose timepoint on any dosing day, if DBP $\geq$ 110 mmHg but <120 mmHg, further intranasal dosing should be interrupted, and the subject should be referred.” However, the subject was not referred for a medical follow-up and continued to be dosed at Day 25.

Reviewer's comment: Dr. Litman considered the BP of 159/111 not clinically significant. The pre-dose BP was 121/80 mmHg for the subsequent dose (on Day 25), so Dr. Litman considered that it was safe to dose the subject. However, because of this incident, re-training was conducted on 07/20/18 for staff on the blood pressure monitoring. This protocol deviation was not reported. Although the clinical investigator failed to report the above protocol deviation, based on OSI's review of the EIR and the clinical investigator's response, the finding appears to be isolated there was no evidence to support this subject experienced any harm.

- The adverse events for the following subjects were not reported:
 - Subjec (b) (6) (placebo group): sore throat
 - Subjec (b) (6) (placebo group): cold sore

Reviewer's comment: Since both subjects were in the placebo group, it is less likely that the assessment of the safety profile of the study drug would be impacted. These protocol deviations were not reported.

- Subjec (b) (6) (placebo group) was given benzodiazepine within 8 hours of Day 2 assessments, which was prohibited by the protocol.

Reviewer's comment: Since this subject was in placebo group, it is less likely that the study efficacy assessment would be impacted. This protocol deviation was not reported.

3. Stephanie Kruger, M.D.

Site # DE10004
Am Nordgraben 2,
Zentrum für Seelische
Frauengesundheit, Berlin,
Berlin, 13509 Germany
Inspection dates: 2-6 March 2020

At this site for Protocol 54135419SUI3001, 14 subjects were screened, 12 were enrolled, and 11 subjects completed the study. One subject withdrew consent. All 12 enrolled subjects' records were reviewed. The records reviewed included, but were not limited to, informed consent forms, study eligibility, medical histories, physical examinations, progress notes, the primary and the key secondary efficacy endpoint data, adverse events, protocol deviations, laboratory reports, and concomitant medications. Other documents (in the regulatory files) were also reviewed, including study training records, delegation logs, FDA 1572s, financial

disclosures, drug accountability, correspondence, and monitoring reports.

The primary and the key secondary efficacy endpoint data were verifiable. Two adverse events were not reported to FDA. One was bitter taste for Subjec (b) (6), and the other was blurred vision For Subjec (b) (6). These adverse events appeared during or right after the dosing of esketamine.

Reviewer's comment: since the two unreported adverse events were described, this no reporting of adverse events is not expected to have an impact on the safety evaluation this drug.

4. Lucas Quarantini, M.D.

Site # BR10007

Rua Augusto Viana, sn, Canela

Sala de pesquisa da psiquiatria,

enfermaria 3B - Hospital das Clinicas.

Salvador, Bahia 40110-060 Brazil

Inspection dates: 09-13 March 2020

At this site for Protocol 54135419SUI3002, 17 subjects were screened, 14 were enrolled, and 11 subjects completed the study. Three subjects withdrew consent. Subject records reviewed included, but were not limited to, informed consent, adverse events, concomitant medications, inclusion/exclusion criteria, the primary and key secondary efficacy endpoint data, and randomization. Other documents reviewed included administrative study files; correspondence files; master subject list; sign-in logs; screening lists; and investigational product availability, distribution, assignment, and storage conditions.

The primary and key secondary efficacy endpoint data were verifiable. One adverse event, rash, for Subjec (b) (6) (esketaamine group) was reported to FDA as "muscle tightness." This was reportedly due to translation error from Portuguese to English.

5. Kashinath Yadalam, M.D.

Site # US10006

One Lakeshore Dr. Suite 1695

Lake Charles, LA 70629

Inspection dates: 27-29 January 2020

At this site for Protocol 54135419SUI3002, 14 subjects were screened, 13 were enrolled, and 5 subjects completed the study. Eight subjects discontinued. Subjec (b) (6) (esketaamine group) discontinued due to the adverse event of depersonalization and derealization symptoms after first dose of esketamine. Subjec (b) (6) (placebo group) discontinued due to the adverse event of worsening of depression and suicidal ideation. These adverse events were reported to FDA. Subje (b) (6) (esketaamine group) withdrew consent due to resolved suicidal ideation and therefore no longer wished to participate in the study. Three other subjects withdrew consent due to reasons not related to study or unknown reasons. Two subjects were lost to follow-up.

The records of all 14 screened subjects were reviewed during the inspection, which included, but were not limited to, study eligibility criteria, medical histories, physical examinations, progress notes, the primary and key secondary efficacy endpoint data, adverse events, protocol deviations, concomitant medications, and laboratory reports. Other documents reviewed

included Independent Review Board (IRB) approvals, CVs and training records, delegation of authority logs, FDA Form 1752, financial disclosures, and drug accountability.

The primary and key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
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Central Doc. Rm. NDA 211243 S004
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DPP/Division Director/Tiffany Farchione
DPP/Medical Officer/Paul Bossie
DPP/Clinical Team Leader/Bernard Fischer
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Ni Khin
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OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/s/

JENN W SELLERS
07/09/2020 05:40:00 PM

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KASSA AYALEW
07/10/2020 09:05:38 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Memorandum

Date: June 17, 2020

Reviewer: Kelly Harbourt, PharmD, BCCCP
Division of Pharmacovigilance I (DPV I)

Team Leader: Vicky Chan, PharmD, BCPS
DPV I

Product Name: Spravato (esketamine)

Applicant: Janssen

Application Type/Number-Submission Number: NDA 211243-S004

Subject: Suicide attempt and Completed suicide

OSE RCM #: 2020-754

1 INTRODUCTION

The purpose of this memorandum is to summarize the FAERS data provided to the Division of Psychiatry (DP). Dr. Paul Bossie, DP Clinical Reviewer, requested the Division of Pharmacovigilance (DPV) to obtain narratives of suicide attempt and completed suicide reports for esketamine identified in the Periodic Adverse Drug Experience Reports (PADERS). DP requested this information in preparation for sending an Information Request (IR) to Janssen, the Applicant for esketamine, for more details regarding the aforementioned suicide-related adverse events. DPV referred DP to a recently completed Postmarket Drug Safety Surveillance Summary (PDSSS) for esketamine,¹ which summarized cases with the Preferred Terms (PTs) *Completed suicide*. DPV performed a search of the FDA Adverse Event Reporting System (FAERS) database to locate cases of esketamine coded with the PTs *Suicide attempt* and *Suspected suicide attempt*. Upon follow-up with DP, they also requested an analysis of the time between the last dose of esketamine and the reported suicide attempt.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of Search	April 6, 2020
Time Period of Search	All reports through April 5, 2020
Search Type	FBIS Quick Query
Product Terms	Product active ingredient: esketamine, esketamine hydrochloride
MedDRA Search Terms (Version 22.1)	Preferred Term (PT): <i>Suicide attempt</i> , <i>Suspected suicide attempt</i>
* See Appendix A for a description of the FAERS database. FBIS=FDA Business Intelligence Solutions; MedDRA=Medical Dictionary for Regulatory Activities	

2.2 PERIODIC SAFETY REPORTS

DPV screened the following PADERS and other documents submitted by the Applicant for esketamine during the completion of the recent PDSSS:

- PADER from March 5, 2019 through June 4, 2019:
<\\cdsesub1\evsprod\nda211243\0056\m5\53-clin-stud-rep\536-postmark-exp\postmarketing-experience\pader-05mar2019-04jun2019.pdf>
- PADER from June 5, 2019 through September 4, 2019:
<\\cdsesub1\evsprod\nda211243\0062\m5\53-clin-stud-rep\536-postmark-exp\postmarketing-experience\pader-05jun2019-04sep2019.pdf>

• PADER from September 5, 2019 through December 4, 2019:
<\\cdsesub1\evsprod\nda211243\0070\m5\53-clin-stud-rep\536-postmark-exp\postmarketing-experience\pader-05sep2019-04dec2019.pdf>

3 RESULTS

3.1 FAERS SEARCH RESULTS

3.1.1 Completed suicide

On April 3, 2020, DPV reconciled cases of PT *Completed suicide* found in FAERS with those DP identified in the PADERs for esketamine to assist with locating narratives for these cases prior to DP sending an IR to the Applicant. **Table 2** below displays the information DPV sent to DP regarding the six PT *Completed suicide* cases that we identified in FAERS at the time of completion of the recent PDSSS. The narratives for these six cases are also attached to this memo.

Number	FAERS Case ID	Manufacturer Control Number	Initial FDA Received Date	DPV Reviewer Comments
1	16610250	GB-JNJFOC-20190712087	7/22/2019	Did not receive esketamine
2	16683361	US-JNJFOC-20190713027	8/8/2019	Received two doses of esketamine, no suicidal ideation or plan, found dead in his ap (b) (6) COD overdose, ruled suicide by medical examiner.
3	16711306	US-JNJFOC-20190812766	8/16/2019	Received esketamine, confounded by TRD and other medications
4	16840789	IL-JNJFOC-20190919770	9/23/2019	TRD, failed 35 ECTs, severe disease
5	16881731	US-JNJFOC-20190928084	10/3/2019	Confounded by disease, other meds
6	17083638	US-JNJFOC-20191131951	11/27/2019	Lacking details to assess
*Data lock date for FAERS search in esketamine PDSSS completed in March 2020 COD = cause of death; TRD = treatment resistant depression; ECT = electroconvulsive therapy				

3.1.2 Suicide attempt

Our FAERS search described in **Table 1** retrieved 12 total reports, two of which were duplicates (10 unique cases). One case was unrelated to esketamine as the report involved ketamine and was initially reported in 2011. We provided to DP the narratives of the remaining nine cases, which are also attached to this memorandum. The time from the last dose of esketamine to suicide attempt ranged from one to eight days and was unknown or not reported in three of these nine cases. Five of the nine cases were from the clinical development program for treatment resistant depression (TRD), Study 3008. One case was stated to be from the Risk Evaluation and Mitigation Strategy (REMS) program and the other three were spontaneous reports. A line listing containing these nine cases is in **Appendix B**.

3.2 PERIODIC SAFETY REPORT RESULTS

DPV reviewed the PADERs referenced in **Section 2.2** when completing the PDSSS¹ for esketamine in March 2020. DPV did not provide any new information from these reports to DP for the purposes of the safety issue discussed in this memo.

4 REVIEWER'S COMMENTS

DPV provided to DP the narratives for the cases of esketamine with the PTs *Completed suicide* discussed in the recent esketamine PDSSS¹ and those with the PT *Suicide attempt* and *Suspected suicide attempt* (see **Appendix C**). DP used this information to prepare and send an IR² to the Applicant requesting narratives for all remaining cases of esketamine related to completed suicide and suicide attempt.

5 REFERENCES

1. Harbourt KM. REV-SURVEPI-39 Postmarket Drug Safety Surveillance Summary: Spravato (esketamine), NDA 211243. DARRTS reference ID: 4580193. 24 March 2020.
2. Zerislassie E. Spravato (esketamine) NDA 211243 PADER Information Request. DARRTS reference ID: 4590232. 10 April 2020.

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6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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6.2 APPENDIX B. FAERS LINE LISTING OF SUICIDE ATTEMPT AND ESKETAMINE CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Time to Onset of SA (days)	Serious Outcome(s)*
1	8/20/2019	16721241	7	BR-JNJFOC- 20190819761	Expedited (15-Day)	39	Male	BRA	8	HO, LT, OT
2	9/18/2019	16822990	1	TW-JNJFOC- 20190908484	Expedited (15-Day)	44	Female	TWN	4	LT
3	10/2/2019	16878132	3	US-JNJFOC- 20191000097	Expedited (15-Day)	49	Male	USA	1	HO, LT
4	10/24/2019	16957918	1	GB-JNJFOC- 20191025519	Expedited (15-Day)	40	Female	GBR	4	LT
5	11/7/2019	17006598	3	US-JNJFOC- 20191104777	Expedited (15-Day)	44	Female	USA	Unknown	OT
6	12/23/2019	17193687	1	US-JNJFOC- 20191229734	Expedited (15-Day)	Unknown	Female	USA	Unknown	HO
7	12/30/2019	17216290	2	FR-JNJFOC- 20191121121	Expedited (15-Day)	60	Female	FRA	4	OT
8	12/31/2019	17220756	3	ES-JNJFOC- 20191247247	Expedited (15-Day)	55	Female	ESP	8	HO
9	2/25/2020	17508534	1	NA	Direct	53	Male	USA	Unknown	HO, OT
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome. Abbreviations: HO=Hospitalization, LT= Life-threatening, OT=Other medically significant, SA=Suicide attempt										

6.3 APPENDIX C. FAERS CASE NARRATIVES OF Esketamine with PTs *COMPLETED SUICIDE*, AND PTs *SUICIDE ATTEMPT* AND *SUSPECTED SUICIDE ATTEMPT*

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Case Information:

Case #: 16840789 Version: 1 Case Type: EXPEDITED eSub: Y HP: Country: ISR Outcomes: DE, Application Type: NDA

FDA Rcvd Date: 23-Sep-2019 Init FDA Rcvd Date 23-Sep-2019 Mfr Rcvd Date: 15-Sep-2019 MfrControl #: IL-JNJFOC-20190919770 Application #: 211243

Patient Information:

Patient ID: PRIVACY Age in Years: 56.00000 Age/Unit: 56 YR Sex: Male Weight: DOB:

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato	S	56 MG/BIW	N/A		Depression	04-Sep-2019		10 DAY	NA	NA
Venlafaxine	C	375 MG/QD	N/A	therapy end date SEP-2019		01-Jul-2019			NA	NA
Seroquel	C	100 MG/QD	N/A			01-Jul-2019			NA	NA
Product Name	Lot #	Exp Date	NDC #	Labeler						
Spravato										
Venlafaxine										
Seroquel										

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed suicide	(b) (6)		FATAL	No, Serious	NA

Event / Problem Narrative:

This individual patient use report was received from a physician via 54135419TRD4003: Esketamine Name Patient Program (NPP) and concerned a 56 year old male (subject number unspecified, site (b) (6))

The patient's height and weight were not reported. The patient's concurrent conditions included severe depression from the age of 18 years old and treatment resistant depression (failed to respond to any other available treatments, including 35 cycles of electroconvulsive therapy [ECT]; last treatment 4 months ago). Past medical history included on and off hospitalizations from the age of 20 years old, with more than 7 episodes. The patient did not have any prior history of suicidality or active suicide attempts. The patient was previously treated with intravenous ketamine.

The patient received esketamine (nasal spray, nasal, batch number not reported) 56 milligram (mg) twice weekly beginning on 04-SEP-2019, for treatment resistant depression (TRD). Concomitant medications included Seroquel (quetiapine fumarate) 100 mg daily beginning in JUL-2019 and venlafaxine 375 mg daily from JUL-2019 to SEP-2019.

On an unspecified date, the patient was hospitalized for more than a month due to very severe TRD.

On 04-SEP-2019, the patient received the first dose of esketamine 56 mg. The second treatment was administered o (b) (6) and third treatment administered o (b) (6) The patient responded well, with a slight improvement in depressive symptoms and expressed positive and hopeful thought future.

On (b) (6) the patient was evaluated by two psychiatrists. He did not have any disturbing thoughts, no suicidal thoughts, and discussed future treatments (increasing esketamine dose to 84 mg). The patient requested (b) (6) with his partner and was released from the hospita (b) (6) On the night of (b) (6) the patient had dinner with his partner and planned a breakfast for the following morning.

On the morning o (b) (6) the patient committed suicide (b) (6) An autopsy was not performed and was not planned. There was no situation or factor that led to the patient's suicide. A suicide note was not left and no alcohol or illicit drugs were involved in the patient's death. The physician confirmed that there was no overdose, suspected abuse/misuse, inadvertent or accidental exposure, or suspected transmission of any infectious agent from the product. There was no failure, no unexpected therapeutic or clinical benefit, and no medication error related to esketamine. The treating physician described the patient as a narcissistic, self-hatred, and self-loathing patient. He was an artist who has not accomplished enough, with no regular job in the past few years (but no economic burden). The patient was in a stable relationship (not married) and lived with his partner.

The action taken with esketamine was not applicable.

The reporter assessed the event as not related to esketamine and related to the severity of the disease.
This report was serious (Death)..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Depression			Yes	from the age of 18
ECT			No	35 cycles of ECT; last treatment 4 months ago
Hospitalisation			No	On and off hospitalizations from the age of 20, with more than 7 episodes
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)
KETAMINE				

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
C	Esketamine NPP	I			
Literature Text					
Country of Event:	ISR	Sender MFR:	JOHNSON AND JOHNSON		
Reporter Name	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	ISR		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				
Reporter Name		Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	ISR		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				

Case Information:

Case #: 16721241 Version: 7 Case Type: EXPEDITED eSub: Y HP: Country: BRA Outcomes: HO, LT, OT Application Type: NDA

FDA Rcvd Date: 12-Feb-2020 Init FDA Rcvd Date 20-Aug-2019 Mfr Rcvd Date: 05-Feb-2020 MfrControl #: BR-JNJFOC-20190819761 Application #: 211243

Patient Information:

Patient ID: UNKNOWN Age in Years: 39.44422 Age/Unit: 39.44422 YR Sex: Male Weight: 96 DOB: (b) (6)

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Esketamine	S	84 MG/wk	N/A	Most recent: 18-OCT-2019 (Med Kit: 20010) and 22-NOV-2019 (batch 4375760, expiry 25-APR-2020; med ki	Depression	11-Dec-2017		610 DAY	NA	NA
Clonazepam	C	2 MG/QD	PO		Sleep Disorder Therapy	09-Sep-2013		6 YR	NA	NA
Bupropion	C	300 MG/QD	PO		Depression	04-Dec-2018	03-Jan-2020	252 DAY	NA	NA
Venlafaxine	C	300 MG/QD	PO		Depression	25-Apr-2019		110 DAY	NA	NA
Lamotrigine	C	100 MG/TID	PO		Depression	29-Jan-2019		196 DAY	NA	NA
Mirtazapine	C	30 MG/QD	PO		Depression	02-May-2019	04-Dec-2019	103 DAY	NA	NA
Lithium	C	900 MG/QD	PO		Depression	12-Jun-2019		62 DAY	NA	NA

Product Name	Lot #	Exp Date	NDC #	Labeler
Esketamine				
Clonazepam				
Bupropion				
Venlafaxine				
Lamotrigine				
Mirtazapine				
Lithium				

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Ankle fracture	13-Aug-2019		RECOVERING/ RESOLVING	No, Serious	NA
Suicide attempt	13-Aug-2019	13-Aug-2019	RECOVERED/ RESOLVED	Yes, Serious	NA

Event / Problem Narrative:

This report was received from clinical trial 54135419TRD3008: An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression, EudraCT #: 2015-003578-34, concerned a 39 years-old male (Subject (b) (6) Site (b) (6)). The subject's weight was 96 kilograms and height was 194 centimeters. The subject's concurrent conditions included treatment resistant depression and sleep disorder. The subject initiated treatment with esketamine (nasal spray, intra-nasal, batch number not reported), 84 milligram (mg) weekly, initiated on 11-DEC-2017 with the most recent dose on 05-

AUG-2019 for treatment resistant depression. Concomitant medications included bupropion, lamotrigine, venlafaxine, mirtazapine and lithium; all for treatment resistant depression and clonazepam for sleep induction

(b) (6) the subject had a fight with his mother and impulsively attempted suicide by throwing himself from the house balcony. Assistance was requested and the subject was taken to the closest hospital. A computerized tomogram (CT) of his legs was normal however, confirmed a right ankle fracture (b) (6) the subject was transferred to another hospital for treatment of his injuries and was admitted. Treatment while hospitalized included: losartan potassium 100 mg every 12 hours beginning on (b) (6) (ongoing), Dipyrone (metamizole sodium; 500 mg/ml) 2 milliliters (ml) intravenous four times daily from (b) (6) and tramadol (50 mg/ml) 2 ml intravenous 3 times daily from (b) (6) (b) (6) On (b) (6) the subject underwent surgery for right ankle fracture and required splint on his ankle. The subject was advised not to stomp on floor for 15 days. On (b) (6) the subject was discharged in stable condition (b) (6) treatment medications included: Dipyrone (metamizole sodium, capsule, oral) 500 mg every 3 times daily from on 22-AUG-2019 to 10-DEC-2019 and codeine (capsule, oral) 30 mg three times weekly from 22-AUG-2019 to 20-OCT-2019. The investigator confirmed that the subject did not have any history of suicide attempts and this was his first episode. The subject was stable and there were no further risks. The investigator confirmed that the corrective medications and hospitalization were related to ankle fracture and not suicide attempt itself. The subject maintained oral depression medication and had missed two dosage of intra-nasal esketamine due to hospitalization. The dose of esketamine was not changed. The most recent dose of esketamine was on 18-OCT-2019 and 22-NOV-2019. The subject recovered from suicide attempt o (b) (6) and was recovering from right ankle fracture. The subject continued with physiotherapy. The investigator assessed the severity of suicide attempt and right ankle fracture as grade 3 severe adverse event. The investigator considered the causality between esketamine and suicide attempt, and right ankle fracture as not related. The events were not related to trial procedure or device. Suicide attempt was considered an anticipated event per the protocol. This report was serious (Life Threatening, Hospitalization Caused / Prolonged, Other Medically Important Condition: required medical or surgical intervention to prevent permanent impairment to damage).

Additional information was received from the investigator on 23-AUG-2019. The following information was updated and incorporated into the report narrative: The serious adverse event (SAE) Outcome was updated, treatment medications, course of events and negative past medical history.

Additional information was received from the investigator on 11-SEP-2019. The following information was updated and incorporated into the report narrative: Corrective treatment details and the event outcome were updated. Seriousness criterion on Other Medically Important Condition was added.

Follow-up information received via DURF on 20-SEP-2019: No new information and no updates to case.

Additional information was received from the investigator on 23-OCT-2019. The following information was updated and incorporated into the report narrative: The event outcome and clarification from investigator about corrective treatment was added. Most recent dose information was added.

Additional information was received via serious adverse event reconciliation on 15-NOV-2019. The following information was updated and incorporated into the report narrative: The serious criterion of hospitalization was removed from this case.

Additional information was received from the investigator on 25-NOV-2019. The following information was updated and incorporated into the report narrative: a new SAE of right ankle fracture was added to the case. The seriousness criteria, causality, action taken with study drug, and event details were all updated.

Additional information was received from the investigator on 05-FEB-2020. The following information was updated and incorporated into the report narrative: treatment medications therapy dates and dosing information..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Sleep disorder				
Depression			Yes	
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
(b) (6)	CT scan					N
Comment						

Confirmatory Test Comments

CT Sca (b) (6) : All Results normal except ankle fracture

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
C	2015-003578-34#Open label long term extension safety study of intranasal esketamine in TRD	C			
Literature Text					
Country of Event:	BRA	Sender MFR:	JOHNSON AND JOHNSON		
Reporter Name	(b) (6)	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	BRA		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				
Reporter Name	(b) (6)	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	BRA		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				

Case Information:

Case #: 16822990 Version: 1 Case Type: EXPEDITED eSub: Y HP: Country: TWN Outcomes: LT, Application Type: NDA

FDA Rcvd Date: 18-Sep-2019 Init FDA Rcvd Date 18-Sep-2019 Mfr Rcvd Date: 06-Sep-2019 MfrControl #: TW-JNJFOC-20190908484 Application #: 211243

Patient Information:

Patient ID: Unknown Age in Years: 44.00000 Age/Unit: 44 YR Sex: Female Weight: 54 DOB:

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Esketamine	S	84 MG/QOW	N/A	most recent 30-AUG-2019	Depression	28-Jun-2017		797 DAY	NA	NA
Modipanol	C	/	N/A						NA	NA
Product Name	Lot #	Exp Date	NDC #	Labeler						
Esketamine	T248920									
Modipanol										

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide attempt	03-Sep-2019	03-Sep-2019	RECOVERED/ RESOLVED	Yes, Serious	NA

Event / Problem Narrative:

This report received from clinical trial 54135419TRD3008: An Open-label Long-term Extension Safety Study of Intranasal Esketamine in Treatment-resistant Depression, EudraCT#: 2015-003578-34, concerned a 44 year old female (subject (b) (6) site (b) (6)). The subject's weight was 54 kilograms and height was 168 centimeters. The subject's past medical history included degenerative disc disease at L4/L5, and concurrent conditions included treatment resistant depression, mitral valve prolapse, spondylosis, sleep disorder, constipation and intermittent dizziness. Informed consent was signed on 28-JUN-2017. The subject initiated treatment with esketamine (nasal spray, intra-nasal, batch T248920) 84 milligram, 1 every 2 weeks, from 28-JUN-2017 with the most recent administration on 30-AUG-2019, for treatment resistant depression. Concomitant medications included Modipanol (flunitrazepam). On 03-SEP-2019, the subject experienced suicide attempts. The subject was laid off on 02-SEP-2019 and had psychological stress. The subject had impulsive behavior and had no structure plan. On 03-SEP-2019, the subject overdosed on all Modipanol (flunitrazepam) of this month. She denied further suicide plan. The subject was provided reeducation psychotherapy with aim of psychoeducation to improve adherence and prevent relapse. The dose of esketamine was not changed. The subject recovered from suicide attempts on 03-SEP-2019. Suspect causes included psychosocial stress and lay off. The investigator assessed the severity of suicide attempts as moderate and not related to trial procedure. The investigator considered the causality between esketamine and suicide attempts as not related. Suicide attempts was considered an anticipated event per the protocol. This report was serious (Life Threatening)..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Sleep disorder	01-Jan-2005		Yes	
Dizziness	01-Jan-2016		Yes	
Depression			Yes	

Degenerative disc disease	21-Aug-2014	22-Aug-2014	No	L4/L5
Mitral valve prolapse	14-Mar-2005		Yes	
Spondylosis	20-Feb-2014		Yes	
Constipation	26-Nov-2005		Yes	
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
C	2015-003578-34#Open label long term extension safety study of intranasal esketamine in TRD	C			

Literature Text

Country of Event:	TWN	Sender MFR:	JOHNSON AND JOHNSON	
Reporter Name:	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:
Reporter Org:		Reporter Email:		
Reporter Street:		Reporter State:		
Reporter City:		Reporter Country:	TWN	
Reporter Zip:		Sent To:		
Health Prof:		Identity Disclosed:		
Occupation:	MD			
Reporter Name:	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:
Reporter Org:		Reporter Email:		
Reporter Street:		Reporter State:		
Reporter City:		Reporter Country:	TWN	
Reporter Zip:		Sent To:		
Health Prof:		Identity Disclosed:		
Occupation:	MD			

Case Information:

Case #: 16878132 Version: 3 Case Type: EXPEDITED eSub: Y HP: Country: USA Outcomes: HO, LT, Application Type: NDA

FDA Rcvd Date: 19-Nov-2019 Init FDA Rcvd Date 02-Oct-2019 Mfr Rcvd Date: 07-Nov-2019 MfrControl #: US-JNJFOC-20191000097 Application #: 211243

Patient Information:

Patient ID: (b) (6) Age in Years: 49.51677 Age/Unit: 49.51677 YR Sex: Male Weight: DOB: (b) (6)

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato	S	56 MG/	N/A		Depression	04-Sep-2019		1 DAY	Unk	Yes
Zolpidem	C	10 MG/	N/A		Insomnia				NA	NA
Fluoxetine	C	80 MG/	N/A		Depression				NA	NA
Lamotrigine	C	400 MG/	N/A		Depression				NA	NA
Viibryd	C	40 MG/	N/A		Depression				NA	NA
Alprazolam	C	2 MG/TID	N/A		Anxiety				NA	NA
Temazepam	C	30 MG/	N/A						NA	NA
Clonazepam	C	4 MG/	N/A						NA	NA
Gabapentin Enacarbil	C	600 MG/	N/A						NA	NA
Ropinirole	C	5 MG/	N/A						NA	NA

Product Name	Lot #	Exp Date	NDC #	Labeler
Spravato	19C6150X			
Zolpidem				
Fluoxetine				
Lamotrigine				
Viibryd				
Alprazolam				
Temazepam				
Clonazepam				
Gabapentin Enacarbil				
Ropinirole				

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	05-Sep-2019		RECOVERING/ RESOLVING	Yes, Serious	NA
Suicide attempt	05-Sep-2019		RECOVERING/ RESOLVING	Yes, Serious	NA

Event / Problem Narrative:

This spontaneous report was received from a physician and concerned a 49-year-old male patient.

The patient's weight, and height, were not reported. The patient's concurrent conditions included major depressive disorder (recurrent and severe), no alcohol, prior suicide attempt and is disabled. Other pre-existing medical conditions included no known allergies, and no history of drug abuse. The patient had at least 5 prior hospitalizations including 2 prior admissions for extended treatment. The patient has been treated by the same outpatient psychiatrist for approximately 10 years. The patient had a prior course of TMS and prior intravenous ketamine infusions.

The patient received SPRAVATO (esketamine, nasal spray, intra-nasal, 19C6150X, expiry: AUG/2020) 56 milligram, on 04-SEP-2019 for depression. Concomitant medications included clonazepam, gabapentin enacarbil, ropinirole, temazepam, alprazolam for anxiety, zolpidem for insomnia, fluoxetine for depression, lamotrigine for depression and vilazodone hydrochloride for depression.

The patient had been in fairly good spirits on the day of his 1st SPRAVATO treatment and denied suicidal ideation (SI). The patient's ex-wife (by phone) and therapist (hear say via ex) did not observe any warning signs of a suicide attempt.

On (b) (6) the patient experienced depression and attempted suicide (b) (6) by taking an overdose of pills and ETOH. The patient was admitted to a local med-surg hospital and received care in the intensive care unit (ICU). Diagnosis was severe major depressive disorder. When medically stable he was transferred to a sub-acute hospital and remained hospitalized. The patient is disabled and generally picked the children up after school. They had to hire a babysitter so that he could be free for SPRAVATO administration and observation. The patient reported lack of purpose and meaning with that job being taken away.

The physician was not clear if the suicide attempt was a direct consequence of the patient using SPRAVATO.

The physician causality between depression and SPRAVATO was possible.

The action taken with esketamine was withdrawn.

The outcome of attempted suicide and depression was recovering/resolving.

This report was serious (Hospitalization, Life Threatening).

Additional information was received on 07-OCT-2019 via a Health care professional adverse event follow-up form. Information provided was incorporated into the narrative and included age, medical history and concurrent conditions, concomitant medications, date and dose of SPRAVATO, HCP causality, additional seriousness criteria of hospitalization, and history of the suicide attempt.

Additional information received from investigator on 07-NOV-2019. The following information was updated and incorporated into the case narrative. The patient had an episode of depression on 05-SEP-2019. Upon review the following information was amended: the event of attempted suicide was re-entered as an event..

Relevant Medical History:

no known allergies, no history of drug abuse

Disease / Surgical Procedure

Suicide attempt

Disability

Major depressive disorder

Abstains from alcohol

Medical History Products

Start Date

End Date

Continuing?

Comment

Yes

recurrent severe

Start Date

End Date

Indications

MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
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Literature Text

Country of Event: USA

Reporter Name: (b) (6)

Reporter Org: (b) (6)

Reporter Street: (b) (6)

Reporter City: (b) (6)

Reporter Zip: (b) (6)

Health Prof: (b) (6)

Occupation: MD

Reporter Name: PRIVACY PRIVACY

Reporter Org: PRIVACY PRIVACY

Reporter Street: PRIVACY PRIVACY

Reporter City: PRIVACY PRIVACY

Reporter Zip: PRIVACY PRIVACY

Health Prof: PRIVACY PRIVACY

Occupation: CON

Sender MFR: JOHNSON AND JOHNSON

Reporter Type: Other

Reporter Email: Other

Reporter State: TX

Reporter Country: USA

Sent To: Other

Identity Disclosed: Other

Reporter Phone:

Reporter Type: Other

Reporter Email: Other

Reporter State: Other

Reporter Country: USA

Sent To: Other

Identity Disclosed: Other

Reporter Phone:

Case Information:

Case #: 16957918 Version: 1 Case Type: EXPEDITED eSub: Y HP: Country: GBR Outcomes: LT, Application Type: NDA

FDA Rcvd Date: 24-Oct-2019 Init FDA Rcvd Date 24-Oct-2019 Mfr Rcvd Date: 16-Oct-2019 MfrControl #: GB-JNJFOC-20191025519 Application #: 211243

Patient Information:

Patient ID: Unknown Age in Years: 40.00000 Age/Unit: 40 YR Sex: Female Weight: 57.4 DOB:

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Esketamine	S	28 MG/BIW	N/A		Depression	17-Aug-2017		606 DAY	NA	NA
Product Name	Lot #	Exp Date	NDC #	Labeler						
Esketamine	4374743									

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide attempt	15-Apr-2019	15-Apr-2019	RECOVERED/ RESOLVED	No, Serious	NA

Event / Problem Narrative:

This report received from clinical trial 54135419TRD3008: An Open-label Long-term Extension Safety Study of Intranasal Esketamine in Treatment-resistant Depression, EudraCT#: 2015-003578-34, concerned a 40 year old female (subject (b) (6) site (b) (6)). The subject's weight was 57.4 kilograms and height was 165.5 centimeters. The subject's concurrent conditions included treatment resistant depression. The subject initiated treatment with esketamine (nasal spray, intra-nasal) 28 milligram, 2 every 1 week, from 17-AUG-2017 with most recent dose on 11-APR-2019, for treatment resistant depression. No concomitant medications were reported. On 15-APR-2019, the subject experienced suicide attempt (aborted) reported as interrupted/aborted suicide attempt. The subject reported to the investigator that she had feelings of wanting to harm herself. She reported driving her car into a wall but stopped because she received a phone call from her father. At the time, the investigator assessed that the subject would not have actually continued and completed the attempt to harm herself and as such it was probably medically not significant. The investigator later reported it as a serious adverse event per protocol guidelines. The dose of esketamine was not changed. The subject recovered from suicide attempt (aborted) on 15-APR-2019. The investigator assessed the severity of suicide attempt (aborted) as grade 3 severe and not related to trial procedure. The investigator considered the causality between esketamine and suicide attempt (aborted) as not related. Suicide attempt (aborted) was considered an anticipated event per the protocol. This report was serious (Life Threatening)..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Depression				
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report C	Study Name 2015-003578-34#Open label long term extension safety study of intranasal esketamine in TRD	Study Type C	Sponsor Study	Protocol	IND #
Literature Text					
Country of Event:	GBR	Sender MFR:	JOHNSON AND JOHNSON		
Reporter Name	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	GBR		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				
Reporter Name	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:		Reporter State:			
Reporter City:		Reporter Country:	GBR		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				

Case Information:

Case #: 17006598 Version: 3 Case Type: EXPEDITED eSub: Y HP: Country: USA Outcomes: OT Application Type: NDA

FDA Rcvd Date: 13-Dec-2019 Init FDA Rcvd Date 07-Nov-2019 Mfr Rcvd Date: 04-Dec-2019 MfrControl #: US-JNJFOC-20191104777 Application #: 211243

Patient Information:

Patient ID: (b) (6) Age in Years: 44.50103 Age/Unit: 44.50103 YR Sex: Female Weight: DOB: (b) (6)

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato	S	28 MG/	N/A		Drug Use For Unknown Indication	19-Sep-2019			Unk	Unk
Product Name	Lot #	Exp Date	NDC #	Labeler						
Spravato										

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Abdominal pain	18-Nov-2019		UNKNOWN	No, Not Serious	NA
Muscle spasms	18-Nov-2019		UNKNOWN	No, Not Serious	NA
Suicide attempt			UNKNOWN	No, Serious	NA

Event / Problem Narrative:

This spontaneous report received from a 44 year old female patient (Local case number: PAT-1000720299667, AE-92886930) REMS ID (b) (6). The patient's weight, height, and medical history were not reported. The patient received esketamine (nasal spray, intra-nasal) 28 milligram, frequency not provided, 7 treatments from 19-SEP-2019 to most recent dose on 26-NOV-2019, for an unknown indication. No concomitant medications were reported. On an unspecified date, the patient stated she had "committed suicide before due to not having medication" (captured as attempted suicide). While on a call with the patient on 18-NOV-2019, the patient experienced pain up and down her side and in her gut with severe cramping. The action taken with esketamine was not reported. The outcome of the attempted suicide, pain up and down side and in her gut and severe cramping was not reported. This report was serious (Other Medically Important Condition).

Additional information was received from the patient on 18-NOV-2019: (Local case number: PAT-1000720299667, AE-79230842). The following information was updated and incorporated into the case narrative: age of the patient, and two non-serious events were added to the case (abdominal pain and severe cramping).

Additional information was received on 04-DEC-2019. Information incorporated into the narrative included dates of treatment and REMS ID number..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
Study Report S Literature Text Country of Event: Reporter Name Reporter Org: Reporter Street: Reporter City: Reporter Zip: Health Prof: Occupation:	USA (b) (6)	Sender MFR: Reporter Type: Reporter Email: Reporter State: Reporter Country: Sent To: Identity Disclosed:	JOHNSON AND JOHNSON Other NC USA	Reporter Phone:	

Case Information:

Case #: 17193687 Version: 1 Case Type: EXPEDITED eSub: Y HP: Country: USA Outcomes: HO, Application Type: NDA
 FDA Rcvd Date: 23-Dec-2019 Init FDA Rcvd Date 23-Dec-2019 Mfr Rcvd Date: 13-Dec-2019 MfrControl #: US-JNJFOC-20191229734 Application #: 211243

Patient Information:

Patient ID: UNKNOWN Age in Years: Age/Unit: Sex: Female Weight: DOB:

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato	S	/	N/A		Product Used For Unknown Indication				Unk	NA

Product Name	Lot #	Exp Date	NDC #	Labeler
Spravato				

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide attempt			UNKNOWN	No, Serious	NA

Event / Problem Narrative:

This spontaneous report was received from a nurse practitioner and concerned a female of unspecified age.
 The patient's weight, height, and medical history were not reported.
 The patient received SPRAVATO (esketamine, nasal spray, intra-nasal, batch number not reported) dose, frequency, and therapy dates not reported, for an unknown indication. No concomitant medications were reported.
 On an unspecified date, the patient experienced attempted suicide, and was hospitalized (date unspecified) .
 Treatment with esketamine was withdrawn.
 The outcome of attempted suicide was not reported.
 This report was serious (Hospitalization Caused / Prolonged)..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
S					

Literature Text

Country of Event: USA

Reporter Name: (b) (6)

Reporter Org: (b) (6)

Reporter Street: (b) (6)

Reporter City: (b) (6)

Reporter Zip: (b) (6)

Health Prof: (b) (6)

Occupation: CON

Reporter Name: (b) (6)

Reporter Org: (b) (6)

Reporter Street: (b) (6)

Reporter City: (b) (6)

Reporter Zip: (b) (6)

Health Prof: (b) (6)

Occupation: HP

Sender MFR: JOHNSON AND JOHNSON

Reporter Type: Other

Reporter Email: (b) (6) **Reporter Phone:** (b) (6)

Reporter State: (b) (6)

Reporter Country: USA

Sent To: (b) (6)

Identity Disclosed: (b) (6)

Reporter Type: Other

Reporter Email: (b) (6) **Reporter Phone:** (b) (6)

Reporter State: CA

Reporter Country: USA

Sent To: (b) (6)

Identity Disclosed: (b) (6)

Case Information:

Case #: 17216290 Version: 2 Case Type: EXPEDITED eSub: Y HP: Country: FRA Outcomes: OT Application Type: NDA

FDA Rcvd Date: 20-Feb-2020 Init FDA Rcvd Date 30-Dec-2019 Mfr Rcvd Date: 12-Feb-2020 MfrControl #: FR-JNJFOC-20191121121 Application #: 211243

Patient Information:

Patient ID: UNKNOWN Age in Years: 60.00000 Age/Unit: 60 YR Sex: Female Weight: 57 DOB:

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato	S	56 MG/BIW	N/A		Drug Use For Unknown Indication	05-Nov-2019	06-Feb-2020	24 DAY	Unk	Unk
Anafranil	C	75 MG/	N/A			30-Oct-2019		30 DAY	NA	NA
Diprosone /00008502/	C	2 DF/QD	N/A						NA	NA
Theralene	C	20 MG/QD	N/A						NA	NA

Product Name
Spravato
Anafranil
Diprosone /00008502/
Theralene

Lot # Exp Date NDC # Labeler

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Dizziness	12-Nov-2019		UNKNOWN	No, Not Serious	NA
Rash	20-Nov-2019		UNKNOWN	No, Serious	NA
Suicide attempt	29-Nov-2019		UNKNOWN	No, Serious	NA

Event / Problem Narrative:

This individual patient use report received from physician via 54135419SUI4001: Esketamine ATU TRD, concerned a 60-year-old female patient (Patient# (b) (6)). The patient's weight was 57 kilograms and height was 162 centimeters. No past medical history or concurrent conditions were reported. The patient received SPRAVATO (esketamine nasal spray, intra-nasal, batch number not reported), 56 mg twice a week, initiated on 05-NOV-2019, for unknown indication. Concomitant medications included Anafranil (clomipramine hydrochloride). On 12-NOV-2019, the patient experienced sensation of dizziness. On 15-NOV-2019, the patient experienced dizziness persisting for a few hours. Corrective treatment included monitoring and rest. The dose of esketamine was not changed. The outcome of dizziness persisting for a few hours/sensation of dizziness was not reported. During the treatment session on 20-NOV-2019, the patient experienced dizziness that resolved after 2 hours and neck eruption of upper thorax, of allergy aspect (skin eruption). Treatment for skin eruption included ZYRTEC (cetirizine) 20 mg daily. The outcome of skin eruption was not reported. The action taken with esketamine was not reported. During the treatment session on 22-NOV-2019, the patient experienced dizziness. The event resolved within 2 hours. During the treatment session on 27-NOV-2019, the patient experienced again experienced dizziness. The outcome of dizziness was not reported. During the treatment session on 12-DEC-2019 (week 5 dose number 10; 56 mg the patient's Montgomery sberg Depression Rating Scale (MADRS) score was 14 and Clinical Global Impression of Severity of Suicidality Scale (CGI-SS Scale) was 1. On an unspecified date the patient experienced suicide attempt by strangulation twice following the decreased from 2 esketamine administrations to 1. Each time the suicide attempt was 4-5 days after the administration and disappeared upon resumption of esketamine.

On 06-FEB-2020, esketamine treatment was withdrawn due to insufficient therapeutic effect.

The outcome of the suicide attempt, dizziness, and skin eruption was unknown.

The reporter considered the causality between esketamine and skin eruption as possible. The reporter did not provide a causality assessment between esketamine, suicide attempt and dizziness. Company causality was possible.

This report was serious (other medically important).

Additional information was received from the physician on 21-NOV-2019, 25-NOV-2019, and 28-NOV-2019. The following information was updated and incorporated into the case narrative: esketamine dosing frequency, treatment session details (from 20-NOV-2019, 22-NOV-2019 and 27-NOV-2019) and a new event of skin eruption, outcome of dizziness, treatment medications, and concomitant medications.

Additional information was received on 20-DEC-2019. Based on the follow-up information this case was reassessed as serious. The following additional information was updated and incorporated into the narrative and included: Additional serious event of suicide attempt added as the patient attempted suicide twice by strangulation upon dose reduction.

Additional information was received from the physician on 12-FEB-2020. The following information was updated and incorporated into the case narrative: esketamine stop date and reason for discontinuation..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
C	Esketamine ATU TRD	I			
Literature Text					
Country of Event:	FRA	Sender MFR:	JOHNSON AND JOHNSON		
Reporter Name	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:	PRIVACY	Reporter State:			
Reporter City:	PRIVACY	Reporter Country:	FRA		
Reporter Zip:	PRIVACY	Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				
Reporter Name	PRIVACY PRIVACY	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:	PRIVACY	Reporter State:			
Reporter City:	PRIVACY	Reporter Country:	FRA		
Reporter Zip:	PRIVACY	Sent To:			

Health Prof:
Occupation: MD

Identity Disclosed:

APPEARS THIS WAY ON
ORIGINAL

Case Information:

Case #: 17220756 Version: 3 Case Type: EXPEDITED eSub: Y HP: Country: ESP Outcomes: HO, Application Type: NDA

FDA Rcvd Date: 15-Jan-2020 Init FDA Rcvd Date 31-Dec-2019 Mfr Rcvd Date: 08-Jan-2020 MfrControl #: ES-JNJFOC-20191247247 Application #: 211243

Patient Information:

Patient ID: UNKNOWN Age in Years: 55.73443 Age/Unit: 55.73443 YR Sex: Female Weight: 79 DOB: (b) (6)

All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Esketamine	S	56 MG/	N/A		Depression	06-Sep-2017		843 DAY	Unk	Unk
Eutirox	C	100 UG/QD	PO		Hypothyroidism	01-Jan-2010			NA	NA
Sertralina	C	150 MG/QD	PO		Depression	13-Sep-2016		3 YR	NA	NA
Zolpidem	C	10 MG/	PO		Depression	18-Oct-2017		801 DAY	NA	NA
Simvastatin	C	20 MG/QD	PO		Hypercholesterolemia	01-Jun-2018		575 DAY	NA	NA
Omeprazole	C	20 MG/QD	PO		Gastrointestinal Disorder Therapy	01-Jun-2019		210 DAY	NA	NA
Lorazepam	C	5.5 MG/QD	PO			01-Jun-2019		210 DAY	NA	NA

Product Name	Lot #	Exp Date	NDC #	Labeler
Esketamine	4374511, 4374743			
Eutirox				
Sertralina				
Zolpidem				
Simvastatin				
Omeprazole				
Lorazepam				

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide attempt	28-Dec-2019	29-Dec-2019	RECOVERED/ RESOLVED	No, Serious	NA

Event / Problem Narrative:

This report received from clinical trial 54135419TRD3008: An Open-label Long-term Extension Safety Study of Intranasal Esketamine in Treatment-resistant Depression, EudraCT#: 2015-003578-34, concerned a 55 year old female (subject (b) (6) site (b) (6)). The subject's weight was 79 kilograms and height was 163 centimeters. The subject's past medical history included suicide attempt (intake of pills), and concurrent conditions included treatment resistant depression, hypothyroidism and hypercholesterolemia. The subject initiated treatment with esketamine (nasal spray, intra-nasal, batch number 4374511, 4374743) 56 mg, 1 every 4 weeks, from 06-SEP-2017 at 11:35, for treatment resistant depression. Concomitant medications included simvastatin for hypercholesterolemia, levothyroxine sodium for hypothyroidism, omeprazole for stomach protector, lorazepam for suicide attempt (intake of pills), and sertraline hydrochloride and zolpidem for treatment resistant depression. On optimization week 108 on 25-SEP-2019, the Montgomery-Asberg Depression Rating Scale (MADRS) was 1. On optimization week 112 on 21-OCT-2019, MADRS was 0.

On optimization week 116 on 21-OCT-2019, MADRS was 2.

The most recent dose administered on 20-DEC-2019 at 10:25 (medical kit numbers (b) (6)) MADRS score was 4.

On (b) (6) the subject experienced suicide attempt (intake of pills), and was hospitalized. The subject had been separated from her husband for a year and was in the process of divorce. She has two children with whom she has a good relationship and she recognized a real improvement in her mood over the last two months. However, on (b) (6) she has received a telephone call from her ex-husband and stated "it all came to me; it was like going back in time and going through everything bad." She called the emergency clinical trial phone indicating that she was going to leave this life because nobody understood her. She called and hung up. Consequently, the study coordinator called the subject's sister and daughter to inform them of this risk. The subject's sister went to the subject's house and found that she had taken several pills in attempt to commit suicide. However, the real intention of the subject was to be out of the stressful environment. The subject was taken to the local hospital for evaluation. During the physical examination, the subject presented with continuous crying and stated that she spent the holiday alone and it was not the first time she presented with this similar case. The subject reported an intake of 50 pills of lormetazepam 1 mg and 2 pills of zolpidem and alcohol intake with autolytic ideation. Upon psychopathology evaluation, the subject was vigilant, well oriented in person, time and space. Memory and attention preserved. Insight adequate, euthymic, calm, collaborative. Spontaneous speech. She coherently recounted the facts and made repeated criticism of a behavior, which she described as impulsive, not premeditated, and that she would not repeat, mentioning protective factors including sisters and children. The subject did not present alterations in the course or in the content of thought or sensory perception. FIS preserved. The evaluating psychiatrist considered the suicide attempt as an impulsive reaction to stress. The subject reported that she did not want to die and she looked for help. The subject refused hospital admission in the presence of family, who agreed to accompany and supervise the subject. The subject was discharged on (b) (6).

On 02-JAN-2020, the subject was evaluated by her psychiatrist. She regretted all facts that happened and promised not to do this again. The psychiatrist did not find relevant psychopathy and the suicide attempt was not committed under depressive symptomatology. She was euthymic and aware of her difficulties managing life events. In order to prevent future suicide attempts, the psychiatrist proposed to start support psychotherapy and cognitive behavioral therapy (CBT) in order to improve her skills for coping with stressful events. Additionally, the psychiatrist reported that the esketamine was working well enough and the subject continued with treatment.

The action taken with esketamine was not reported.

The subject recovered from suicide attempt (intake of pills) o (b) (6)

The investigator assessed the severity of suicide attempt (intake of pills) as grade 2 moderate adverse event.

The investigator considered the causality between esketamine and suicide attempt (intake of pills) as not related. The event was not related to trial procedure.

Suicide attempt (intake of pills) was considered an anticipated event per the protocol.

This report was serious (Hospitalization Caused / Prolonged).

Hospital records, initially received on (b) (6) were translated and received on (b) (6) The following information was updated and incorporated into the case narrative: additional event details were updated in the case narrative.

Additional information was received from the investigator on 08-JAN-2020. The following information was updated and incorporated into the case narrative: additional event details were added to the case narrative..

Relevant Medical History:

Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Depression			Yes	
Hypercholesterolemia			Yes	
Hypothyroidism			Yes	
Suicide attempt	01-Jun-2019		No	
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail. Y/N
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Confirmatory Test Comments

Reporter Source:

Study Report C	Study Name 2015-003578-34#Open label long term extension safety study of intranasal esketamine in TRD	Study Type C	Sponsor Study	Protocol	IND #
Literature Text					
Country of Event:	ESP	Sender MFR:	JOHNSON AND JOHNSON		
Reporter Name	(b) (6)	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:	(b) (6)	Reporter State:	07		
Reporter City:		Reporter Country:	ESP		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				
Reporter Name	(b) (6)	Reporter Type:	Other	Reporter Phone:	
Reporter Org:		Reporter Email:			
Reporter Street:	(b) (6)	Reporter State:	07		
Reporter City:		Reporter Country:	ESP		
Reporter Zip:		Sent To:			
Health Prof:		Identity Disclosed:			
Occupation:	MD				

Case Information:

Case #: 17508534	Version: 1	Case Type: DIRECT	eSub: N	HP: Y	Country: USA	Outcomes: HO, OT	Application Type:
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FDA Rcvd Date:	25-Feb-2020	Init FDA Rcvd Date	25-Feb-2020	Mfr Rcvd Date:		MfrControl #:		Application #:	
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Patient Information:

Patient ID:	(b) (6)	Age in Years:		Age/Unit:		Sex:	Male	Weight:		DOB:	(b) (6)
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All Products:

Product Name	Role	Dose / Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
Spravato 56mg Spr	S	56 MG/	N/A	OTHER FREQUENCY:Q4D;OT HER ROUTE:SPR	Major Depressive Disorder				NA	NA
Spravato 84mg Spr	S	84 MG/BIW	N/A	OTHER ROUTE:SPR	Major Depressive Disorder				NA	NA
Product Name	Lot #			Exp Date	NDC #		Labeler			
Spravato 56mg Spr					50458002802		Janssen			
Spravato 84mg Spr					50458002803		Janssen			

Event Information:

MedDRA® PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide attempt					NA

Event / Problem Narrative:

PATIENT'S MDO REPORTED THAT PATIENT IS HOSPITALIZED DUE TO SUICIDE ATTEMPT (b) (6) HAS NEVER FILLED FOR PATIENT
MD (b) (6)
(b) (6) FAX (b) (6) PHONE (b) (6)
(b) (6)

Relevant Medical History:

UNKNOWN				
Disease / Surgical Procedure	Start Date	End Date	Continuing?	Comment
Medical History Products	Start Date	End Date	Indications	MedDRA® PreferredTerm(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	info Avail. Y/N
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Confirmatory Test Comments

UNKNOWN

Reporter Source:

Study Report	Study Name	Study Type	Sponsor Study	Protocol	IND #
S					
Literature Text					
Country of Event:	USA	Sender MFR:	FDA-CTU		
Reporter Name	(b) (6)	Reporter Type:	Health Professional		
Reporter Org:		Reporter Email:	(b) (6)	Reporter Phone:	(b) (6)
Reporter Street:	(b) (6)	Reporter State:			
Reporter City:		Reporter Country:	USA		
Reporter Zip:		Sent To:			
Health Prof:	Y	Identity Disclosed:	N		
Occupation:	HP				

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: May 22, 2020

To: Paul M. Bossie, M.D., Clinical Reviewer
Division of Psychiatry (DP)

Sandy Chang, PharmD, Regulatory Project Manager, (DP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for SPRAVATO® (esketamine) nasal spray, CIII

NDA: 211243 / Supplement 004

In response to DP consult request dated November 21, 2019, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for SPRAVATO® (esketamine) nasal spray, CIII. This supplement (S004) proposes a new indication for Major Depressive Disorder in adults (b) (4)

PI: OPDP's comments on the proposed labeling are based on the draft PI downloaded from DP SharePoint on May 14, 2020, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 18, 2020.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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MEMORANDUM
REVIEW OF LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 12, 2020
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 211273/S-004
Product Name and Strength:	Spravato (esketamine) nasal spray, 56 mg kit and 84 mg kit (28 mg per nasal spray device)
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2019-2277
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Janssen submitted efficacy supplement NDA 211243/S-004 on October 2, 2019 to support approval of a new indication, “rapid reduction of depressive symptoms in adult patients with Major Depressive Disorder who have active suicidal ideation with intent”.

The Division of Psychiatry (DP) requested that we review the proposed Prescribing Information (see Appendix A) to determine if it is acceptable from a medication error perspective.

2 ASSESSMENT

We reviewed the proposed Prescribing Information (PI), submitted on October 2, 2019, as well as DP’s current revisions (as of May 8, 2020). We focused on the Dosage and Administration sections of the PI and did not identify any areas that are prone to medication errors. We also considered whether the revisions made to provide for S-004 require subsequent updates to the Spravato container labels and carton labeling to ensure consistency and to minimize the risk of confusion. We did not identify any areas where updates (e.g., proprietary name, dosage form, route of administration, or usual dosage statement) to the container labels and carton labeling are needed. As such, we have no comments regarding the revised PI, container labels, and carton labeling.

3 CONCLUSION

We find the revised Prescribing Information acceptable from a medication error perspective. Therefore, we have no recommendations at this time.

APPENDIX A. LINKS TO LABELING RECEIVED ON OCTOBER 2, 2019

The proposed Prescribing Information was submitted on October 2, 2019 and can be accessed via the Electronic Document Room (EDR) with these links:

<\\cdsesub1\evsprod\nda211243\0063\m1\us\annotated-draft-labeling-text-mdsi.pdf>

or

[Application 211243 - Sequence 0063 - Annotated Draft Labeling Text.pdf - mdsi](#)

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 18, 2020

To: ShinYe (Sandy) Chang, PharmD
Regulatory Project Manager
Division of Psychiatry (DP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Domenic D'Alessandro, PharmD, MBA, BCPS, CDE
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SPRAVATO (esketamine)

Dosage Form and Route: Nasal Spray, for intranasal use, CIII

Application Type/Number: NDA 211243

Supplement Number: S-004

Applicant: Janssen Research & Development, LLC

1 INTRODUCTION

On October 2, 2019, Janssen Research & Development, LLC submitted for the Agency's review a Prior Approval Supplement-Efficacy (PAS-004), to the New Drug Application (NDA-211243) for SPRAVATO (esketamine) Nasal Spray, for intranasal use, CIII. The purpose of the submission is to support approval of a new indication of use for the rapid reduction of depressive symptoms in adult patients with Major Depressive Disorder who have active suicidal ideation with intent (MDSI).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on November 21, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SPRAVATO (esketamine) Nasal Spray, for intranasal use, CIII.

2 MATERIAL REVIEWED

- Draft SPRAVATO (esketamine) MG received on October 2, 2019 and received by DMPP and OPDP on May 14, 2020.
- Draft SPRAVATO (esketamine) Prescribing Information (PI) received on October 2, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2020.
- Approved SPRAVATO (esketamine) labeling approved March 5, 2019.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
05/18/2020 02:15:42 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s004

**RISK ASSESSMENT AND RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
Supplement Number, Date Received	Supplement 4 received October 2, 2019 (sequence 0063 on July 2, 2020 (sequence 0098), July 24, 2020 (sequence 0108) and July 30, 2020 (sequence 0110)
OND Review Division	Division of Psychiatry Products (DP)
Action Date	August 2, 2020
OSE RCM #	2019-2398
Reviewer Name(s)	Somya Dunn, MD Anahita Tavakoli, M.A. Victoria Sammarco, PharmD, MBA Barbara Bergquist, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH Shelly Harris, ScD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 31, 2020
Subject	Review of Proposed Major REMS Modification
Established Name	esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration

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Executive Summary

This review evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for Spravato (esketamine) New Drug Application (NDA) 211243 submitted by Janssen Pharmaceuticals, Inc (the Sponsor) on October 2, 2019 and amended on July 2, 2020, July 24, 2020, and July 30, 2020. The REMS for Spravato was originally approved on March 5, 2019 to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and abuse and misuse. The most recent REMS modification was approved on June 25, 2019. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The Sponsor's proposed modification to the REMS was based on their efficacy supplement submitted for the added indication of "rapid reduction of depressive symptoms in adult patients with Major Depressive Disorder (MDD) who have active suicidal ideation with intent." During the course of the review, the following changes to their proposal were communicated to the Sponsor:

- (b) (4)
- (b) (4) policies and procedures to ensure all patients are monitored until resolution of sedation and dissociation.

The modification requires that healthcare settings (e.g. hospitals) that dispense Spravato for inpatient use (including emergency departments with in a certified healthcare setting) must become certified. As part of that certification they must train all relevant staff involved in prescribing, dispensing and administering Spravato on: 1) Counseling the patient on the need for monitoring, risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours. Patients that continue treatment with Spravato in the outpatient setting will be required to enroll in the REMS.

DRM finds the proposed modifications to the Spravato REMS to be acceptable for approval. There are no changes to the Timetable for submission of the assessment of the REMS. Changes to the Assessment plan were made to be consistent with this modification.

1 Introduction

This review evaluates the proposed modifications for the risk evaluation and mitigation strategy (REMS) for Spravato (esketamine) New Drug Application (NDA) 211243, submitted by Janssen Pharmaceuticals, Inc. on October 2, 2019 and amended on July 2, 2020, July 24, 2020 and July 30, 2020. The Sponsor proposed modifications to the REMS to support an additional indication for Spravato as proposed treatment for "rapid reduction of depressive symptoms in adult patients with Major Depressive Disorder (MDD) indica (b) (4)

- (b) (4)
- (b) (4)

2 B

2.1 PRODUCT INFORMATION

Spravato is a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist approved for treatment of treatment-resistant depression in conjunction with an oral antidepressant. Spravato is available as 28 mg solution drug-device combination that the patient administers intranasally.

Spravato was approved on March 5, 2019 with a REMS to ensure that the benefits of the drug outweigh the increased risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

The goals of this REMS are 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

The most recently approved REMS (approved June 25, 2019) for Spravato consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The REMS elements include:

- Healthcare setting certification
- Pharmacy certification
- Patient monitoring
- Safe use conditions
- Patient registry

2.2 REGULATORY HISTORY

The regulatory history relevant to the proposed REMS modification is summarized below:

- March 5, 2019: Spravato was approved with a REMS.
- May 1, 2019: The Sponsor submitted Supplement 2, proposed minor REMS modification (EDR Sequence 0054).
- June 25, 2019: REMS modification was approved. The REMS was modified to amend and clarify some of the data-capturing fields in the Healthcare Setting Enrollment Form, Pharmacy Enrollment Form, and Patient Monitoring Form to make them more user-friendly.
- October 2, 2019: Efficacy supplement 004 (EDR Sequence 0063) was submitted. This submission is the subject of this review.
- March 11, 2020: Information Request issued to the Sponsor requesting estimate of turnaround time for REMS materials.
- March 17, 2020: The Sponsor submitted response to Information Request from March 11 indicating 14-28 day turnaround times for revisions to REMS materials.
- April 15, 2020: The Agency sent the Sponsor a communication stating that we did not agree with the proposed indication due to lack of supporting data and instead were considering the following

“...major depressive disorder (MDD) in patients appropriate for inpatient psychiatric care.” In addition, the Agency was considering the Limitation of Use: “Spravato has not been proven to be effective in preventing suicide or in reducing suicidal ideation or behavior. Use of Spravato does not preclude the need for hospitalization, if clinically warranted.”

- April 15, 2020: The Sponsor acknowledged FDA’s April 15, 2020 communication and stated that they were in agreement with this proposal.
- April 24, 2020: The Sponsor sent another correspondence in response to the Agency’s April 15th indication proposal. They proposed the indication, “...for the rapid reduction of depressive symptoms... (b) (4) Limitations of Use: Spravato has not been proven to be effective in preventing suicide or in reducing suicidal ideation or behavior. Use of Spravato does not preclude the need for hospitalization, if clinically warranted.” They supported this proposal in part by discussing how “inpatient psychiatric care” may potentially be misinterpreted as a need to treat patients only while they are hospitalized, rather than for the recommended 4 full weeks of treatment. In addition, they argued that stating “inpatient care” could lead to misinterpretation as real-world practice data suggests that the decision to hospitalize a patient is complicated by many factors and transitions from inpatient to outpatient care in the US mental health system are often difficult.
- May 1, 2020: Information Request issued to the Sponsor requesting 1.) the rationale (b) (4) (b) (4) (b) (4) and 2.) thought process regarding the requirement to (b) (4) (b) (4)
- May 26, 2020: The Sponsor submitted a response to Information Request from May 1 outlining their rationale (b) (4) (b) (4) because they claim that this enables clear follow up to assess adverse events (AEs) and REMS compliance. The Sponsor also proposed adding notation to (b) (4) (b) (4)
- June 19, 2020: The Agency provided the Sponsor feedback on the materials originally submitted with efficacy supplement 4 (Sammarco, V. Spravato REMS Review, darrted June 19, 2020).
- July 2, 2020: The Sponsor submitted revised REMS materials in response to Agency feedback on June 19, 2020 (Seq 0098).
- July 20, 2020: The Agency provided the Sponsor feedback on the REMS amendment and REMS materials to supplement 4 submitted on July 2, 2020 (Dunn, S. Spravato REMS Review, darrted July 20, 2020).
- July 24, 2020: The Sponsor submitted revised REMS materials, a REMS amendment, in response to Agency feedback on July 27, 2020 (Seq0108).
- July 29, 2020: The Agency provided the Sponsor feedback on the REMS amendment and REMS materials to supplement 4 submitted on July 2, 2020 (Dunn, S. Spravato REMS Review, darrted July 29, 2020).

- July 30, 2020: The Sponsor submitted revised and final REMS materials, a REMS amendment, in response to Agency feedback on July 29, 2020 (Seq0110).

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITIONS

Major depressive disorder (MDD) is a life-threatening, chronic condition. In 2017, an estimated 11 million U.S. adults aged 18 or older had at least one major depressive episode with severe impairment.¹ 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 with a median rate of 10 years of life lost.² Furthermore, approximately 45,000 people committed suicide in 2016, representing a continuous upward trend in suicide since 1999.³

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

No pharmacological treatment is approved specifically for the rapid reduction of depressive symptoms in patients with MDD (with or without suicidal ideation and behavior), or for the reduction of the severity of suicidal ideation in patients with MDD with suicidal ideation and behavior. Electroconvulsive therapy (ECT) is approved for the treatment of severe major depressive episodes or catatonia in individuals aged 13 or over who are either treatment-resistant or require a rapid response.⁴ Pharmacologic therapies for MDD generally require at least 2-4 weeks for symptom improvement with many patients requiring different or additional therapy.

4 Benefit Assessment

The clinical program for this supplement consisted of data from two identical phase 3, short-term (4-week), randomized, double-blind, multicenter, placebo-controlled studies in subjects 18 to 64 years of age with moderate-to-severe major depressive disorder with active suicidal ideation and intent (studies SUI3001 and SUI3002). In these studies, patients received eight treatments with intranasal esketamine 84 mg or placebo nasal spray twice weekly over a 25-day double-blind treatment period. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD) (either as AD monotherapy or AD plus augmentation therapy). After the first dose, a one-time dose reduction to esketamine 56 mg was allowed for patients unable to tolerate the 84 mg dose.

A total of 452 subjects were treated. The primary efficacy measure was the change-from-baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours after first dose (Day 2). MADRS is scale designed to measure depression severity and detect changes due to AD treatment. The test consists of 10 items, each scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. The MADRS evaluation includes apparent sadness, reported sadness, sleep, interest level, and suicidal thoughts. Patients had a total score of >28

¹ Major Depression. National Institute of Mental Health. <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>. Accessed June 12, 2020.

² Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis [published correction appears in JAMA Psychiatry. 2015 Jul;72(7):736] [published correction appears in JAMA Psychiatry. 2015 Dec;72(12):1259]. JAMA Psychiatry. 2015;72(4):334-341. doi:10.1001/jamapsychiatry.2014.2502

³ Suicide rising across the US. (2018, June 07). Retrieved June 16, 2020, from <https://www.cdc.gov/vitalsigns/suicide/index.html>

⁴ Commissioner of the FDA issues order to regulate ECT devices based on benefits and risks. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-takes-action-ensure-regulation-electroconvulsive-therapy-devices-better-protects>. Accessed June 12, 2020.

pre-dose on Day 1. In both studies, esketamine plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care (Table 1).

Table 1 Primary Efficacy Results for Change From Baseline in MADRS Total Score at 24 Hours⁵

Study	Placebo		Esketamine		LS Mean Difference (95% CI)	Two-sided p-value
	N	LS Mean (SE)	N	LS Mean (SE)		
SUI3001	112	-12.7 (0.97)	111	-16.5 (0.97)	-3.82 (-6.60, -1.04)	0.0064
SUI3002	113	-12.1 (0.97)	114	-16.0 (0.97)	-3.85 (-6.60, -1.11)	0.0062

Table 51, Division of Psychiatry NDA/BLA Multi-Disciplinary Review and Evaluation For Spravato Supp 4, dartrted July 31, 2020

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-R) score at 24 hours after first dose (Day 2). In both studies, esketamine plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-R.

As discussed, the Sponsor proposed additional indication language for Spravato be used for “rapid reduction of depressive symptoms in adult patients with MDD who have active suicidal ideation with intent.” The Sponsor could not support this claim with data from their secondary endpoint. In addition the proposed language for the indication did not include language consistent with common medical terminology. Therefore, their proposed indication was not accepted. The Agency has revised the Sponsor’s proposed indication to (new indication in bold):

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- **Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.**

Please see the Division of Psychiatry (DP) full review for details on the efficacy data and discussion of the labeling language.⁵

5 Risk Assessment and Safe-Use Conditions

No new safety signals were identified in the studies for this supplement, and safety results were comparable to the treatment-resistant depression program. Adverse events in the clinical program were similar amongst treatment groups and (SAEs) were also consistent among the varying analyses done by the review

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⁵ Division of Psychiatry NDA/BLA Multi-Disciplinary Review and Evaluation For Spravato Supp 4, dartrted July 31, 2020.

Table 2 Severe Adverse Events Occurring During the Treatment Phase in ≥1% of Subjects in Any Treatment Group in Pooled Studies SUI3001 and SUI3002 ⁵

MedDRA System Organ Class MedDRA Preferred Term	Placebo + SOC (N=225) n (%)	Esketamine + SOC (N=227) n (%)
Psychiatric disorders	10 (4.4%)	20 (8.8%)
Dissociation*	0	11 (4.8%)
Anxiety	1 (0.4%)	4 (1.8%)
Suicide attempt	2 (0.9%)	3 (1.3%)
Depression*	4 (1.8%)	2 (0.9%)
Suicidal ideation	3 (1.3%)	1 (0.4%)
<i>Grouped: depression suicidal, suicidal ideation</i>	4 (1.8%)	2 (0.9%)
Gastrointestinal disorders	0	7 (3.1%)
Nausea	0	5 (2.2%)
Investigations	0	5 (2.2%)
Blood pressure increased*	0	5 (2.2%)

Source: Adapted from Integrated Summary of Safety Table 12, p. 43, and ADAE dataset

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

Table 60, Division of Psychiatry NDA/BLA Multi-Disciplinary Review and Evaluation For Spravato Supp 4, drafted July 31, 2020

Treatment emergent adverse events did not suggest or reveal safety signals that were not seen in the original clinical program for treatment resistant depression. Since safety results were comparable to the treatment-resistant depression program, the significant risks of concern that the REMS addresses, remain those of adverse events that may result from sedation and dissociation, and potential misuse and abuse.

The additional labeling indication for adults with MDD with acute suicidal ideation or behavior may increase the likelihood of patients receiving Spravato in hospital settings; patients may be more likely to initiate therapy in an emergency room or during a hospital admission in response to urgent need for treatment. (b) (4)

(b) (4) the Agency agrees that modifications to the REMS program are necessary as the ability and requirements to monitor patients are different between clinics/offices and hospitals. Hospitals with on-site pharmacies, several inpatient wards, operating suites and emergency departments generally have or develop policies to ensure that patients that undergo treatments or procedures are monitored for adverse events; and also are required to document in the medical chart on these patients. They also have staffing, including physicians, physician assistants, nurses, nurse practitioners, and various therapy specialists on-site at all times to provide patient care and continuously monitor patient health status. In these hospital settings, the Agency is more assured that patient monitoring will occur. In addition, potential necessary interventions are already on-site (b) (4)

Due to the expected operations of typical hospital, the Agency is recommending that hospitals be required to become certified to ensure that policies and procedures are in place, staff is trained and patients are informed and monitored.

In the outpatient healthcare settings, the adverse events of sedation, dissociation and misuse and abuse will continue to be mitigated by requiring certification of outpatient health care settings to ensure Spravato is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients, that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring and to enroll all out patients in a registry to further characterize the risks and support safe use.

The six-month (1st) REMS assessment was completed on March 6, 2020. The REMS assessment reviewer asserted that the REMS was meeting its goals.

6 Expected Postmarket Use

The additional indication may increase the patient population that could receive Spravato in a hospital setting though most therapy is still likely to be administered in an outpatient clinic or office setting. Prescribers in hospital settings may include emergency room physicians, psychiatrists, and hospitalists. A diverse collection of prescribers will likely continue to prescribe Spravato through clinic and office-based therapy.

7 Review of Proposed REMS Modifications

7.1 REMS Goals

The Agency amended the goals of the currently approved REMS to convey that only patients receiving Spravato in an outpatient healthcare settings should be enrolled in the registry. This goal is:

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 patients are informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrolling of patients who receive treatment in an outpatient healthcare setting in a registry to further characterize the risks and support safe use

(b) (4)

(b) (4) Another purpose of patient enrollment is to inform the patient of the requirements for monitoring; by virtue of the inpatient setting, patients will be monitored.

7.2 REMS Document

The Sponsor has updated and aligned the REMS Document to provide details on the different certification requirements for inpatient and outpatient settings. This includes that the patient enrollment and patient monitoring forms are required only in outpatient settings. Although emergency departments are considered outpatient, for the purpose of this REMS, they will be considered as inpatient settings; this is clearly stated in the REMS. The rationale is that emergency departments are equipped to monitor patients during and after treatment, and if Spravato is initiated in the emergency department, the patient would likely be subsequently transferred to an inpatient care setting. In addition, the REMS Document was updated to (b) (4)

(b) (4) the new REMS program and the need for monitoring of patients. However, with this modification, the requirement changes are more relevant to stakeholders that are involved in the certification process, this information is described on the enrollment forms, in the REMS Program Overview and is readily available on the Spravato REM website for any interested stakeholder. The need for at least two hours of monitoring does not change regardless of the patient setting.

During enrollment, patients in outpatient settings must be counseled that they must make arrangements for travel home and should not operate machinery for the rest of the day on which they received Spravato.

They attest that they are aware of this during the enrollment process. Certified inpatient settings must ensure that the patients are counseled they must make arrangements for travel home and should not operate machinery for the rest of the day on which they received Spravato. This requirement is clearly stated in the REMS Document.

7.3 REMS Requirements

7.3.1 REMS Participant Requirements and Materials

7.3.1.1 Inpatient Healthcare Setting Enrollment Form

The original Spravato REMS included one Healthcare Setting Enrollment Form for all HCS. The requirements were the same regardless of the patient setting as the expectation was that Spravato would be administered in outpatient offices and clinics. With the known risks of sedation and dissociation, the Agency felt that the need for monitoring patients until resolution of sedation and dissociation before sending them home was critical in preventing adverse events that could result such as accidents. However, during this modification, the Agency requested that the Sponsor create a separate Inpatient Healthcare Setting Enrollment because patients who exhibit “depressive symptoms” with “acute suicidal ideation or behavior” may be more likely to be given Spravato in hospital settings. In these cases, as discussed, the inpatient HCS would be better equipped to monitor patients and also more likely to keep patients for longer stays/visits. The Inpatient Healthcare Setting Enrollment Form details the specific requirements for inpatient settings. The certification requirements include that staff involved in prescribing, dispensing and administering Spravato must: 1) Counseling the patient on the need for monitoring, risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities; 2) Patient administration occurs under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours. (b) (4)

(b) (4) We expect that most patients are likely to continue treatment with Spravato after discharge. (b) (4) Furthermore, (b) (4)

(b) (4) The attestations are specific to the setting and help assure the Agency that these setting-specific policies and procedures are in place.

7.3.1.2 Outpatient Healthcare Setting Enrollment Form

The requirements for outpatient settings will remain consistent with the original approved Spravato REMS. This form will be filled out in these settings. Patients will need to be enrolled prior to obtaining Spravato and monitoring forms will need to be filled out for each administration. Outpatient settings and the providers and staff that work in these settings do not typically have processes in place to enable this level of monitoring. This enrollment process serves to ensure that patients are monitored for at least the full two hours and until symptoms are resolved in these outpatient settings. The attestations are specific to the setting and help assure the Agency that these setting-specific policies and procedures are in place.

7.3.1.3 Pharmacy Enrollment Form

The Pharmacy Enrollment Form is now only for enrollment of pharmacies working with outpatient settings. Pharmacies in hospital settings will be certified under the umbrella of healthcare setting certification.

7.3.1.4 REMS Program Overview

The Spravato REMS Fact Sheet was replaced with the REMS Program Overview—a more comprehensive document with more detailed guidance for stakeholders. The overview describes the requirements of the Spravato REMS Program and the responsibilities of each relevant stakeholder. The document contains product distribution that was removed from other REMS materials and answers the following questions:

- What is the Spravato REMS?
- How does the Spravato REMS work?
- What are the requirements of the Spravato REMS?
- What are the Spravato REMS resources?

7.3.1.5 REMS Patient Enrollment Form

As discussed, most patients who are started on Spravato in the inpatient setting will likely continue treatment as an outpatient and can be enrolled in the patient registry at that time. Furthermore, patients will be monitored: (b) (4) in outpatient settings where this form will be required, it will help serve to inform the patient of the requirements for monitoring informing them of the risks, and enroll the patients in the registry. The REMS Patient Enrollment Form was amended to clarify that patient enrollment is only required in outpatient clinic and office settings. In inpatient settings, information that was conveyed to patients in the process of reviewing and signing this form is still required to be communicated (b) (4)

7.3.1.6 REMS Patient Monitoring Form

The monitoring form is required to be completed each time a patient receives treatment with Spravato in the outpatient setting. The form serves to ensure that these patients are monitored for at least the full two hours and until symptoms are resolved in these outpatient settings. The monitoring form also serves to collect data for the registry to further characterize the risks, support the safe use of Spravato, and to further inform the Agency the risks and the appropriateness of the risk mitigation.

7.3.1.7 REMS Program Website

The REMS Program Website was amended to align with the new and different REMS requirements for inpatient and outpatient settings previously discussed in this review.

7.4 REMS Assessment Timetable

The timetable for submission of the assessments does not need to be modified due to the supplement approval.

8 Supporting Document

The REMS Supporting Document (SD) was changed to include the background of the REMS Modification currently under review. The REMS Supporting Document was amended to align with the new and different REMS requirements for inpatient and outpatient settings previously discussed in this review. The Sponsor submitted the plans detailing the processes that will occur to ensure the REMS requirements are carried out. For example, they describe their plans to deal with noncompliance and list the information that they plan to gather and evaluate among the various stakeholders. They also provide details on their audit plan. The updated Assessment Plan provided by the Agency was incorporated into the SD. It was revised to include additional metrics resulting from the modification.

9 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter. The agreed upon REMS Assessment Plan is provided in attached appendices.

The metrics in the Spravato REMS revised Assessment Plan is used to assess whether the REMS program is meeting its risk mitigation goals. Revisions to the Spravato REMS Assessment Plan as outlined in the March 5, 2019 approval letter include the following:

- aligned metrics with the draft guidance “REMS Assessment: Planning and Reporting,”
- deleting REMS outreach and communication metrics as these requirements have been met
- updated program implementation metrics to reflect new REMS requirements
- differentiating inpatient and outpatient healthcare settings to applicable metrics as patient enrollment and patient monitoring forms will not be required for inpatient settings
- reporting the mean, median and range of time for resolution of sedation and dissociation symptoms in patients who required less than two hours of monitoring and those patients that required more than two hours of monitoring after Spravato administration for analysis.

The modified Spravato REMS assessment plan is comprised of metrics from the following assessment categories and will be used to capture program processes and outcomes:

Program Implementation and Operations-measures the extent to which the intended stakeholders are participating in the program, how effectively the REMS program is being implemented and compliance with the REMS requirements. Program implementation data will be collected to determine when the website and REMS Coordinating Center will be fully functional with the new REMS requirements and certification of inpatient and outpatient healthcare settings. Stakeholder certification and enrollment data, which includes the number of active entities, setting type and demographics where applicable, will be utilized to assess stakeholder participation in the program; demographics can also be utilized to determine representativeness of survey respondents to the REMS program population. Metrics related to the REMS Coordinating Center are assessed to determine if there are any problems with REMS implementation or operations, as well assess burden or access issues related to REMS program processes or procedures. Utilization data is provided, in part, to determine if the restricted distribution of Spravato as required per the safe-use conditions are associated with treatment delays or potential barriers to therapy. Audits of inpatient and outpatient healthcare settings, pharmacies, and wholesalers-distributors will determine if the required documentation of training and processes and procedures are in place; any deficiencies identified and subsequent corrective and preventative plans are to be reported. In addition, data on stakeholder non-

compliance events are captured to determine if the REMS system is functioning as intended or if changes need to be implemented.

Assessment of these metrics contributes to the determination if the goal of ensuring that Spravato is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients and that of ensuring pharmacies and healthcare settings that dispense Spravato are certified.

Safe Use Behaviors-measures the extent to which safe use conditions are being followed. The metrics assess if healthcare providers submit the required documentation (*Patient Monitoring Forms*) and that the safe use conditions were implemented as described in the prescribing information. Metrics also include reporting of any outreach activities to obtain forms not received within the required timeframe and the reasons why the forms may not have been submitted. In addition, the data collected from *Patient Monitoring Forms* will be added to a patient registry to further characterize the risks and support the safe use of Spravato. Assessment of these metrics will determine if the objective of documentation of the safe-use conditions was achieved.

Health Outcomes and/or Surrogates of Health Outcomes- measures the safety-related health adverse outcomes resulting from sedation and dissociation caused by Spravato administration and abuse and misuse of Spravato. Known, or suspected adverse events related to abuse or misuse of Spravato as well as cases of sedation, dissociation, and changes in vital signs are to be reported regardless of outcomes. Sources of the reports include but are not limited to the following: *Patient Monitoring Form*, adverse events reported in the REMS registry, spontaneous adverse event reports, literature searches, social media and national databases (can include poison center calls as well as data regarding drug diversion). The Sponsor is to include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication. Assessment of these metrics allows for determination if the occurrence of known events (sedation, dissociation and changes in vital signs) are similar to those seen in the clinical trials and if the appropriate monitoring parameters as required by the REMS were followed.

Knowledge-measures the extent of stakeholders' knowledge about the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration and abuse and misuse of Spravato. Knowledge will be assessed via the results of the REMS Knowledge, Attitudes and Behavior (KAB) surveys for authorized representatives and healthcare professionals within the certified healthcare settings and enrolled patients. The surveys are used to assess awareness of the REMS educational materials, knowledge of the risks associated with treatment and knowledge of the REMS requirements to ensure the safe use of Spravato. In addition, the results of the KAB surveys are assessed to determine if the goal of ensuring that patients are informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring was achieved by meeting pre-determined knowledge thresholds.

The revised REMS Assessment Plan must include, but is not limited to, the following (strikethroughs are deletions and additions are underlined):

Program Implementation and Operations

(b) (4)

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

10 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on July 17, 2020 to provide feedback on the content of the updated Spravato REMS modification materials for Supplement 4. The OPDP review was completed by Domenic D'Alessandro on July 24, 2020. The OPDP recommendations are summarized below.

DRM appreciates the feedback provided by OPDP, considered all comments and noted OPDP's concerns. However, DRM did not accept the following OPDP comments. DRM comments and rationale follows the OPDP concerns:

REMS STATEMENT 1:

“Monitor each patient for at least 2 hours following administration of SPRAVATO[®] for resolution of sedation and dissociation, and changes in vital signs” (SPRAVATO[®] REMS Program Overview, page 3),

“Have a healthcare provider[(s) onsite to] monitor every [each] patient for at least 2 hours [following administration of SPRAVATO[®]] for resolution of sedation and dissociation, and changes in vital signs after every dose” (SPRAVATO[®] REMS Program Overview, page 4; Inpatient Healthcare Setting Enrollment Form, page 2; Outpatient Healthcare Setting Enrollment Form, page 2)

(b) (4) receive counseling on safety risks and the need for monitoring to observe for resolution of sedation and dissociation, and for any changes in vital signs” (Patient Enrollment Form, page 2; SPRAVATO[®] REMS Program Overview, page 7).

OPDP CONCERNS:

These claims minimize the risks associated with Spravato by omitting material risk information.

Specifically, the term, “resolution” of sedation and dissociation is promotional in tone and minimizes the risks of the drug. According to the Boxed Warning section of the draft PI (in pertinent part, underlined emphasis added): “**Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session . . .**”

In addition, the phrase, “changes in vital signs” is ambiguous and omits material risk information that these changes pertain to increases in blood pressure. According to the WARNINGS AND PRECAUTIONS Increase in Blood Pressure section of the draft PI (in pertinent part, emphasis added): “SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses . . .” Therefore, OPDP recommends revising the draft REMS materials to include this material

risk information and to be consistent with the draft PI.

Furthermore, the draft REMS materials fail to disclose material risk information pertaining to the REMS related risk. Specifically, according to the WARNINGS and PRECAUTIONS, Dissociation section of the draft PI, “Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.” We recommend including this material risk information.

DRM Response:

DRM is not in agreement with OPDP’s comment in regard to the language because we want the providers to understand that the above-mentioned symptoms must resolve prior to discharge of patients. In addition, we believe risks noted by OPDP are adequately addressed in the PI and HCPs are encouraged to review the PI.

REMS STATEMENT 2:

“A healthcare provider counsels the patient on the need for enrollment, monitoring, and risks of sedation and dissociation, and changes in vital signs prior to receiving SPRAVATO[®].” (page 2, Outpatient Healthcare Setting Enrollment Form)

“A healthcare provider counsels the patient prior to receiving SPRAVATO[®] on the need for monitoring due to risks of sedation and dissociation, and changes in vital signs.” (page 2, Inpatient Healthcare Setting Enrollment Form)

Page two of the Patient Enrollment Form includes information regarding a patient’s understanding of the risks associated with Spravato treatment.

OPDP CONCERNS:

While the above presentation includes some information pertaining to the REMS risks of sedation and dissociation, it omits the REMS risk of abuse and misuse. We recommend including information regarding the REMS risk of abuse and misuse.

DRM Response:

DRM is not in agreement with OPDP’s comment because we feel those risks are adequately addressed throughout the REMS materials and in the PI for HCPs, and HCPs are encouraged to review all those materials. Additionally the risks of misuse and abuse are mitigated through the REMS, Spravato is not to be directly dispensed to patients for treatment at home.

REMS STATEMENT 3:

(b) (4)

“ . . . Until these effects resolve, I may feel: sleepy and/or. . . disconnected from myself, my thoughts, feelings and things around me.” (page 2, Patient Enrollment Form)

OPDP CONCERNS:

The above claims omit material risk information regarding the REMS risk of sedation pertaining to loss of consciousness. We recommend including loss of consciousness, in consumer-friendly language. For example, the draft Medication Guide describes the risk of loss of consciousness as

“fainting” or “. . . feel like you are going to pass out.”

DRM Response:

DRM agrees with OPDP in part, but did not modify language based on OPDP’s concern, as the Medication Guide includes that information written in patient-friendly language.

REMS STATEMENT 4:

“A healthcare provider monitors every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose.” (page 2, Outpatient Healthcare Setting Enrollment Form; page 2 Inpatient Healthcare Setting Enrollment Form)

OPDP CONCERNS:

In addition to our comments above regarding the term, “resolution” of sedation and dissociation and phrase, “changes in vital signs”, the claim also minimize the REMS risks of the drug by omitting material risk information that following the monitoring period, the patient must be assessed. According to the Boxed Warning, **“Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.”** We recommend revising the above claim to include this material risk information.

DRM Response:

DRM is not in agreement with OPDP’s comment regarding the language because we want the providers to understand that the above-mentioned symptoms must resolve prior to discharge of patients. REMS materials should support the information in the PI, however the intent is not to repeat the label in throughout the REMS materials. The risks noted by OPDP are adequately addressed in the PI and HCPs are encouraged to review the PI.

REMS STATEMENT 5:

“I should not drive or use heavy machinery for the rest of the day on which I receive SPRAVATO®” (page 2, Patient Enrollment Form)

“Do not drive or use heavy machinery for the rest of the day after receiving SPRAVATO®” (page 7, SPRAVATO® REMS Program Overview)

OPDP CONCERNS:

These claims minimize the REMS risks of sedation by omitting material risk information. According to the draft Medication Guide, **“What should I avoid while taking SPRAVATO? Do not drive, operate machinery, or do anything where you need to be completely alert after taking SPRAVATO. Do not take part in these activities until the next day following a restful sleep.”** We recommend revising the above claims to include this material risk information.

DRM Response:

DRM is not in agreement with OPDP’s comment in regard to the language because we believe the risks noted by OPDP are adequately addressed in the PI and HCPs are encouraged to review the PI.

REMS STATEMENT 6:

“List concomitant medications (e.g., adjunctive depression medications, sedative hypnotics, psychostimulants, monoamine oxidase inhibitors [MAOIs])*”(page 1, Patient Enrollment Form)

“Concomitant Medication” Table included on Page 1, Patient Monitoring Form:

OPDP CONCERNS:

The above claims and table minimize the risks of sedation and associated with Spravato by omitting material risk information from the Drug Interactions section of the draft PI. According to the subsection Central Nervous System Depressants of the draft PI, “Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation.”

In addition, the phrase, “blood pressure changes” included on the Patient Monitoring Form is ambiguous and fails to convey that certain medications concomitantly used with Spravato may increase blood pressure, as described in the Psychostimulants and Monoamine Oxidase Inhibitors (MAOIs) subsections of the draft PI.

Therefore, we recommend revising the above claims and table to include this material risk information.

DRM Response:

We are not in agreement with OPDP’s comment because we feel this information is fully addressed in the Drug Interaction section of the PI and HCPs are encouraged to review the PI. The REMS materials are utilized to convey information on the risks the REMS was put in place to mitigate.

REMS STATEMENT 7:

“REMS Evaluation Question* | *If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring? _____minutes from start of administration* (page 1, Patient Monitoring Form)

OPDP CONCERNS:

This information may minimize the risks by implying that patients may be discharged with less than a 2-hour period of monitoring. Furthermore, it undermines the REMS requirement for a monitoring period of at least 2 hours. We acknowledge that the Patient Monitoring Form includes information that, patient must be monitored for at least two hours; however, this information is not sufficient to mitigate the potential misleading impression. Therefore, OPDP recommends revising the above information to mitigate any misleading impressions that some patients may be monitored for less than two hours

DRM Response:

DRM is not in agreement with OPDP’s comment because we feel the complete risk message on period of monitoring is adequately addressed in the PI and REMS materials for HCPs.

11 Discussion

The goal of Spravato REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and abuse and misuse of the product. The Agency remains concerned that outpatient settings such as individual practitioner offices, large office practices and outpatient clinics may not be accustomed to administering medications that cause such effects and may not expect to provide on-site monitoring for patients by healthcare providers. Therefore, the requirements for outpatient clinics remain the same as those in the REMS dated June 2019, which requires these outpatient settings continue to enroll and monitor patients. However, hospitals with on-site pharmacies, several inpatient wards, operating suites, and emergency departments generally have policies and procedures in place or develop them for patients that undergo treatments that require monitoring and also are required to document these procedures (e.g. anesthesia, analgesia). The modification requires that

healthcare settings (e.g. hospitals) that dispense Spravato for inpatient use (including emergency departments within a certified healthcare setting) must become certified. As part of that certification they must establish processes and procedures to counsel the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs, establish processes and procedures to verify Spravato is not dispensed for use outside the certified healthcare setting. Also they must train all relevant staff involved in prescribing, dispensing and administering Spravato on: 1) Counseling the patient on the need for monitoring, risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.

Furthermore, patients that are initiated on Spravato in inpatient settings will likely be continued in outpatient settings where they will complete the enrollment process and will be eventually captured in the registry. Instead, inpatient HCS will be required to certify that policies and procedures are in place to ensure that staff is trained, and patients are informed of the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and abuse and misuse and the needed to be monitored. (b) (4)

(b) (4) The Assessment Plan was updated with program implementation metrics to reflect these modifications to the new REMS goals, requirements, differentiation of inpatient and outpatient healthcare settings to applicable metrics (b) (4)

12 Conclusions and Recommendations

DRM finds the proposed REMS modification for Spravato (esketamine) as submitted on July 30, 2020, to be acceptable, as described in Section 7 of this review. In particular, DRM does not believe (b) (4)

(b) (4) The requirements for outpatient clinics remains unchanged and are the same as the current approved REMS. The timetable for submission of assessments of the REMS remains the same as that approved on March 5, 2019. The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised to be consistent with the REMS Modification for Spravato and will be included in the REMS Modification Approval letter.

13 Appendices

REMS Document

Outpatient Healthcare Setting Enrollment Form

Inpatient Healthcare Setting Enrollment Form

Patient Enrollment Form

Pharmacy Enrollment Form

REMS Program Overview

Patient Monitoring Form

REMS Program Website

Assessment Plan

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/

SOMYA V DUNN
07/31/2020 06:12:18 PM

BARBARA A BERGQUIST
07/31/2020 06:17:43 PM

ANAHITA TAVAKOLI
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07/31/2020 06:28:17 PM

CAROLYN N TIEU
07/31/2020 06:32:54 PM

CYNTHIA L LACIVITA
07/31/2020 06:33:49 PM
Concur

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
Supplement Number, Date Received	Supplement 4 received October 2, 2019 (sequence 0063), amended on July 2, 2020 (0098) and July 24, 2020 (sequence 0108)
PDUFA Goal Date	August 2, 2020
OSE RCM #	2019-2398
Reviewer Name(s)	Dunn, Somya, MD Sammarco, Victoria, PharmD, MBA Tavakoli, Anahita, M.A.
Team Leader	Tieu, Carolyn, PharmD, MPH
Division Director	LaCivita, Cynthia, PharmD
Review Completion Date	July 29, 2020
Subject	Interim comments for the proposed REMS relating to efficacy supplement 4
Established Name	Esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation	28 mg esketamine solution drug-device combination for intranasal (IN) administration

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1 Introduction

This review evaluates and provides comments and necessary changes on the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Spravato (esketamine), (NDA 211243), submitted by Janssen Pharmaceuticals, Inc. on October 2, 2019 and amended on July 2, 2020 and July 24, 2020. The REMS for Spravato was originally approved on March 5, 2019 to mitigate the risk of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

In Supplement 4, the Sponsor submitted changes to the REMS program to allow for more urgent administration of Spravato if needed. The modification proposal was reviewed by the Division of Risk Management (DRM) and comments and edits were sent to the Sponsor on June 19, 2020 and July 20, 2020. The Sponsor submitted updated materials in response on July 24, 2020. These are the subject of this review.

2 Background

2.1 PRODUCT INFORMATION

Spravato is a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist approved for treatment of treatment-resistant depression in conjunction with an oral antidepressant. Spravato is available as 28 mg solution drug-device combination administered intranasally.

Spravato was approved on March 5, 2019 with a REMS to ensure that the benefits of the drug outweigh the increased risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

The goals of this REMS are 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

The REMS for Spravato consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The REMS elements include:

- Healthcare setting certification
- Pharmacy certification
- Patient monitoring
- Safe use conditions
- Patient registry

2.2 REGULATORY HISTORY

- July 2, 2020: The Sponsor submitted revised REMS materials, a REMS amendment, in response to Agency feedback on June 19, 2020 (Seq 0098).
- July 20, 2020: The Agency provided the Sponsor feedback on the REMS amendment and REMS materials to supplement 4 submitted on July 2, 2020 (Dunn, S. Spravato REMS Review, drafted July 20, 2020).

- July 24, 2020: The Sponsor submitted revised REMS materials, a REMS amendment, in response to Agency feedback on July 20, 2020 (Seq0108).

3 Risk Assessment & Safe-Use Conditions

Spravato is under review for a proposed additional indication of “the rapid reduction of depressive symptoms in patients with Major Depressive Disorder who have active suicidal ideation with intent” in combination with an oral antidepressant. The clinical review team did not identify any new safety signals during their review of this supplement; the safety profile was comparable to the original treatment-resistant depression program. Therefore, the major risks that the REMS addresses remain serious adverse outcomes resulting from sedation and dissociation and potential misuse and abuse.

Due to the expected operations of typical hospital, DRM recommended that hospitals be required to certify that policies and procedures are in place to ensure that staff is trained, patients are counseled on the risks of Spravato and are monitored following Spravato administration. The adverse events of sedation and dissociation and misuse and abuse will be continued to be mitigated in the outpatient setting by requiring that Spravato can only be distributed to certified outpatient healthcare settings. The Sponsor agreed to this proposal and their amended materials are consistent with this recommendation.

4 Review of Proposed REMS Modifications

4.1 REMS DOCUMENT

The Agency updated and aligned the REMS Document to provide details on the different certification requirements for inpatient and outpatient settings. This includes that the patient enrollment and patient monitoring forms are required only in outpatient settings. In addition, details on certification requirements for settings and pharmacies are described on the enrollment forms and in the REMS Program Overview (b) (4). A preliminary REMS Document was provided in the July 20, 2020 Agency communication. The Sponsor removed the word “(b) (4)” from (b) (4) in the REMS Document. They also removed the (b) (4) but retained this in the outpatient setting.

Reviewers Comment: (b) (4) was removed, (b) (4) and does not need to be a requirement in the REMS.

The Medication Guide, though not part of the REMS however, similar to the Prescribing Information it must still be listed in the REMS Document as a Sponsor requirement to support REMS operations. Other edits are acceptable. For this material only, we have edited on the tracked changes version and highlighted areas where we made changes. See the redlined version for clarification.

4.2 REMS REQUIREMENTS

4.2.1 REMS Participant Requirements and Materials

4.2.1.1 Inpatient Healthcare Setting Enrollment Form

The Agency had requested that the Sponsor create a separate Inpatient Healthcare Setting Enrollment Form since inpatient and outpatient settings will have different REMS requirements. The Sponsor submitted this form and it was designed similarly to the original with setting-appropriate differences. The Agency provided attestations that would also be setting-specific. The Sponsor has sent back a version that incorporates these attestations with other minor clarifications.

Reviewer's Comment: This form is acceptable with some minor edits for clarity. See the FDA redlined version for clarification.

4.2.1.2 Outpatient Healthcare Setting Enrollment Form

The Agency had requested that the Sponsor create a separate Outpatient Healthcare Setting Enrollment Form since inpatient and outpatient settings will have different REMS requirements. The Sponsor submitted this form and it was designed similarly to the original with setting-appropriate differences. The Agency provided attestations that would also be setting-specific. The Sponsor has sent back a version that incorporates these attestations with other minor clarifications.

Reviewer's Comment: This form is acceptable.

4.2.1.3 REMS Program Overview

The Sponsor created a REMS Program Overview document at the direction of the Agency which contains instructions to all stakeholders regarding important aspects of the REMS program. The Agency requested some clarifications to the processes for the HCS. The Sponsor made these changes. The word (b) (4) should not be used to describe adverse events.

Reviewer's Comment: We have removed the word (b) (4) from description of adverse events. This material must align with other materials and the REMS Document. Otherwise, this form is acceptable. See FDA redlined version for clarification.

4.2.1.4 REMS Patient Enrollment Form

The Agency provided updated attestations that are setting-specific to outpatient settings only. The Sponsor has sent back a version that incorporates these attestations with other minor clarifications.

Reviewer's Comment: This form is acceptable.

4.2.1.5 REMS Patient Monitoring Form

The Sponsor has sent back a version that incorporated clarifications provided by the Agency. They made additional minor clarifications and formatting changes.

Reviewer's Comment: This form is acceptable.

4.2.1.6 REMS Pharmacy Enrollment Form

The Sponsor has sent back a version that incorporated clarifications provided by the Agency. They made additional minor clarifications and formatting changes.

Reviewer's Comment: This form is acceptable.

4.2.1.7 REMS Program Website

The REMS Program Website transcript was submitted with the requested clarifications on instructions. The Sponsor also aligned this document with other materials and other requested changes including the updated labeling language.

Reviewer's Comment: We have removed the word (b) (4) from description of adverse events. This material must align with other materials and the REMS Document. Otherwise, this form is

acceptable. See FDA redlined version for clarification.

4.2.2 REMS Assessment Time Table

The timetable for submission of the assessments does not need to be changed if this supplement is approved.

4.2.1 REMS Supporting Document

The REMS Supporting Document (SD) was further revised to incorporate all the changes to the REMS Document that were communicated and to include individualized stakeholder requirements for inpatient and outpatient healthcare settings. References to (b) (4) were removed as requested.

Reviewer's Comment: This document is acceptable, except for the changes needed to the Assessment Plan (see section 4.3).

4.3 REMS ASSESSMENT PLAN

The Agency drafted the following updated plan to align with this modification. The strikethroughs will need to be deleted and comments are meant for the Sponsor:

(b) (4)

(b) (4)

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/

SOMYA V DUNN
07/29/2020 02:25:59 PM

BARBARA A BERGQUIST
07/29/2020 02:31:15 PM

CAROLYN N TIEU
07/29/2020 03:01:29 PM

Internal Consult

Pre-decisional Agency Information

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Anahita Tavakoli, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Domenic D'Alessandro, Regulatory Review Officer, OPDP

CC: Aline Moukhtara, Team Leader, OPDP
Phuong B. Nguyen, Safety Regulatory Project Manager, OSE
Jacqueline Sheppard, Team Leader, DRM
Somya Dunn, Risk Management Analyst, DRM
Victoria Sammarco, Risk Management Analyst, DRM
Doris Auth, Associate Director, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: July 24, 2020

Re: NDA 211243
SPRAVATO® (esketamine) nasal spray, CIII

Comments on Draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission Dates: 7/17/20 & 7/20/20)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for SPRAVATO® (esketamine) nasal spray, CIII (Spravato):

- Healthcare Provider (HCP) REMS Materials:
 - SPRAVATO® REMS Program Overview
 - Inpatient Healthcare Setting Enrollment Form
 - Outpatient Healthcare Setting Enrollment Form
 - Patient Monitoring Form
 - Pharmacy Enrollment Form
- Direct-to-Consumer (Patient) REMS Materials:
 - Patient Enrollment Form
- www.SPRAVATOrem.com Transcript

The version of the draft REMS materials used in this review were sent from DRM (Anahita Tavakoli) via email on July 17, 2020, and July 20, 2020. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Spravato.

General Comments

Please remind Janssen Pharmaceuticals, Inc. (Janssen) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.SpravatoREMS.com, and toll-free numbers, such as 1-855-382-6022. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Janssen that the REMS specific website should not be the sole source of approved REMS materials.

OPDP notes that the Spravato PI and Medication Guide are still being reviewed and modified. OPDP's review is based on the draft PI and draft Medication Guide. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label.

- **Risk:**

The draft REMS materials include claims such as (bolded emphasis original, underlined emphasis added):

- “**Monitor** each patient for at least 2 hours following administration of SPRAVATO® for resolution of sedation and dissociation, and changes in vital signs” (SPRAVATO® REMS Program Overview, page 3),
- “**Have a healthcare provider[(s) onsite to] monitor** every [each] patient for at least 2 hours [following administration of SPRAVATO®] for resolution of sedation and dissociation, and changes in vital signs after every dose” (SPRAVATO® REMS Program Overview, page 4; Inpatient Healthcare Setting Enrollment Form, page 2; Outpatient Healthcare Setting Enrollment Form, page 2)
- (b) (4) receive counseling on safety risks and the need for monitoring to observe for resolution of sedation and dissociation, and for any changes in vital signs” (Patient Enrollment Form, page 2; SPRAVATO® REMS Program Overview, page 7).

These claims minimize the risks associated with Spravato by omitting material risk information.

Specifically, the term, “resolution” of sedation and dissociation is promotional in tone and minimizes the risks of the drug. According to the Boxed Warning section of the draft PI (in pertinent part, underlined emphasis added):

“Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session”

In addition, the phrase, “changes in vital signs” is ambiguous and omits material risk information that these changes pertain to increases in blood pressure. According to the WARNINGS AND PRECAUTIONS Increase in Blood Pressure section of the draft PI (in pertinent part, emphasis added):

“SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses” Therefore, OPDP recommends revising the draft REMS materials to include this material risk information and to be consistent with the draft PI.

Furthermore, the draft REMS materials fail to disclose material risk information pertaining to the REMS related risk. Specifically, according to the WARNINGS and PRECAUTIONS, Dissociation section of the draft PI, “Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.” We recommend including this material risk information.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comments” below):

- SPRAVATO® REMS Program Overview
- Inpatient Healthcare Setting Enrollment Form
- Outpatient Healthcare Setting Enrollment Form
- Patient Monitoring Form
- Pharmacy Enrollment Form
- Patient Enrollment Form
- www.SPRAVATOrems.com Transcript

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

SPRAVATO® REMS Program Overview, www.SPRAVATOrems.com Transcript, Patient Enrollment Form, Inpatient Healthcare Setting Enrollment Form, Outpatient Healthcare Setting Enrollment Form, Patient Monitoring Form

The draft REMS materials include the following claims (bolded emphasis original, underlined emphasis added):

- “A healthcare provider counsels the patient on the need for enrollment, monitoring, and risks of sedation and dissociation, and changes in vital signs prior to receiving SPRAVATO®.” (page 2, Outpatient Healthcare Setting Enrollment Form)
- “A healthcare provider counsels the patient prior to receiving SPRAVATO® on the need for monitoring due to risks of sedation and dissociation, and changes in vital signs.” (page 2, Inpatient Healthcare Setting Enrollment Form)
- Page two of the Patient Enrollment Form includes information regarding a patient’s understanding of the risks associated with Spravato treatment.
 - **Risk**
 - While the above presentation includes some information pertaining to the REMS risks of sedation and dissociation, it omits the REMS risk of abuse and misuse. We recommend including information regarding the REMS risk of abuse and misuse.
- “**Report** all suspected (b) (4) adverse events to the SPRAVATO® REMS.” (page 3, SPRAVATO® REMS Program Overview)

- “Inpatient Healthcare Settings are required to report all suspected (b) (4) adverse events to the SPRAVATO® REMS at 1-855-382-6022.” (pages 3-4, www.SPRAVATOrems.com Transcript)

(b) (4)

- **Risk**

- The term (b) (4) is promotional in tone and may minimize the risks associated with the drug. The draft PI does not describe any of the adverse reactions as (b) (4). Specifically, the HIGHLIGHTS section of the draft PI states, “**To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**” Therefore, we recommend deleting this term.

- “As part of the REMS, your healthcare provider will discuss the risks of misuse, abuse, sedation (feeling sleepy), dissociation (feeling disconnected from yourself, including thoughts, feelings, and things around you) while on SPRAVATO® with you.” (page 8, www.SPRAVATOrems.com Transcript)
- “. . . Until these effects resolve, I may feel: sleepy and/or. . . disconnected from myself, my thoughts, feelings and things around me.” (page 2, Patient Enrollment Form)

- **Risk**

- The above claims omit material risk information regarding the REMS risk of sedation pertaining to loss of consciousness. We recommend including loss of consciousness, in consumer-friendly language. For example, the draft Medication Guide describes the risk of loss of consciousness as “fainting” or “. . . feel like you are going to pass out.”

- “A healthcare provider monitors every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose.” (page 2, Outpatient Healthcare Setting Enrollment Form; page 2 Inpatient Healthcare Setting Enrollment Form)

- **Risk**

- In addition to our comments above regarding the term, “resolution” of sedation and dissociation and phrase, “changes in vital signs”, the claim also minimize the REMS risks of the drug by omitting material risk information that following the monitoring period, the patient must be assessed. According to the Boxed Warning, **“Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.”** We recommend revising the above claim to include this material risk information.
- “I should not drive or use heavy machinery for the rest of the day on which I receive SPRAVATO®” (page 2, Patient Enrollment Form)
- **“Do not** drive or use heavy machinery for the rest of the day after receiving SPRAVATO®” (page 7, SPRAVATO® REMS Program Overview)
 - **Risk**
 - These claims minimize the REMS risks of sedation by omitting material risk information. According to the draft Medication Guide, **“What should I avoid while taking SPRAVATO? Do not** drive, operate machinery, or do anything where you need to be completely alert after taking SPRAVATO. **Do not** take part in these activities until the next day following a restful sleep.” We recommend revising the above claims to include this material risk information.
- “List concomitant medications (e.g., adjunctive depression medications, sedative hypnotics, psychostimulants, monoamine oxidase inhibitors [MAOIs])*” (page 1, Patient Enrollment Form)
- “Concomitant Medication” Table included on Page 1, Patient Monitoring Form:

Concomitant Medication		
Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?		
• Benzodiazepines*	☐ Yes	☐ No
• Non-benzodiazepine sedative hypnotics*	☐ Yes	☐ No
• Psychostimulants*	☐ Yes	☐ No
• Monoamine oxidase inhibitors (MAOIs)*	☐ Yes	☐ No

- **Risk**
 - The above claims and table minimize the risks of sedation and associated with Spravato by omitting material risk information from the Drug Interactions section of the draft PI. According to the subsection Central Nervous System

Depressants of the draft PI, “Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation.”

In addition, the phrase, “blood pressure changes” included on the Patient Monitoring Form is ambiguous and fails to convey that certain medications concomitantly used with Spravato may increase blood pressure, as described in the Psychostimulants and Monoamine Oxidase Inhibitors (MAOIs) subsections of the draft PI.

Therefore, we recommend revising the above claims and table to include this material risk information.

- **“REMS Evaluation Question* |** *If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring?* _____ *minutes from start of administration* (page 1, Patient Monitoring Form)

- **Risk**

- This information may minimize the risks by implying that patients may be discharged with less than a 2-hour period of monitoring. Furthermore, it undermines the REMS requirement for a monitoring period of at least 2 hours. We acknowledge that the Patient Monitoring Form includes information that, patient must be monitored for at least two hours; however, this information is not sufficient to mitigate the potential misleading impression. Therefore, OPDP recommends revising the above information to mitigate any misleading impressions that some patients may be monitored for less than two hours.

- **“SPRAVATO® Indication**

. . .

The rapid reduction of depressive symptoms in patients with Major Depressive Disorder who have active suicidal ideation with intent” (page 2, www.SPRAVATOrem.com Transcript)

- **Indication**

- This claim is promotional in tone and may create misleading impressions about the use or benefits of the drug. Please remind Janssen to revise the above claim to reflect the FDA-approved indication in the final PI.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
Supplement Number, Date Received	Supplement 4 received October 2, 2019 (sequence 0129)
PDUFA Goal Date	August 2, 2020
OSE RCM #	2019-2398
Reviewer Name(s)	Dunn, Somya, MD Sammarco, Victoria, PharmD, MBA Tavakoli, Anahita, M.A.
Team Leader	Tieu, Carolyn, PharmD
Division Director	LaCivita, Cynthia, PharmD
Review Completion Date	July 20, 2020
Subject	Interim comments for the proposed REMS relating to efficacy supplement 4
Established Name	Esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation	28 mg esketamine solution drug-device combination for intranasal (IN) administration

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1 Introduction

This review evaluates and provides comments and necessary changes on the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Spravato (esketamine), (NDA 211243), submitted by Janssen Pharmaceuticals, Inc. on October 2, 2019 and amended on July 2, 2020. The REMS for Spravato was originally approved on March 5, 2019 to mitigate the risk of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

In Supplement 4, the Sponsor submitted changes to the REMS program to allow for more urgent administration of Spravato if needed. The modification proposal was reviewed by the Division of Risk Management (DRM) and comments and edits were sent to the Sponsor on June 19, 2020. The Sponsor submitted updated materials in response on July 2, 2020, which is the subject of this review.

2 Background

2.1 PRODUCT INFORMATION

Spravato is a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist approved for treatment of treatment-resistant depression in conjunction with an oral antidepressant. Spravato is available as 28 mg solution drug-device combination administered intranasally.

Spravato was approved on March 5, 2019 with a REMS to ensure that the benefits of the drug outweigh the increased risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

The goals of this REMS are 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

The REMS for Spravato consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The REMS elements include:

- Healthcare setting certification
- Pharmacy certification
- Patient monitoring
- Safe use conditions
- Patient registry

2.2 REGULATORY HISTORY

- June 19, 2020: The Agency provided the Sponsor feedback on the materials originally submitted with efficacy supplement 4 (Sammarco, V. Spravato REMS Review, dated June 19, 2020).
- July 2, 2020: The Sponsor submitted revised REMS materials in response to Agency feedback on June 19, 2020 (Seq 0098).

3 Risk Assessment & Safe-Use Conditions

Spravato is under review for a proposed additional indication of “ the rapid reduction of depressive symptoms in patients with Major Depressive Disorder who have active suicidal ideation with intent” in combination with an oral antidepressant. The clinical review team did not identify any new safety signals during their review of this supplement; the safety profile was comparable to the original treatment-resistant depression program. Therefore, the major risks that the REMS addresses remain serious adverse outcomes resulting from sedation and dissociation and potential misuse and abuse.

Due to the expected operations of typical hospital, DRM recommended that hospitals be required to certify that policies and procedures are in place to ensure that staff is trained, patients are counseled on the risks of Spravato and are monitored following Spravato administration. The adverse events of sedation and dissociation and misuse and abuse will be mitigated by the original enrollment and monitoring processes in outpatient healthcare settings. The Sponsor agreed to this proposal and their amended materials are consistent with this recommendation.

4 Review of Proposed REMS Modifications

4.1 REMS DOCUMENT

With the initial supplement, the REMS Document was submitted with editorial changes to support the proposed (b) (4)

Reviewer Comment: The Agency has updated and aligned the REMS Document to provide details on the different certification requirements for inpatient and outpatient settings. This includes that the patient enrollment and patient monitoring forms are required only in outpatient settings. In addition, (b) (4)

(b) (4) Also, during enrollment, patients in outpatient settings are counseled that they must make arrangements for travel home and also not to operate machinery for the rest of the day on which they received Spravato. In the inpatient setting, the setting must ensure that the patients are counseled on this in case they leave the facility on the same day of dosing. The details on certification requirements for settings and pharmacies are described on the enrollment forms and in the REMS Program Overview (b) (4)

A preliminary REMS Document has been drafted for this modification but is still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

See updated REMS Document for details.

4.2 REMS REQUIREMENTS

4.2.1 REMS Participant Requirements and Materials

4.2.1.1 Inpatient Healthcare Setting Enrollment Form

The Agency requested that the Sponsor create a separate Inpatient Healthcare Setting Enrollment Form since inpatient and outpatient settings will have different REMS requirements. The Sponsor submitted this form and generally the format mirrors the original Healthcare Setting Enrollment Form with the following changes that the Agency requested:

- Appropriate inpatient HCS choices and relevant attestations
- Directions for reporting (b) (4) adverse events

Reviewer Comments: Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming. Draft attestations will be provided to the Sponsor. Attestations include that patients should be counseled that they must make arrangements for travel home and also not to operate machinery on the day they receive Spravato, in case they are discharged on the day of dosing.

Please see redlined version attached for clarifications.

4.2.1.2 Outpatient Healthcare Setting Enrollment Form

The Outpatient Healthcare Setting Enrollment Form was resubmitted with editorial changes and the requested changes from the Agency including:

- Directions as to which settings should use this form
- Appropriate HCS choices and relevant attestations
- Directions for reporting (b) (4) adverse events

Reviewer Comment: Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming. Draft attestations will be provided to the Sponsor.

Please see redlined version attached for clarifications.

4.2.1.3 REMS Program Overview

The Sponsor created a REMS Program document submitted at the direction of the Agency which contains instructions to all stakeholders regarding important aspects of the REMS program. This document has taken the place of the REMS Fact Sheet while offering more information to relevant stakeholders.

Reviewer Comment: As there are clear instructions for each healthcare setting type, the statement,

is not necessary. Language should be included to make clear that inpatient pharmacies should be certified with their inpatient healthcare setting where applicable. In addition, sections referencing attestations will need to be updated as the preliminary attestations for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

Please see redlined version attached for clarifications.

4.2.1.4 REMS Patient Enrollment Form

The REMS Patient Enrollment Form was resubmitted with editorial changes and the requested changes from the Agency including:

- Removal of (b) (4)
- Instructions that enrollment is only required for outpatient healthcare settings
- Removal of (b) (4)

Reviewer's Comments: Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

Please see redlined version attached for clarifications.

4.2.1.5 REMS Patient Monitoring Form

The REMS Patient Monitoring Form was resubmitted with editorial changes and the requested changes from the Agency including:

- Removal of (b) (4)
- Information fields to reflect only outpatient settings

Reviewer's Comments: This form was generally acceptable.

Please see redlined version attached for clarifications.

4.2.1.6 REMS Pharmacy Enrollment Form

The REMS Pharmacy Enrollment Form was resubmitted with editorial changes and the requested changes from the Agency including:

- Clarification that inpatient pharmacies are certified under the HCS

Reviewer's Comments: Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

Please see redlined version attached for clarifications.

4.2.1.7 REMS Program Website

The REMS Program Website transcript was submitted with the requested changes including:

- Revision of the goal of the REMS on the homepage
- Updated linked pdf and electronic forms reviewed above for each appropriate stakeholder
- Instruction on outpatient and inpatient HCS requirements

Reviewer Comment: As there are clear instructions for each healthcare setting type, the statement,

is not necessary.

Please see redlined version attached for clarifications.

4.2.2 REMS Assessment Time Table

The timetable for submission of the assessments does not need to be changed if this supplement is approved.

4.2.3 REMS Supporting Document

The REMS Supporting Document (SD) was revised to include individualized stakeholder requirements for inpatient and outpatient healthcare settings.

Reviewer Comment: References to (b) (4) should be removed. The SD should be otherwise updated to align with the REMS Document.

5 Conclusion & Recommendations

Updated materials provided by the Sponsor were generally consistent with comments provided by the FDA. However, DRM does not find the proposed amendment for the Spravato (esketamine) modification as submitted on July 2, 2020 to be acceptable, as described in Section 4 of this review. DRM requests that the REMS Document and materials be updated to align with updated labeling, REMS Document, and attestations. Further edits to materials are also necessary for clarification purposes.

6 Comments for the Applicant

We have the following comments on the proposed REMS modification(s), submitted on July 2, 2020. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 4 business days that addresses these comments. Include all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version.

- The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.

REMS Document

The Agency has updated and aligned the REMS Document to provide details on the different certification requirements for inpatient and outpatient settings. This includes that the patient enrollment and patient monitoring forms are required only in outpatient settings. In addition, (b) (4)

(b) (4). Also, during enrollment, patients in outpatient settings are counseled that they must make arrangements for travel home and also not to operate machinery for the rest of the day on which they received Spravato. In the inpatient setting, the setting must ensure that the patients are counseled on this in case they leave the facility on the same day of dosing. The details on certification requirements for settings and pharmacies are described on the enrollment forms and in the REMS Program Overview (b) (4)

A preliminary REMS Document has been drafted for this modification but is still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

See updated REMS Document for details.

Attestations

The Agency has updated and aligned the attestations from the forms to provide details on the different certification requirements for inpatient and outpatient settings. Replace these in the relevant forms.

Inpatient Healthcare Setting Enrollment Form

Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming. Draft attestations are provided. Attestations include that patients should be counseled that they must make arrangements for travel home and also not to operate machinery on the day they receive Spravato, in case they are discharged on the day of dosing.

Please see redlined version attached for clarifications.

Outpatient Healthcare Setting Enrollment Form

Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming. Draft attestations are provided.

Please see redlined version attached for clarifications.

REMS Program Overview

As there are clear instructions for each healthcare setting type, the statement, ‘(b) (4)
(b) (4)
(b) (4) is not necessary.

Language should be included to make clear that inpatient pharmacies should be certified with their inpatient healthcare setting where applicable. In addition, sections referencing attestations will need to be updated as the preliminary attestations for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

Please see redlined version attached for clarifications.

REMS Patient Enrollment Form

Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming.

Please see redlined version attached for clarifications.

REMS Patient Monitoring Form

Reviewer’s Comments: This form was generally acceptable.

Please see redlined version attached for clarifications.

REMS Pharmacy Enrollment

Preliminary attestations have been drafted for this modification but are still undergoing discussion in the Agency and additional comments or edits may be forthcoming. Draft attestations are provided.

Please see redlined version attached for clarifications.

REMS Program Website

As there are clear instructions for each healthcare setting type, the statement, (b) (4)

(b) (4)

(b) (4), is not necessary.

Please see redlined version attached for clarifications.

REMS Supporting Document

References to (b) (4) should be removed. The SD should be otherwise updated to align with the REMS Document. The Assessment Plan is still undergoing discussion in the Agency.

7 Appendices

REMS Document

Attestations

Inpatient Healthcare Setting Enrollment Form

Outpatient Healthcare Setting Enrollment Form

REMS Program Overview

REMS Patient Enrollment Form

REMS Patient Monitoring Form

REMS Program Website

REMS Pharmacy Enrollment Form

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
Supplement Number, Date Received	Supplement 4 received October 2, 2019 (sequence 0129)
Action Date	August 2, 2020
OSE RCM #	2019-2398
Reviewer Name(s)	Victoria Sammarco, PharmD, MBA Somya Dunn, MD Anahita Tavakoli, M.A.
Team Leader	Carolyn Tieu, PharmD
Associate Division Director	Doris Auth, PharmD
Review Completion Date	June 19, 2020
Subject	Interim comments for the proposed REMS relating to efficacy supplement 4
Established Name	Esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration

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1 Introduction

This review evaluates and provides recommendations on the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Spravato (esketamine), (NDA 211243), submitted by Janssen Pharmaceuticals, Inc. on October 2, 2019. The REMS for Spravato was originally approved on March 5, 2019 to mitigate the risk of misuse, abuse, and serious adverse outcomes from dissociation and sedation. The REMS consist of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The most recent REMS modification was approved on June 25, 2019 and included clarifying edits to data capturing fields on the Spravato REMS Healthcare Setting Enrollment Form, Spravato REMS Pharmacy Enrollment Form, and Spravato REMS Patient Monitoring Form.

Spravato is currently approved for treatment resistant depression in conjunction with an oral antidepressant. On October 2, 2019, Janssen Pharmaceuticals, Inc. submitted an efficacy supplement for a proposed indication for treatment of adults with Major Depressive Disorder (MDD) who have active suicidal ideation with intent. The proposed modifications to the REMS are needed if this supplement is approved. The Applicant has proposed changes to the materials for (b) (4)

(b) (4) Generally, the Sponsor proposed the following changes:

- **Spravato REMS Document**—edited to (b) (4)
(b) (4)
- **Spravato REMS Patient Monitoring Form and Spravato REMS Patient Enrollment Form**—
(b) (4)

2 Background

2.1 PRODUCT INFORMATION

Spravato is a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist approved for treatment of treatment-resistant depression in conjunction with an oral antidepressant. Spravato is available as 28 mg solution drug-device combination administered intranasally.

Spravato was approved on March 5, 2019 with a REMS to ensure that the benefits of the drug outweigh the increased risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

The goals of this REMS are 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

The REMS for Spravato consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The REMS elements include:

- Healthcare setting certification

- Pharmacy certification
- Patient monitoring
- Safe use conditions
- Patient registry

2.2 REGULATORY HISTORY

The regulatory history relevant to the proposed REMS modification is summarized below:

- March 6, 2019: Spravato was approved with a REMS.
- May 1, 2019: The Sponsor submitted Supplement 2, proposed minor REMS modification (EDR Sequence 0054).
- June 25, 2019: REMS modification was approved. The REMS was modified to amend and clarify some of the data-capturing fields in the Healthcare Setting Enrollment Form, Pharmacy Enrollment Form, and Patient Monitoring Form to make them more user-friendly.
- October 2, 2019: Efficacy supplement 004 (EDR Sequence 0129) was submitted. This submission is the subject of this review.
- March 11, 2020: Information Request issued to the Sponsor requesting estimate of turnaround time for REMS materials.
- March 17, 2020: The Sponsor submitted response to Information Request from March 11 indicating they would need 14-28 day turnaround times for revisions to REMS materials.
- April 15, 2020: The Agency sent the Sponsor a communication stating that we did not agree with the proposed indication due to lack of supporting data and instead were considering the following "...major depressive disorder (MDD) in patients appropriate for inpatient psychiatric care." In addition, the Agency was considering the Limitation of Use: "SPRAVATO has not been proven to be effective in preventing suicide or in reducing suicidal ideation or behavior. Use of SPRAVATO does not preclude the need for hospitalization, if clinically warranted."
- April 15, 2020: The Sponsor acknowledged FDA's April 15, 2020 communication and stated that they were in agreement with this proposal.
- April 24, 2020: The Sponsor sent another correspondence in response to the Agency's April 15th indication proposal. They proposed the indication, "...for the rapid reduction of depressive symptoms..." (b) (4) Limitations of Use: SPRAVATO has not been proven to be effective in preventing suicide or in reducing suicidal ideation or behavior. Use of SPRAVATO does not preclude the need for hospitalization, if clinically warranted." They supported this proposal in part by discussing how "inpatient psychiatric care" may potentially be misinterpreted as a need to treat patients only while they are hospitalized, rather than for the recommended 4 full weeks of treatment. In addition, they argued that stating "inpatient care" could lead to misinterpretation as real-world practice data suggests that the decision to hospitalize a patient is complicated by many factors and transitions from inpatient to outpatient care in the US mental health system are often difficult.
- May 1, 2020: Information Request issued to the Sponsor requesting 1.) the rationale for (b) (4) (b) (4) (b) (4) and 2.) thought process regarding the requirement to (b) (4)

- May 27, 2020: The Sponsor submitted a response to Information Request from May 1 outlining their rationale. (b) (4)
(b) (4) They wanted to retain these requirements because they claim that this enables clear follow up to assess adverse events (AEs) and REMS compliance. The Sponsor also proposed adding (b) (4)
(b) (4)

3 Risk Assessment and Safe-Use Conditions

Spravato is under review for a proposed additional indication of “... the rapid reduction of depressive symptoms in patients with Major Depressive Disorder who have active suicidal ideation with intent” in combination with an oral antidepressant. As discussed, the clinical review team did not identify any new risks during their review of the studies; since safety results were generally comparable to the treatment-resistant depression program, the major risks that the REMS addresses are still those of sedation and dissociation and potential misuse and abuse.

Approval of the proposed or a similar/edited indication (the review is ongoing and indication statement is actively being discussed) may increase the likelihood of patients receiving Spravato in hospital settings; patients may be more likely to initiate therapy in an emergency room or during a hospital admission in response to urgent need for treatment. (b) (4)
(b) (4)

Modifications to the REMS program are necessary as the ability and requirements to monitor patients are different between clinics/offices and hospitals. Hospitals with on-site pharmacies, inpatient wards, operating suites, and emergency departments generally have policies and procedures in place to provide informed consent to patients that undergo treatments that require anesthesia, analgesia and/or monitoring (as is needed for medical procedures) and are required to document these procedures. They also have staffing, including physicians, physician assistants, nurses, nurse practitioners, and various therapy specialists (i.e. respiratory therapists) on-site to provide patient care and continuously monitor patient health status. In these hospital settings, the Agency is more assured that the risk mitigation strategies of monitoring and patient counseling of Spravato risks will occur. In addition, potential necessary interventions are available on-site. (b) (4)

Due to the expected operations of typical hospital, DRM is recommending that hospitals be required to certify that policies and procedures are in place to ensure that staff is trained, patients are counseled on the risks of Spravato and are monitored following Spravato administration. The adverse events of sedation and dissociation and misuse and abuse will be mitigated by the original enrollment and monitoring processes in outpatient healthcare settings.

4 Expected Postmarket Use

The additional indication, while still under discussion, may increase the patient population that could receive Spravato in a hospital setting though most therapy is still likely to be administered in an outpatient clinic or office setting on a more chronic basis. Prescribing providers in hospital settings may include emergency room physicians, psychiatrists, and hospitalists.

5 Review of Proposed REMS Modifications

5.1 REMS Goals

The Sponsor did not amend the REMS Goals. However, the Agency is working to amend the goals to convey that only patients receiving Spravato in outpatient healthcare settings should be enrolled in the registry. This draft goal by DRM is under preliminary and still under discussion:

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 patients are informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrollment of patients who receive treatment in an outpatient healthcare setting in a registry to further characterize the risks and support safe use

5.2 REMS Document

The REMS Document was submitted with editorial changes to support the proposed

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The Agency does not agree

(b) (4)

(b) (4)

In these hospital settings, the Agency is more assured that the risk mitigation strategies of monitoring and patient counseling of Spravato risks will occur and that potential necessary interventions are readily available. Thus, the requirements will be different for hospitals than offices/clinics and this must be clarified in the REMS Document.

The Agency is requesting that hospitals be required to certify that policies and procedures are in place to ensure that staff is trained, patients are made aware of the risks and are monitored following Spravato administration. A new HCS enrollment form is needed for hospitals that outlines requirements for these settings. The hospital enrollment form should not

(b) (4)

(b) (4)

(b) (4) *In*

addition, (b) (4) is not needed

(b) (4)

(b) (4)

The REMS Document must clarify and outline these changes. The Agency is continuing to work to update and align the REMS Document with this modification.

5.3 REMS Requirements

(b) (4)

See redlined version (attached) for further clarification.

5.3.1.2 Healthcare Setting Enrollment Form

The Healthcare Setting Enrollment Form was submitted with an addition of an individual DEA holder field and deletions of various provider identification options. The Sponsor also added

(b) (4)

(b) (4)

Reviewer Comments: The editorial changes are acceptable; however, separate Healthcare Setting Enrollment Forms must be developed and must clearly outline the requirements for both types of healthcare settings, inpatient and outpatient. These should be titled Outpatient Healthcare Setting Enrollment Form and Inpatient Healthcare Setting Enrollment Form. These forms should include:

- *Directions as to which settings should use which form; emergency departments, though technically considered outpatient, will fall under the inpatient requirements for the purposes of the Spravato REMS, as they will be encompassed by their hospital setting requirements*
- *Appropriate HCS choices for each form (e.g., “outpatient clinic,” “long term care”).*
- *Attestations for the relevant setting’s Authorized Representative that comply with requirements specific to each setting—outpatient and inpatient (including emergency departments) (e.g. inpatient settings should have an attestation that there are policies and procedures in place for patients to be counseled on the risks since there will be no patient enrollment form in these settings)*
- *The Inpatient Healthcare Setting Enrollment Form should also describe the process for reporting (b) (4) adverse events through the REMS and FDA reporting mechanisms as described in the REMS Program Overview document (discussed below).*

These items should be removed from the forms:

-
-
-

(b) (4)

See redlined version (attached) for further clarification.

5.3.1.3 Pharmacy Enrollment Form

The Pharmacy Enrollment Form was submitted with editorial changes and a new email address field for alternate contacts.

Reviewer Comment: The editorial changes are acceptable. The pharmacy types should be limited to those working with outpatient settings. Pharmacies in hospital settings should be certified under the umbrella of healthcare setting certification. A heading stating this should be added to the Pharmacy Enrollment Form. The (b) (4) should also be removed as it is covered elsewhere in the REMS.

See redlined version (attached) for further clarification.

(b) (4)

Reviewer Comment: (b) (4) The overview should describe the requirements of the Spravato REMS Program and the responsibilities of each relevant stakeholder. The document should be 3-4 pages in length, can contain product distribution information and answer the following questions:

- What is the Spravato REMS?
- How does the Spravato REMS work?
- What are the requirements of the Spravato REMS?
- What are the Spravato REMS resources?

5.3.1.5 REMS Patient Enrollment Form

The REMS Patient Enrollment Form was submitted with the following edits:

- (b) (4)
- (b) (4)
- (b) (4)
- plain language clarification of sedation and dissociation
- editorial changes

Reviewer Comment: The editorial changes are acceptable. Since patient enrollment will only occur in outpatient healthcare settings, the (b) (4) is not needed.

Additionally, since enrollment forms will not need to be filled out inpatient settings, the (b) (4) should be removed as well as the (b) (4) (b) (4)

The REMS Patient Enrollment Form should clearly state in the header and instructions that enrollment is only required for outpatient healthcare settings. The (b) (4) statement should be removed as it is covered elsewhere in the REMS. The relevant clinical information history should be updated to include esketamine history to ensure all relevant history is collected.

See redlined version (attached) for further clarification.

5.3.1.6 REMS Patient Monitoring Form

The REMS Patient Monitoring Form was submitted with the following edits:

- updated instructions including directions to submit form within 7 days
- (b) (4)
- rework of patient treatment session information field
- rework of sedation/dissociation field
- healthcare provider conducting monitoring field added
- adverse event expanded to include specific adverse events
- (b) (4) instructions removed
- editorial changes

Reviewer Comment: The editorial changes are acceptable. The (b) (4) question should be removed since the monitoring forms are only required for outpatient office and clinical administrations (b) (4)

The REMS Patient Monitoring form should clearly state in the header and instructions that this form should only be used for outpatient healthcare settings administrations of Spravato. Session information fields should also be updated to reflect only settings that fit this description.

See redlined version (attached) for further clarification.

5.3.1.7 REMS Program Website

Predominately editorial changes were submitted for the REMS website.

Reviewer Comment: The editorial changes are acceptable.

The goal of the REMS on the homepage should be replaced with this language below to align with the Agency's current REMS website recommendations:

What is the SPRAVATO REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. SPRAVATO® is available only through a restricted distribution program called the SPRAVATO® REMS because of the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and abuse and misuse of SPRAVATO. SPRAVATO® is intended for use only in a certified Healthcare Setting.

All linked pdf forms and electronic forms should be updated as per the previously listed requests. Clear instruction should also be added to appropriate site pages regarding the requirement of only outpatient healthcare settings to enroll and fill out patient monitoring forms. The pharmacy page should also contain language that states inpatient pharmacy certification can be included in emergency room/inpatient HCS enrollment form.

See redlined version of website transcript (attached) for further clarification.

5.4 REMS Assessment Timetable

The Sponsor indicated that the next assessment would occur six months post approval of the supplement under review if approved, therefore, the timetable for submission of the assessments does not need to be modified due to the supplement approval, if it occurs.

Reviewer Comment: The Agency will correct this and retain the timetable from the original approved REMS Document.

6 Supporting Document

The REMS Supporting Document (SD) was revised to include the background of the REMS Modification currently under review.

Reviewer Comment: The Sponsor will be asked to update and align the SD with the other REMS changes.

7 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be revised to include additional metrics resulting from the modification. Revisions to the assessment plan will be sent with a later communication.

8 Discussion

The goal of Spravato REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and abuse and misuse of the product. The Spravato

REMS was required to ensure that outpatient settings such as individual practitioner offices, large office practices and outpatient clinics, that may not be accustomed to administering medications that cause such effects, understand and monitor for these risks, and only administer Spravato in these settings. Hospitals with on-site pharmacies, and emergency departments generally have policies and procedures in place to provide informed consent to patients that undergo treatments that require anesthesia, analgesia and/or monitoring (as is needed for medical procedures) and are required to document these procedures. The Agency is requesting that as part of certification hospitals agree that policies and procedures are in place to ensure that staff is trained, and patients are monitored. (b) (4)

(b) (4) In these hospital settings, the Agency is more assured that the risk mitigation strategies of monitoring and patient education will occur.

9 Conclusions and Recommendations

DRM does not find the proposed REMS modification for Spravato (esketamine) as submitted on October 2, 2019 to be acceptable, as described in Section 5 of this review. In particular, DRM does not believe (b) (4)

10 Comments to the Applicant

We have the following comments on the proposed REMS modification(s), submitted on October 2, 2019. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 10 business days that addresses these comments. Include all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version.

- The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.
- We have renamed the titles of several forms to be in line with our current thinking of how we believe the REMS should be best modified.

REMS Document

The ability and requirements to monitor patients are different between clinics/offices and hospitals. Full-service hospitals with on-site pharmacies, inpatient wards, operating suites, and emergency departments generally have policies and procedures in place to provide informed consent to patients that undergo treatments that require anesthesia, analgesia and/or monitoring (as is needed for medical procedures) and are required to document these procedures. They also have staffing, including physicians, physician assistants, nurses, nurse practitioners, and various therapy specialists (i.e. respiratory therapists) on-site to provide patient care and continuously monitor patient health status. In these hospital settings, the Agency is more assured that the risk mitigation strategies of monitoring and patient counseling of Spravato risks will occur. In addition, potential necessary interventions are available on-site (b) (4)

Due to the expected operations of typical hospital, the Agency does not agree (b) (4)

(b) (4) Thus, the requirements will be different for hospitals than offices/clinics and this must be clarified in the REMS Document. The Agency is requesting that hospitals be required to certify that policies and procedures are in place to ensure that staff is trained, and patients are monitored.

The REMS Document is under internal discussion and an updated version incorporating these requirements will be sent in a separate communication during this course of this review. You do not need to revise the REMS Document at this time.

(b) (4)

The editorial changes are acceptable; however, separate Healthcare Setting Enrollment Forms must be developed and must clearly outline the requirements for both types of healthcare settings, inpatient and outpatient. These should be titled *Outpatient Healthcare Setting Enrollment Form* and *Inpatient Healthcare Setting Enrollment Form*. These forms should include:

- Directions as to which settings should use which form; emergency departments, though technically considered outpatient, will fall under the inpatient requirements for the purposes of the Spravato REMS, as they will be encompassed by their hospital setting requirements
- Appropriate HCS choices for each form (e.g., “outpatient clinic,” “long term care”).
- Attestations for the relevant setting’s Authorized Representative that comply with requirements specific to each setting—outpatient and inpatient (including emergency departments) (e.g. inpatient settings should have an attestation that there are policies and procedures in place for patients to be counseled on the risks since there will be no patient enrollment form in these settings)
- The *Inpatient Healthcare Setting Enrollment Form* should also describe the process for reporting ^{(b) (4)} adverse events through the REMS and FDA reporting mechanisms as described in the REMS Program Overview document (discussed below).

These items should be removed from the forms:

(b) (4)

See redlined version (attached) for further clarification.

Pharmacy Enrollment Form

The editorial changes are acceptable. The pharmacy types should be limited to those working with outpatient settings. Pharmacies in hospital settings should be certified under the umbrella of healthcare setting certification. A heading stating this should be added to the Pharmacy Enrollment Form. The ^{(b) (4)} should also be removed as it is covered elsewhere in the REMS.

See redlined version (attached) for further clarification.

(b) (4)

(b) (4)

REMS Program Overview. The overview should describe the requirements of the Spravato REMS Program and the responsibilities of each relevant stakeholder. The document should be 3-4 pages in length, can contain product distribution information and answer the following questions:

- What is the Spravato REMS?
- How does the Spravato REMS work?
- What are the requirements of the Spravato REMS?
- What are the Spravato REMS resources?

REMS Patient Enrollment Form

The editorial changes are acceptable. Since patient enrollment will only occur in outpatient healthcare settings, the instruction (b) (4) is not needed. Additionally, since enrollment forms will not need to be filled out inpatient settings, (b) (4)

(b) (4) should be removed (b) (4)

The *REMS Patient Enrollment Form* should clearly state in the header and instructions that enrollment is only required for outpatient healthcare settings. The Spravato (b) (4) should be removed as it is covered elsewhere in the REMS. The relevant clinical information history should be updated to include esketamine history to ensure all relevant history is collected.

See redlined version (attached) for further clarification.

REMS Patient Monitoring Form

The editorial changes are acceptable. The (b) (4) should be removed since the monitoring forms are only required for outpatient office and clinical administrations (b) (4)

The REMS Patient Monitoring form should clearly state in the header and instructions that this form should only be used for outpatient healthcare settings administrations of Spravato. Session information fields should also be updated to reflect only settings that fit this description.

See redlined version (attached) for further clarification.

REMS Program Website

The editorial changes are acceptable.

The goal of the REMS on the homepage should be replaced with this language below to align with the Agency's current REMS website recommendations:

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All linked pdf forms and electronic forms should be updated as per the previously listed requests. Clear instruction should also be added to appropriate site pages regarding the requirement of only outpatient healthcare settings to enroll and fill out patient monitoring forms. The pharmacy page should also contain

language that states inpatient pharmacy certification can be included in emergency room/inpatient HCS enrollment form.

See redlined version of website transcript (attached) for further clarification.

15 **Appendix**

(b) (4)

Healthcare Setting Enrollment Form

Pharmacy Enrollment Form

Patient Enrollment Form

Patient Monitoring Form

REMS Website

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

VICTORIA C SAMMARCO
06/19/2020 02:35:06 PM

DORIS A AUTH
06/19/2020 02:50:31 PM