FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

February 12, 2019

Agenda Topic: The committees will discuss the efficacy, safety, and risk-benefit profile of New Drug Application (NDA) 211243, esketamine 28 mg single-use nasal spray device, submitted by Janssen Pharmaceuticals, Inc., for the treatment of treatment-resistant depression
The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought New Drug Application 211243, esketamine for the treatment of treatment-resistant depression to this Advisory Committee to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2019

FROM: Tiffany R. Farchione, M.D.
Acting Director
Division of Psychiatry Products, HFD-130

TO: Members of the Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

SUBJECT: February 12, 2019 Meeting of the PDAC and DSaRM

Introduction:
This single-day combined meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee will focus on a number of issues critical to the Center for Drug Evaluation and Research (CDER) in evaluating a pending New Drug Application (NDA) for a drug-device combination of esketamine for intranasal administration to be used for the treatment of treatment-resistant depression (TRD). The combination product consists of a single-use nasal spray device that administers two sprays per device, each spray containing 14 mg of esketamine HCL. Thus, each device contains 28 mg of esketamine HCL.

For regulatory purposes, FDA considers patients to have TRD if they have Major Depressive Disorder (MDD) and, despite at least two trials of antidepressant treatment given at adequate doses for an adequate duration in the current episode, they have not responded to treatment. To date, only one medication has been approved for the treatment of TRD—a fixed-dose combination of fluoxetine (a selective serotonin reuptake inhibitor) and olanzapine (an atypical antipsychotic).

The esketamine development program received a Breakthrough Therapy Designation (BTD) in November 2013. The decision was based on preliminary evidence of efficacy from Study 2001, a phase 2a study exploring the effect of intravenous (IV) esketamine in patients with inadequate
response to antidepressants (referred to as “TRD,” although the definition in Study 2001 did not require failure of trials of two antidepressant drugs in the current episode), suggesting the potential for a rapid (within 24 hours) onset of effect, which was viewed as a potential substantial improvement over existing therapy for TRD, a serious or life-threatening condition.

Study 2001 also informed dose selection for a subsequent fixed-dose, dose-finding study of intranasal (IN) esketamine (Study 2003). A second study using IV dosing (Study 2002) suggested that once-weekly administration may not be sufficient to maintain antidepressant effect, thus informing the dosing frequency for subsequent studies. In Study 2003, the Applicant investigated IN esketamine doses from 14 to 84 mg in patients ages 18 to < 65 years with TRD. The results of Study 2003 suggested a dose-response relationship for esketamine; therefore, the Applicant selected the 56- and 84-mg doses for further development in phase 3. An additional study of esketamine 84 mg in patients with MDD deemed to be at imminent risk of suicide (Study SUI2001) may be viewed as supportive given that the population is similar (severe MDD, though treatment resistance was not required). Data from Study SUI2001 were included in this application to provide support for the claim that esketamine acts rapidly to reduce depressive symptoms; the primary efficacy endpoint in Study SUI2001 was change from baseline (CFB) to 4 hours post-dose on the Montgomery Asberg Depression Rating Scale (MADRS). In Study SUI2001, patients who received esketamine 84 mg experienced statistically significantly greater symptom improvement as measured by the MADRS at both 4 and 24 hours post-dose. Patients continued double-blind treatment with either twice weekly esketamine 84 mg or placebo, together with an oral antidepressant, for a total of four weeks; however, there was no statistical difference between the two treatment groups at the end of the study.

In addition to the four phase 2 studies described above, the Applicant has conducted five phase 3 studies in support of the TRD development program for esketamine. The phase 3 studies include two short-term, double-blind, placebo-controlled studies—one fixed-dose and one flexible-dose—in adult patients younger than 65 years of age; one short-term, double-blind, placebo-controlled, flexible-dose study in geriatric patients ≥ 65 years of age; one randomized withdrawal design study; and one long-term, open-label safety study. Patients in all of these studies had failed at least two prior antidepressant trials and, at study entry, had more severe symptoms on average than patients entering antidepressant trials for previously approved drugs. Thus, rather than randomizing severely ill patients to placebo alone, each study involved the addition of a new antidepressant at the same time that either esketamine or placebo was initiated, ensuring that all patients were receiving some form of active treatment.

Because of the purported rapid action of esketamine, it seemed feasible to start all patients on a new antidepressant without compromising the ability to detect a treatment effect in the esketamine treatment group. Given that approved antidepressants typically take 6 to 8 weeks to exert their full effect, if an effect was observed as early as 24 hours post-dose and was maintained throughout the treatment period, that would support esketamine’s effectiveness. This is an important distinction as one considers whether, if approved, this drug would be indicated for the treatment of TRD or as an adjunct to treatment with an oral antidepressant.

The evidence in support of esketamine’s effectiveness derives primarily from two positive phase 3 trials—the flexible-dose trial in adults younger than 65 years of age and the randomized
withdrawal study. In the fixed-dose study of adults younger than 65 years of age, the
prespecified analysis plan dictated that efficacy of the 84-mg dose would be evaluated first,
followed by evaluation of the 56-mg dose. However, the 84-mg dose did not separate from
placebo and the testing sequence ended there. The geriatric study included flexible doses ranging
from 28 to 84 mg; the effect of esketamine in the combined dose group was not statistically
superior to placebo (1-sided \( p = 0.029 \)).

For most approved antidepressants, the evidence of effectiveness comes from at least two
positive adequate and well-controlled short-term trials, with additional maintenance data
provided via a randomized withdrawal trial conducted as a post-marketing commitment. In this
application, there is only one positive short-term trial. The second positive trial is the randomized
withdrawal study. The Division of Psychiatry Products has not previously considered a
randomized withdrawal trial as one of the two adequate and well-controlled trials comprising
substantial evidence of effectiveness, but it is not unreasonable to do so. It is important to note
that the population randomized to continue drug or switch to placebo in a randomized
withdrawal study is an enriched population—these are individuals who have already tolerated the
drug and have already experienced clinical benefit from treatment with the drug. Whether and
how these details would be reflected in labeling has not yet been determined.

The safety of esketamine was evaluated in the short-term double-blind trials relative to placebo
and in a single long-term, open-label study. Because esketamine is the S-enantiomer of ketamine,
special attention was paid to known adverse events associated with ketamine use as intended and
with ketamine misuse and abuse. Sedation, dissociation, cognitive impairment, and suicidal
ideation and behavior were treated as adverse events of special interest; thus, the clinical studies
included specific assessments for these events.

The adverse events of greatest concern in the clinical development program were sedation,
dissociation, and increases in blood pressure. Most of these events occurred within the first 2
hours following drug administration. FDA is proposing a Risk Evaluation and Mitigation
Strategy (REMS) to assure safe use of esketamine. Among the key elements of the proposed
REMS, esketamine administration would occur only in certain healthcare settings where the
patient could be monitored for 2 hours after administration, the drug would not be dispensed
directly to patients, and patients would be enrolled in a registry to better characterize the risks
associated with esketamine administration.

The Agency is seeking input from the Committees on the following questions:

1. Has the Applicant provided substantial evidence of the effectiveness of esketamine for the
treatment of treatment-resistant depression?

2. Has the applicant adequately characterized the safety profile of esketamine for the treatment
of treatment-resistant depression?
3. Given the effectiveness and safety of esketamine and the FDA’s proposed risk evaluation and mitigation strategy (REMS), do the benefits outweigh the risks of esketamine for the treatment of treatment-resistant depression?

4. Discuss whether the FDA’s proposed REMS would assure safe use of esketamine and what additional safeguards would be needed, if any.

5. Are additional data needed pre- or post-approval to address outstanding issues? Discuss whether such data should be required prior to approval.
2. Purpose

The purpose of this Advisory Committee meeting is to obtain input from the committee on whether data provided by the applicant support a favorable benefit-risk profile of esketamine to support approval.

3. Treatment of Treatment-Resistant Depression

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. Over 16 million people in the United States\(^1\) and over 300 million people worldwide\(^2\) have depression. Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates (at a median rate of 10 years of life lost)\(^3\). About 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), etc.) and/or psychotherapy\(^4\). In addition, the onset of treatment response for these modalities, even when effective, often takes at least four weeks, leading to greater suffering, expense, and risk.

Patients who have failed at least two trials of antidepressant treatment generally comprise the population with treatment-resistant depression (TRD). During an externally-led Patient-Focused Drug Development Meeting held on November 16, 2018, feedback from patient representatives noted a variety of concerns including inadequate or incomplete treatment responses, the need for multiple drug trials, and the side effects of existing MDD treatments\(^5\). Relative to other patients with MDD, patients with TRD can incur even more severe morbidity, with higher rates of hospitalization, suicidal ideation and behavior, and medical complications. The urgent need for a rapid-acting, safe, and effective way to interrupt a severe major depressive episode, and to prevent future episodes, remains a major concern; TRD treatments remain an unmet medical need.

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5. [https://secure2.convio.net/dabsa/site/SPageServer/?sessionid=00000000.app268b?NONCE_TOKEN=68B6AC0BF8CA6ED6EA73E7D0B6B258A9&NONCE_TOKEN=8E5900F85A7E46F4D8095EE821724DA1&pagename=FDA_videos](https://secure2.convio.net/dabsa/site/SPageServer/?sessionid=00000000.app268b?NONCE_TOKEN=68B6AC0BF8CA6ED6EA73E7D0B6B258A9&NONCE_TOKEN=8E5900F85A7E46F4D8095EE821724DA1&pagename=FDA_videos) Accessed January 9, 2019.
Standard of care measures for TRD include switching to a different antidepressant (of either the same or a different class), adding an adjunctive treatment to an ongoing antidepressant (typically a drug with a different mechanism of action), adding or switching psychotherapy, or referral for a procedure such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)\(^6\).

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

## Table 1: Summary of FDA-Approved Products for Treatment of TRD

<table>
<thead>
<tr>
<th>Product(s) Name</th>
<th>Relevant Indication</th>
<th>Year of Approval</th>
<th>Route and Frequency of Administration</th>
<th>Efficacy Information</th>
<th>Important Safety and Tolerability Issues</th>
<th>Regulatory Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbyax (Fluoxetine plus Olanzapine)</td>
<td>TRD</td>
<td>2003</td>
<td>Oral daily</td>
<td>MADRS Total Score Change from Baseline of -16 vs. olanzapine -12 and placebo -10 for Study 1, -18 vs. -14 and -9 for Study 2</td>
<td>Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and extrapyramidal symptoms/akathisia</td>
<td>CDER</td>
</tr>
<tr>
<td>ECT</td>
<td>TRD (associated with either MDD or Bipolar Disorder)</td>
<td>1976 (most recent update 2018)</td>
<td>Bitemporal or unilateral temporal; up to 3 times a week for 6 to 10 treatments initially</td>
<td>Not available; approval based on various studies from research literature.</td>
<td>Memory concerns, use of general anesthesia</td>
<td>CDRH</td>
</tr>
<tr>
<td>TMS</td>
<td>TRD (patients who failed only 1 antidepressant)</td>
<td>2008</td>
<td>Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)</td>
<td>MADRS Total Score Change from Baseline of -6 at Week 4 and Week 6 active TMS vs. -4 at Week 4 and Week 6 sham TMS. Approval based on post-hoc analysis and responder/remission rates.</td>
<td>No major safety issues, limited long-term safety data</td>
<td>CDRH</td>
</tr>
<tr>
<td>VNS</td>
<td>TRD</td>
<td>2005</td>
<td>Once (surgical implant)</td>
<td>12-week sham placebo-controlled study not statistically significant. Approval was based on long-term open-label HAM-D responder data (30% response in 1 year versus 13% treatment as usual), 12-week open-label pilot study showed 34% MADRS responders.</td>
<td>Surgical intervention risks (allergies, infection, etc.)</td>
<td>CDRH</td>
</tr>
</tbody>
</table>

There are several other FDA-approved drugs for the separate indication of adjunctive treatment for partial response in MDD: quetiapine XR, aripiprazole, and brexpiprazole. From a regulatory standpoint, the adjunctive treatment indication applies to patients who have insufficient but partial response to their current oral antidepressant and may benefit from add-on treatment. This population is usually less severely ill than for the TRD population; these patients are frequently on their first antidepressant and adjunctive...
treatment trials have lower depression scale cutoff scores for study entry than TRD trials. See Section 6.1 for further explanation of our regulatory definition of TRD.

Additional off-label pharmacological interventions for TRD include ketamine, and augmentation with other antidepressants or antipsychotics, lithium, thyroid hormone, buspirone, and other drugs.

4. Product Under Review

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

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

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

Under this NDA, the Applicant proposes esketamine nasal spray for intranasal use for the treatment of TRD. After mutual agreement between FDA and the Applicant, TRD has been defined (from a regulatory standpoint) as a lack of clinically meaningful improvement in depressive symptoms after treatment with at least two different oral antidepressant medications as monotherapy, taken at adequate doses for adequate duration (at least 6 weeks) for their current episode of depression. The previous oral antidepressants could be from the same or different drug classes, which could include SSRIs, SNRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or any other oral antidepressants. (See Section 6.1 for more details.)

The Applicant proposes that esketamine be administered intranasally twice a week for an initial 4 weeks in addition to a newly initiated oral antidepressant. The proposed initial adult esketamine dose is 28 to 56 mg at each administration; it can be titrated to 84 mg by
Week 2. The Applicant proposes continuation of treatment on a weekly basis for an additional 4 weeks, and then weekly or every other week during an ongoing maintenance phase.

5. Regulatory Background

- May 8, 2012, Pre-IND Meeting: FDA and the Applicant discussed nonclinical and clinical pharmacology study requirements, including carcinogenicity studies, repeat Olney lesion studies, and comparison studies to ketamine. The clinical reviewer discussed the regulatory definition of TRD (failure of treatment of at least two different antidepressant classes; this requirement later was modified in March 2014 to any two antidepressants), and the acceptability of the proposed phase 2 dose frequency and phase 3 study designs. The Applicant agreed to modify the proposed parallel-group phase 3 studies to incorporate a longer acute treatment period of at least four weeks to assess for persistence of effect; FDA and the Applicant agreed on the use of the Montgomery-Asberg Depression Rating Scale (MADRS) as the assessment scale during the studies to be measured at each timepoint. They also agreed upon other scales for adverse event (AE) assessment (Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) (later switched to Cogstate in April 2014)). FDA required abuse potential assessment studies and PDAC review.

- November 7, 2013: FDA granted Breakthrough Therapy Designation (BTD) status to the esketamine for TRD development program. TRD is a serious condition with an unmet clinical need for additional treatments, and phase 2 esketamine studies provided sufficient preliminary evidence of efficacy to grant BTD status.

- March 13, 2014, and May 6, 2014, BTD Advice Meetings: The Applicant and FDA agreed upon the regulatory definition of TRD for this program (failure of treatment of at least two different antidepressants of the same or different classes, given at an adequate dose and duration); determination that TRD criteria were met was to include retrospective determination of prior treatment failures if validated via scales and prior records (e.g., pharmacy, medical). FDA did not agree that an adjunctive treatment design (add-on to existing antidepressant) would merit a TRD treatment indication because adding a medication to a failed treatment in TRD was not sound clinical practice. Studies would start all participants on a new antidepressant in the acute phase, and – in addition – randomize subjects to esketamine or placebo, a so-called “add-on” design.

FDA also requested a maintenance-of-effect study; the Applicant then proposed a randomized withdrawal design. FDA emphasized the use of centralized, blinded, remote raters in all phase 3 studies. FDA requested the use of active intranasal placebo but later agreed not to require it (accepting inactive intranasal placebo instead) if the Applicant instituted all blinding precautions for on-site staff. FDA also
recommended a severe renal impairment study. The Applicant inquired whether they could file their application with only acute efficacy data, provided that they had sufficient safety data to fulfill ICH E1 criteria; the Agency did not agree, noting that we viewed this product very differently from previously approved oral antidepressants and would require maintenance data at the time of filing. FDA agreed that including at least 30% US subjects in phase 3 pivotal studies would allow for adequate representation relevant to our treatment population.

- June 5, 2014, BTD Advice Meeting: The Applicant and FDA discussed Chemistry, Manufacturing, and Controls (CMC) and abuse liability study requirements. FDA requested a phase 1 abuse liability study.

- June 18, 2014, Nonclinical Meeting: FDA and the Applicant discussed Olney lesion study (neurotoxicity) specifications for nonclinical requirements. FDA required a 14-day repeat-dose neurotoxicity rat study with post-dosing histological assessment to rule out vacuolization prior to phase 3 initiation.

- September 12, 2014, BTD Advice Meeting: FDA and the Applicant agreed to the proposed phase 3 short-term study and maintenance designs, with one short-term study being a flexible-dose study. FDA agreed that the maintenance study could be used as one of two positive studies to support a marketing application, along with a short-term fixed-dose study with statistically very persuasive results (later switched to any short-term study in March 2018, see below).

- December 8, 2014, End-of-Phase 2 Meeting: FDA and the Applicant agreed upon doses of 56 mg and 84 mg esketamine for the phase 3 studies. Patients with cardiovascular and cerebrovascular risk factors were to be excluded because of the risk for hypertension (HTN) with esketamine, and blood pressure (BP) was to be monitored pre- and post-dose. FDA agreed that the Applicant’s nonclinical study program proposal for esketamine in combination with specific bridging studies to ketamine would be sufficient for NDA submission.

- June 24, 2015, Guidance Meeting: FDA’s nonclinical team requested an additional acute neurotoxicity rat study due to concerns about NMDA antagonist class-related drug issues. The nonclinical team agreed the study could be conducted in parallel with phase 3 human studies.

- March 1, 2016, BTD Advice Meeting: FDA and the Applicant agreed on defining the important secondary endpoint of Onset of Clinical Response as the point at which a ≥50% improvement (instead of score ≤19) in MADRS total score was achieved, with sustained response at each subsequent timepoint (with one permitted excursion) for the phase 3 short-term studies. FDA also agreed to the proposed additional secondary endpoint of Sheehan Disability Scale (SDS) total score for potential inclusion in the label.
- March 14, 2018, Pre-NDA Meeting: FDA agreed that the completed (to-date) phase 3 studies (3001, 3002, 3003, 3004, and 3005) were adequate to support filing of an NDA for review, and that phase 2 studies and studies conducted under a separate IND for a related indication would also be taken into consideration during our review. The Applicant was to provide demographic-based exploratory efficacy analyses for the pooled phase 3 short-term studies, 3001 and 3002. FDA requested a list of safety preferred terms in advance for review and agreement (which was provided April 18, 2018).

- June 28, 2018, Second Pre-NDA Meeting: FDA encouraged the Applicant to submit a proposed REMS with the NDA. FDA agreed to inclusion of bridging nonclinical studies with ketamine from Javelin in the submitted NDA.

6. Effectiveness of Esketamine for Treatment of Treatment-Resistant Depression

6.1. Phase 3 Study Design

There were four phase 3 randomized controlled trials conducted and submitted under NDA 211243. Three of them (3001, 3002, 3005) were of similar short-term parallel-group design, and one (3003) was a randomized withdrawal maintenance-of-effect design. In two studies (one parallel-group study and the randomized withdrawal study), esketamine was statistically superior to placebo on the study’s primary efficacy endpoint; in the other two short-term parallel group studies, esketamine was not. All studies were international, with about a third of patients in the United States. The majority of subjects in all the studies were women in their 40s and 50s, white, with higher body mass index (BMI >24). Depending on the study, around 33 to 40% of enrolled subjects had failed three or more antidepressant (AD) treatments by the start of screening, and 12 to 17% had failed at least four.

The primary outcome measure used for the studies was the Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS is a 10-item instrument with total score ranging from 0 to 60. A higher MADRS score indicates more severe depression. The 10 items are: sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. To decrease the introduction of bias, all MADRS score evaluations were performed by independent, remote (via telephone), blinded raters. Scales were administered on study visit days prior to intranasal esketamine (or placebo) dosing and with a few exceptions (shorter-term secondary endpoints) were meant to assess symptoms over the previous 7 days.

Baseline mean MADRS total scores for Studies 3001, 3002, and 3003 ranged from 37 to 38 (and for the geriatric Study 3005, the mean was 35). These baseline mean scores are higher than those in phase 3 studies for previously FDA-approved antidepressants and adjunctive treatment medications for depression (mean MADRS total scores ranged from
28 to 36; the baseline MADRS means in Symbyax clinical trials ranged from 28 to 30) and indicate greater illness severity for the treatment population in the esketamine phase 3 studies than is typical for MDD development programs.

All the studies compared IN esketamine and IN placebo (with an added embittering agent as a blinding mechanism) each added to one of four newly initiated oral antidepressants (duloxetine, venlafoxine XR, escitalopram, or sertraline), each dosed daily beginning at the start of the treatment phase (except for duloxetine which stayed at the same dose, all were titrated to therapeutic doses over the course of the next 1 to 2 weeks). For the first 4 weeks of treatment (which encompassed the double-blind phase of the parallel-group studies), the nasal spray was administered twice weekly. For the maintenance-of-effect Study 3003 and for long-term open-label safety studies, the nasal spray was administered weekly for the next 4 weeks post-induction phase, then either weekly or every other week for ongoing maintenance.
## Table 2: Esketamine Phase 3 Randomized Double-Blind Active-Controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Arms</th>
<th>Dosing</th>
<th>Duration</th>
<th>Primary Endpoint</th>
<th>Patients Enrolled</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRD3002 (TRANSFORM-2)</td>
<td>Parallel-Group</td>
<td>Flexible-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD both arms</td>
<td>Twice Weekly IN (Oral AD Daily)</td>
<td>4-week treatment phase, 24-week follow-up or TRD3003</td>
<td>Change from Baseline (CFB) in MADRS Total Score at Week 4</td>
<td>224 total (114 on ESK + oral AD; 110 on placebo + oral AD)</td>
<td>Adults (18 to 64 years) with TRD</td>
</tr>
<tr>
<td>TRD3003 (SUSTAIN-1)</td>
<td>Randomized Withdrawal</td>
<td>Flexible or Fixed-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD all arms</td>
<td>Twice Weekly IN during 4-week phase, then weekly for next 4 weeks, then weekly or every other week per response (Oral AD Daily)</td>
<td>4-week treatment initiated during open-label direct-entry phase or during 3001 or 3002. Then 12-week open-label optimization phase. Then ongoing maintenance phase post-randomization.</td>
<td>Time to relapse during maintenance phase for stable remitters</td>
<td>705 total (437 direct entry + 268 from 3001 or 3002); 176 during maintenance phase (90 on ESK + oral AD; 86 on placebo +oral AD)</td>
<td>Adults (18 to 64 years) with TRD</td>
</tr>
<tr>
<td>TRD3001 (TRANSFORM-1)</td>
<td>Parallel-Group</td>
<td>Fixed-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD all arms</td>
<td>Twice Weekly IN (Oral AD Daily)</td>
<td>4-week treatment phase, 24-week follow-up or TRD3003</td>
<td>Change from Baseline (CFB) in MADRS Total Score at Week 4</td>
<td>344 total (115 on ESK 56 mg + oral AD; 116 on ESK 84 mg + oral AD; 113 on placebo + oral AD)</td>
<td>Adults (18 to 64 years) with TRD</td>
</tr>
<tr>
<td>TRD3005 (TRANSFORM-3)</td>
<td>Parallel-Group</td>
<td>Flexible-Dose Esketamine (28 or 56 or 84 mg) vs. Placebo, + Oral AD both arms</td>
<td>Twice Weekly IN (Oral AD Daily)</td>
<td>4-week treatment phase, 24-week follow-up or TRD3004 (long-term safety study)</td>
<td>Change from Baseline (CFB) in MADRS Total Score at Week 4</td>
<td>137 total (72 on ESK + oral AD; 65 on placebo + oral AD)</td>
<td>Geriatric (65 years and older) with TRD</td>
</tr>
</tbody>
</table>
Key inclusion criteria mainly involved the definition of TRD for subjects. TRD diagnostic criteria for the phase 3 studies are derived from both regulatory definitions (from FDA and EMA) and established research criteria (including those derived from the STAR*D trials). The following inclusion criteria are quoted from pages 24 to 25 of the Applicant’s Clinical Overview from their NDA application:

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

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

1. Retrospective assessment of prior AD nonresponse in current episode of depression: all subjects in the phase 3 short-term studies were required to have had documented nonresponse (≤25% improvement per clinical judgment) to at least 1 oral AD treatment taken for the current episode of depression prior to the initial screening visit, at adequate dosage and for an adequate duration, as assessed on the MGH-ATRQ and confirmed by structured interview and documented records.

2. Prospective assessment of AD nonresponse: at the initial screening visit, subjects must have been receiving treatment for the current depression episode with a different oral AD for at least 2 weeks at or above the minimum therapeutic dose (per MGH-ATRQ). This drug was continued prospectively for 4 weeks during the screening/prospective observational phase. Only subjects who demonstrated (prospectively) nonresponse to the current oral AD after at least 6 weeks (≤25% improvement on MADRS total score from Week 1 to 4, together with a MADRS total score of ≥28 on Week 2 and Week 4 [≥24 for elderly subjects in TRD3005]), were eligible for randomization. Medication adherence was documented on the Patient Adherence Questionnaire during the screening/prospective observational phase to ensure that subjects took at least a minimum therapeutic dose of the current oral AD.

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

Key exclusion criteria included:

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

6.2. Phase 3 Efficacy Results

The two studies in which esketamine led to statistically significantly greater improvement in depressive symptoms than placebo will be described first, followed by a description of the other two studies. None of the results on the prespecified key secondary endpoints (only designated in Studies 3001 and 3002) were statistically significant after controlling for type I error based on the prespecified statistical analysis plan. Other secondary endpoints were evaluated without controlling for multiplicity. However, the primary endpoints (and most secondary endpoints) were numerically better for esketamine groups compared to placebo.

There were no clear subgroup efficacy trends. The United States subgroups in all studies generally aligned with the primary efficacy results, indicating generalizability of the overall results to the U.S. population.
6.2.1. Study 3002 (TRANSFORM-2)

Study 3002 was a flexible-dose, randomized, parallel-group trial comparing IN esketamine and IN placebo each added to newly initiated oral antidepressant treatment. All esketamine subjects initially received a 56-mg dose and then could be titrated to 84 mg at the next dose, based on investigator discretion with regard to efficacy and tolerability. (Subjects in the placebo arm would follow the same procedure with the corresponding placebo dose.)

Figure 1: Study 3002 Study Design Schematic

About 40% of subjects in this study were from the U.S., with the rest from Europe. The distribution of demographic characteristics was generally similar for the two treatment groups. The placebo group was heavier (mean weight 82.7 kg±19.5 vs 79.3 kg±20.1 in esketamine) and older (mean age 46.4 years±11.1 vs 44.9 years±12.6 in esketamine) and had more individuals with comorbid HTN (25% vs 16% in esketamine). Baseline illness severity was also comparable between treatment groups (although lifetime suicidal behavior was higher in the placebo arm (13%) than the esketamine arm (8%)). About 2/3 of subjects in the esketamine arm ultimately received 84 mg twice weekly; 1/3 received 56 mg twice weekly. More patients dropped out of the esketamine arm (14%) compared to the placebo arm (10%).

Subjects in the esketamine treatment group experienced statistically significantly greater improvement in depressive symptoms, as measured by the CFB to endpoint in the MADRS, than patients in the placebo group (Table 3). On the MADRS, the mean difference between
esketamine and placebo (Figure 2) was statistically significant at most time points throughout the 28 days of double-blind treatment (except Day 15).

Table 3: Study 3002 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline MADRS Total Score (SD)</th>
<th>LS Mean Change from Baseline (SE) at Week 4</th>
<th>LS Mean Difference from Placebo (SE) at Week 4</th>
<th>1-Sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>109</td>
<td>37.3 (5.7)</td>
<td>-15.8 (1.2)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Esketamine + Oral AD</td>
<td>114</td>
<td>37.0 (5.7)</td>
<td>-19.8 (1.3)</td>
<td>-4.0 (1.7)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Source: Study 3002 Clinical Study Report (CSR)

Figure 2: Study 3002 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

Source: Andrew Potter PhD, Statistical Reviewer

6.2.2. Study 3003 (SUSTAIN-1)

Subjects enrolled in this study came from either direct entry (following an open-label esketamine treatment protocol) or from Studies 3001 or 3002. All subjects who experienced ≥50% reduction from baseline in MADRS total score by the end of acute 4-week treatment were eligible to enter
the optimization phase, where they received at least 12 weeks of open-label esketamine treatment with oral antidepressant ongoing. (Responder subjects who had originally been randomized to placebo during acute treatment in Studies 3001 or 3002 remained blinded to their original treatment but were not included in the final efficacy analysis populations. They all received IN placebo during the withdrawal phase.)

Figure 3: Study 3003 Patient Flowchart

After completion of the optimization phase, in order to be randomized and enter the maintenance phase of Study 3003, subjects had to meet criteria for either stable remission or stable response:

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

- **Stable Response**: ≥50% reduction in MADRS total score from baseline (Day 1 of induction phase prior to first IN dose) in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

Stable remitters were to comprise the analysis population for the primary efficacy endpoint, and stable responders were to comprise the analysis population for the secondary endpoint. Relapse during the maintenance phase was defined as a MADRS total score ≥22 for two consecutive assessments and/or undergoing hospitalization or another serious clinical event (as adjudicated by investigators). An interim analysis determined the number of relapses required to end the
study (at least 59 total relapses). The maintenance period lasted for at least 500 days (3 patients continuing for at least 500 days).

Baseline demographic and psychiatric characteristics were generally similar across treatment groups for stable remitters. Most stable remitter subjects were from Europe (58%) with about 23% US representation (30% North American). One concern in this study was that one site in Poland drives the overall study result due to a 100% rate of placebo arm relapses (16 out of 16 subjects on placebo versus 2 out of 9 on esketamine) in both stable remitters and stable responders.

There was a statistically significant difference in time to relapse of depression favoring those subjects randomized to continue esketamine versus those who were switched to placebo (with oral antidepressant ongoing in both arms) in the stable remitters group. The secondary endpoint of time to relapse in the stable responders group was also statistically significant.

The result tables indicate the number of patients who had relapsed by the end of the study when the total number of observed events was large enough for the study to have a 90% power of detecting a hazard ratio of 0.493 comparing esketamine to placebo. A pre-planned interim analysis (IA), conducted after 31 relapses, determined that the final analysis should occur after at least 59 relapses were observed.

**Table 4: Study 3003 Primary Efficacy Endpoint of Time to Relapse in Stable Remitters**

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

Source: Study 3003 CSR, NE=not estimable
Figure 4: Study 3003 Primary Efficacy Endpoint of Time to Relapse in Stable Remitters

Table 5: Study 3003 Secondary Efficacy Endpoint of Time to Relapse in Stable Responders

<table>
<thead>
<tr>
<th></th>
<th>Esketamine + Oral AD</th>
<th>Placebo + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Assessed</strong></td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td><strong>Number Censored</strong></td>
<td>46 (74%)</td>
<td>25 (42%)</td>
</tr>
<tr>
<td><strong>Number of Relapses</strong></td>
<td>16 (26%)</td>
<td>34 (58%)</td>
</tr>
<tr>
<td><strong>Time to Relapse (Days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25% percentile (95% CI)</td>
<td>217 (56 to 635)</td>
<td>24 (17 to 46)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>635 (264 to 635)</td>
<td>88 (46 to 196)</td>
</tr>
<tr>
<td><strong>Hazard Ratio (HR) (95% CI)</strong></td>
<td>0.30 (0.16 to 0.55)</td>
<td>--</td>
</tr>
<tr>
<td>2-sided p-value (&lt;0.05)</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

Source: Study 3003 CSR, NE=not estimable
Most of the differentiation between relapse on placebo versus esketamine (with oral antidepressant still ongoing in both arms) for the primary endpoint occurred within the first 2 to 4 weeks after randomization. Typically, in other maintenance-of-effect studies for MDD, relapses on drug versus placebo differentiate at a slower rate, beginning at about a month post-randomization according to an FDA meta-analysis. Although the faster rate of relapse in this study may reflect the greater illness severity and fragility of a TRD population, there is some concern that it could reflect functional unblinding, with subjects realizing they are no longer on esketamine after switching to placebo. (The rapid deterioration on placebo is perhaps also surprising, as one might expect some protective effect from the ongoing oral antidepressant.) As compared to oral antidepressants, esketamine has noted immediate effects such as dissociation (for a majority of subjects, with rates as high as 75%) and sedation upon dosing, that do not dissipate with time according to the safety data reviewed. Subjects who have all been exposed to open-label esketamine for at least 16 weeks may be able to notice the difference soon after being switched to placebo. Acute esketamine withdrawal is likely not a factor, as dosing is infrequent during the maintenance phase.

The Applicant conducted an analysis indicating that only a few subjects reported significant changes in dissociation and sedation scale scores before and after randomization; censoring those subjects did not change the overall efficacy result.

FDA conducted further exploratory analysis of both the dissociation symptom trajectories and their association to the time to relapse of depression. The Applicant measured dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS). In Figure 6, CADSS scores decline rapidly in the placebo arm when patients are randomized to stopping esketamine. FDA used a joint model of both CADSS score trajectories and time to depression relapse. This analysis found that both esketamine treatment (HR = 0.45, p = 0.0032) and CADSS score (HR = 0.63 per unit increase in square root CADSS, p = 0.0448) are associated with time to relapse of depression.

Figure 6 Treatment Arm Average CADSS score Trajectories Stratified by Relapse Status (TRD3003: FAS - Remitter Set)

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

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

FDA’s exploratory analysis cannot distinguish between these possibilities. It is thus possible, but not conclusive, that functional unblinding has partially impacted this study’s results.

6.2.3. Study 3001 (TRANSFORM-1)

This study was a fixed-dose randomized parallel-group active-controlled trial. Based on the prespecified statistical plan, esketamine did not separate from placebo.

Figure 7 Study 3001 Study Design Schematic

Baseline demographic characteristics were generally similar across treatment arms for this study. About 40% of subjects were from the U.S., and approximately 70% were women. Baseline psychiatric characteristics were also generally similar; however, there was a higher percentage of subjects in the esketamine 84-mg arm with a history of failing three or more antidepressants (48%, 30%, and 41% in the esketamine 84-mg, esketamine 56-mg, and placebo arms, respectively).

The prespecified statistical analysis plan employed a fixed-sequence testing procedure to control the Type-I error rate. The esketamine 84-mg arm was prespecified as the first group to be tested, as it was the higher dose. Because the change from baseline on MADRS was not significantly different between the 84-mg treatment group and the placebo group, the testing sequence stopped here, and the 56-mg treatment group could not be formally analyzed. In an analysis that would be considered exploratory, subjects in the esketamine 56-mg arm did experience greater improvement in depressive symptoms as measured by the MADRS than patients in the placebo
Of note, the least square mean difference between the esketamine 56-mg group and the placebo group is comparable to estimated treatment effects in other successful phase 3 studies. The nominally statistically significant \( p = 0.0114 \) 56-mg dose arm in TRD3001 could be considered supportive evidence of effectiveness for the 56-mg dose, although this study was not positive based on the prespecified analysis plan.

Given that the esketamine 84-mg arm did not show superior efficacy over the lower dose, another concern is that we may not have sufficient evidence to say that there is a therapeutic dose response for the higher dose, relative to its higher rate of adverse events. This larger study’s results did not confirm the dose-response relationship observed in the phase 2 Study 2003. Study 2003 compared esketamine 28 mg, 56 mg, and 84 mg to placebo (with a background oral antidepressant either ongoing or not). At 8 days post-dose, the placebo adjusted change from baseline in MADRS score was -4.2 (95% CI: -7.67, -0.79), -6.0 (95% CI: -9.71, -2.88), and -9.0 (95% CI: -12.53, -5.52) for 28 mg, 56 mg, and 84 mg esketamine respectively. (See Section 6.3.1 for more details.)

### Table 6: Study 3001 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline MADRS Total Score (SD)</th>
<th>LS Mean Change from Baseline (95% CI) at Week 4</th>
<th>LS Mean Difference from Placebo (95% CI) at Week 4</th>
<th>1-Sided p-value &lt;0.025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>113</td>
<td>37.5 (6.2)</td>
<td>-14.9 (-17.4 to -12.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Esketamine 56 mg + Oral AD</td>
<td>115</td>
<td>37.4 (4.8)</td>
<td>-18.9 (-21.4 to -16.4)</td>
<td>-4.1 (-7.7 to -0.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Esketamine 84 mg + Oral AD</td>
<td>114</td>
<td>37.8 (5.6)</td>
<td>-18.2 (-20.9 to -15.6)</td>
<td>-3.2 (-6.9 to +0.5)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Source: Study 3001 CSR and Andrew Potter, PhD, Statistical Reviewer
6.2.4. Study 3005 (TRANSFORM-3)

This **geriatric** study used flexible dosing from 28 to 84 mg for the esketamine arm. Based on the prespecified statistical analysis plan, esketamine did not separate from placebo.
The TRD inclusion cutoff scores for this study were slightly lower than those used for the non-geriatric adult phase 3 studies. The baseline demographic and psychiatric characteristics were generally similar across treatment groups, with about 51% U.S. representation. Unlike the previous studies, the mean age was 70 years, and the majority of subjects in this study were initiated on an SSRI (56%) instead of an SNRI for their oral antidepressant. A higher number of patients had a previous diagnosis of hypertension (47%), as expected for an older population. About 2/3 of subjects in the esketamine arm received 84 mg doses and 1/3 were on 56 mg.

The difference between the esketamine plus oral antidepressant group and the placebo plus oral antidepressant group was not statistically significant on the primary efficacy endpoint of change from baseline at Day 28 on the MADRS total score. Aside from not reaching statistical significance, this study has additional data integrity concerns given the unusual response curve shift at Day 28 (when a nearly significant effect emerged after a finding of no difference at all for the first 3 weeks, when an effect in other studies was present on Day 2), discrepancies between the locked datasets and reported protocol violations, and the inclusion of outliers with missing data. Study 3005 does not appear to be supportive of an esketamine effect.
Table 7: Study 3005 Primary Endpoint MADRS Total Score Change from Baseline at Day 28 Using MMRM (Full Analysis Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline MADRS Total Score (SD)</th>
<th>LS Mean Change from Baseline (95% CI) at Week 4</th>
<th>LS Mean Difference from Placebo (95% CI) at Week 4</th>
<th>1-Sided p-value &lt;0.025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>65</td>
<td>34.8 (6.4)</td>
<td>-6.5 (-9.4 to -3.6)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Esketamine + Oral AD</td>
<td>72</td>
<td>35.5 (5.9)</td>
<td>-10.1 (-13.1 to -7.1)</td>
<td>-3.6 (-7.2 to 0.07)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Source: Study 3005 CSR and Andrew Potter, PhD, Statistical Reviewer

Figure 10: Study 3005 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

Source: Andrew Potter, PhD, Statistical Reviewer

6.2.5. Secondary Efficacy Endpoints and Other Results of Note

- Although no secondary endpoints in the phase 3 parallel-group studies met criteria for statistical significance, all were numerically better in the esketamine group than in the placebo group, and several reached nominal statistical significance. The only secondary endpoint that was consistently in the nominally significant range for p-values across the
Phase 3 parallel-group studies was the PHQ-9, a self-reported measure. The PHQ-9 is a self-reported depression symptom scale which provides confirmatory support for the MADRS.

**Table 8: Esketamine Secondary Efficacy Endpoints**

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESK 56 mg + Oral AD</td>
<td>ESK 84 mg + Oral AD</td>
<td>Placebo + Oral AD</td>
</tr>
<tr>
<td>MADRS Sustained Response Day 2+</td>
<td>10%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>SDS</td>
<td>-2.5</td>
<td>-2.2</td>
<td>n/a</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>-2.3</td>
<td>-2.2</td>
<td>n/a</td>
</tr>
<tr>
<td>MADRS Responders at Day 28</td>
<td>54%</td>
<td>53%</td>
<td>39%</td>
</tr>
<tr>
<td>MADRS Remitters at Day 28</td>
<td>36%</td>
<td>39%</td>
<td>31%</td>
</tr>
<tr>
<td>MADRS Sustained Response Day 8+</td>
<td>13%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>GAD-7</td>
<td>-1.5</td>
<td>-1.4</td>
<td>n/a</td>
</tr>
<tr>
<td>EQ-5D-5L CFB Mean Sum Score**</td>
<td>-19.0</td>
<td>-19.4</td>
<td>-14.6</td>
</tr>
</tbody>
</table>

*This was the only secondary endpoint that could be formally tested due to a fixed testing sequence. All other secondary endpoints either could not be formally tested due to a previously statistically insignificant endpoint in the fixed testing sequence or were not controlled for multiplicity. p-value is one-sided.

**Scores are mean change from baseline only (SDS, PHQ-9, GAD-7 are mean change from baseline difference from placebo)

Source: CSRs from Studies 3001, 3002, 3005

- Key Secondary Endpoints for Studies 3001 and 3002: The following three outcome measures were prespecified as key secondary endpoints in the two adult (non-geriatric) phase 3 parallel-group studies:

  1. MADRS Sustained Response Starting Day 2 (Total Score Change from Baseline ≥50% response at Day 2, maintained through Day 28 with no worse than 25% response and one excursion allowed)
  2. Sheehan Disability Scale (SDS) total score change from baseline at Day 28
  3. PHQ-9 total score change from baseline at Day 28
These endpoints were to be tested in a fixed sequence approach to adjust for multiplicity and type I error, if the primary endpoint was statistically significant.

For Study 3002, the primary endpoint was significant, so the first key secondary endpoint could be tested. However, that endpoint (MADRS Sustained Response Starting Day 2) was not statistically significant (see Table 7), and therefore, the subsequent key secondaries could not be formally tested for statistical significance. Both of the two subsequent key secondaries (SDS and PHQ-9) would have met nominal significance and showed numerical improvement in the esketamine group versus placebo for their respective endpoints. The SDS and PHQ-9 results here would provide supportive evidence of a greater trend towards efficacy in functional improvement and improvement in self-reported depression symptoms on IN esketamine versus IN placebo, plus an oral antidepressant, by Day 28.

For Study 3001, as the primary endpoint was not found to be significant, the key secondaries could not be formally tested. On an exploratory basis, the first key secondary (MADRS Sustained Response Starting Day 2) would have been nominally significant only for the esketamine 56-mg dose arm, and for both dose arms on the PHQ-9.

- **Remission (MADRS ≤12) and Responder (≥50% MADRS Reduction from Baseline) Rates:** Both percentage rates are numerically better for esketamine arms versus placebo arms in all phase 3 parallel-group studies. (The groups were not statistically compared.) This trend may indicate a clinically relevant subgroup of TRD patients who show marked clinical benefit from esketamine greater than placebo, with oral antidepressant ongoing in all arms. Also, the numerical Day 28 changes from baseline in mean total MADRS score for the esketamine groups in Studies 3001 and 3002 are consistent with the responder definition of ≥50% MADRS reduction from baseline.

- **Distribution of Response:** MADRS mean total score distributions showed a trend towards greater change from baseline values for esketamine treatment groups compared to placebo for the parallel-group phase 3 studies. Again, this result seems to indicate at least a subgroup of TRD patients who show potential strong clinical benefit on esketamine compared to placebo, with oral AD ongoing.
Figure 11: Study 3001 Distribution of Response on MADRS Total Score at Week 4

Source: Andrew Potter PhD, Statistical Reviewer

Figure 12: Study 3002 Distribution of Response on MADRS Total Score at Week 4

Source: Andrew Potter PhD, Statistical Reviewer
Figure 13: Study 3005 Distribution of Response on MADRS Total Score at Week 4

- **Average Change from Baseline in MADRS Scores:** To the extent that one can compare differences across trials, changes from baseline in MADRS mean total scores in the esketamine phase 3 parallel-group studies were comparable to the changes in previously approved antidepressants and adjunctive therapies. These changes are occurring in a treatment population with greater illness severity as based on higher mean baseline MADRS total scores and number of failed antidepressants.

Source: Andrew Potter PhD, Statistical Reviewer
Table 9: MADRS Score Change from Baseline for Prior Approved Antidepressants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antidepressant</th>
<th>MADRS LS Mean CFB at Primary Endpoint Range</th>
<th>MADRS LS Mean CFB Difference from Placebo/Active Control</th>
<th>Baseline MADRS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>Vortioxetine</td>
<td>-13 to -20</td>
<td>-2.8 to -7.1</td>
<td>31 to 34</td>
</tr>
<tr>
<td></td>
<td>Vilazodone</td>
<td>-9.7 to -13</td>
<td>-2.5 to -3.2</td>
<td>31 to 32</td>
</tr>
<tr>
<td></td>
<td>Levomilnacipran</td>
<td>-14 to -17</td>
<td>-1.3 to -4.9</td>
<td>30 to 36</td>
</tr>
<tr>
<td>Adjunctive MDD</td>
<td>Aripiprazole</td>
<td>-8.5 to -8.8</td>
<td>-2.8 to -3.0</td>
<td>31 to 32</td>
</tr>
<tr>
<td></td>
<td>Brexpiprazole</td>
<td>-7.7 to -8.5</td>
<td>-1.3 to -3.1</td>
<td>33 to 35</td>
</tr>
<tr>
<td></td>
<td>Quetiapine XR</td>
<td>-14 to -17</td>
<td>-1.6 to -4.1</td>
<td>28 to 32</td>
</tr>
<tr>
<td>TRD</td>
<td>Olanzapine + Fluoxetine (fixed-dose combination)</td>
<td>-8.6 to -14</td>
<td>n/a</td>
<td>23 to 30</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine (vs. Olanzapine + Fluoxetine)</td>
<td>-1.2 to -11</td>
<td>-1.4 to -12</td>
<td>“</td>
</tr>
<tr>
<td></td>
<td>Olanzapine (vs. Olanzapine + Fluoxetine)</td>
<td>-2.8 to -10</td>
<td>-0.8 to -11</td>
<td>“</td>
</tr>
<tr>
<td></td>
<td>Esketamine</td>
<td>-10.1 to -20.8</td>
<td>-3.2 to -4.1</td>
<td>37 to 38 adult, 35 geriatric</td>
</tr>
</tbody>
</table>

Source: DPP Antidepressant Study Database from Previously Approved NDAs

6.3. Relevant Phase 2 Efficacy Results

6.3.1. Study 2003 (SYNAPSE)

Study 2003 was a fixed-dose study intended to help identify which dose(s) to carry forward to phase 3 studies. This phase 2 randomized, placebo-controlled, sequential parallel comparison design (SPCD), dose-response study consisted of two panels (A and B) and two 1-week double-blind treatment periods (1 and 2) for each panel. Panel A studied 28-, 56-, and 84-mg doses of esketamine and Panel B studied 14- and 56-mg doses. Background oral antidepressant treatment may or may not have been ongoing from previous treatment. The primary efficacy endpoint was the difference between IN esketamine and placebo for change from baseline in the MADRS total score for the combined double-blind treatment periods. The Applicant also analyzed pairwise comparisons of each esketamine dose versus placebo for dose response using a two different weighted combination tests based on estimates and standard errors from an ANCOVA model. The Applicant tested six hypotheses at an alpha of 0.1 that correspond to three pairwise esketamine – placebo comparisons where the test statistics were calculated two different ways. The Applicant did not prespecify any procedure for controlling the Type I error rate across these hypotheses. In addition, multiple, exploratory, dose-response analyses including MCP-mod were
conducted without pre-specifying any method to control the Type-I error rate over these analyses.

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

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

Table 10 MADRS Total Score: Change from Baseline to End Point ANCOVA LOCF Analysis; Double-Blind Phase, Panel A, Periods 1, 2, and Combined

<table>
<thead>
<tr>
<th>Period</th>
<th>Placebo</th>
<th>Esketamine 28 mg</th>
<th>Esketamine 56 mg</th>
<th>Esketamine 84 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>33</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>LS Mean (SE)</td>
<td>-4.9 (1.74)</td>
<td>-9.8 (2.72)</td>
<td>-12.4 (2.66)</td>
</tr>
<tr>
<td></td>
<td>Mean diff Placebo (SE)</td>
<td>--</td>
<td>-5.0 (2.99)</td>
<td>-7.6 (2.90)</td>
</tr>
<tr>
<td></td>
<td>One-sided p-value &lt; 0.025</td>
<td>--</td>
<td>0.051</td>
<td>0.006</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>6</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>-4.5 (2.92)</td>
<td>-7.6 (2.49)</td>
<td>-8.9 (2.51)</td>
</tr>
<tr>
<td></td>
<td>Mean diff Placebo (SE)</td>
<td>--</td>
<td>-3.1 (2.99)</td>
<td>-4.4 (3.06)</td>
</tr>
<tr>
<td></td>
<td>One-sided p-value &lt; 0.025</td>
<td>--</td>
<td>0.152</td>
<td>0.083</td>
</tr>
<tr>
<td>Combined</td>
<td>Mean diff Placebo (SE)</td>
<td>--</td>
<td>-4.2 (2.1)</td>
<td>-6.3 (2.1)</td>
</tr>
<tr>
<td></td>
<td>90% CI</td>
<td>--</td>
<td>-7.7 to -0.8</td>
<td>-9.7 to -2.9</td>
</tr>
<tr>
<td></td>
<td>One-sided p-value &lt; 0.025</td>
<td>--</td>
<td>0.021</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Source: Applicant’s Advisory Committee Briefing Document
Due to a failed consistency test between Periods 1 and 2, the combined analysis was not performed for Panel B. The individual period results showed no clear efficacy trends. The Applicant did not report detailed results.

Study 2003’s results suggest a dose response where higher doses have superior efficacy; however, Study 2003 has limited applicability as a pivotal study to claim this dose response, and Study 3001 did not confirm this dose response. The Applicant analyzed multiple dose-response models and chose the model most supportive of the claimed dose response. Study 2003 differs from the phase 3 studies in its lack of consistency for background oral antidepressants, its smaller sample size, the use of SPCD that might not be valid depending on whether the required statistical assumptions are met, and its shorter treatment period.

In addition, Study 2003 may not have met the prespecified assumptions for the validity of either of the SPCD combination tests conducted. However, the Period 1 results suggest increasing antidepressant efficacy without the requirement of the SPCD assumptions, for Panel A only.

### 6.3.2 Study SUI2001

Study SUI2001 was a phase 2 double-blind randomized placebo-controlled study to evaluate the efficacy and safety of IN esketamine for the rapid reduction of symptoms of MDD including suicidal ideation, in subjects at imminent risk of suicide (under a separate Investigational New Drug application). The study was conducted at ten US sites. The primary endpoint was the efficacy of IN esketamine 84 mg versus placebo as measured by mean change from baseline on the MADRS total score at 4 hours post-dose on Day 1, with secondary endpoints looking at other timepoints (24 hours post-dose (Day 2), Day 25 (end of double-blind treatment), and Day 81 (end of follow-up treatment)).

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

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

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

Results: There were 66 subjects (35 on esketamine, 31 on placebo) who received at least one dose of study medication and comprised the intent-to-treat (ITT) population. There were 49
completers (27 on esketamine, 22 on placebo). The majority of the 19 subjects who discontinued the study early were due to adverse events and lack of efficacy.

The majority of subjects were female (65%), with a mean age of 35.8 years (55% of subjects were under age 35). The mean MADRS score was 38.6 (SD 6.53). All had answered “yes” to having current suicidal ideation with intent on Question B5 of the Mini-International Neuropsychiatric Interview (MINI). These demographics reflect a severely ill study population, comparable to the one studied in the TRD adult phase 3 trials.

The efficacy results on the MADRS show numerical improvement at all timepoints on esketamine compared to placebo, although there was no statistically significant difference between treatment groups at Day 25.

| Table 11 Study SUI2001 MADRS Mean Total Score Change from Baseline |
|------------------|---------------|---------------|---------------|
|                  | Day 1         | Day 2         | Day 25        |
| Esketamine (SD)  | -13.4 (9.0)   | -19.3 (12.0)  | -26.4 (14.5)  |
| Placebo (SD)     | -9.1 (8.4)    | -12.8 (9.8)   | -23.0 (10.8)  |
| LS Mean Difference (SE) | -5.3 (2.1) | -7.2 (2.9)   | -4.5 (3.1) |
| 2-sided p-value <0.05 | **0.015** | **0.015** | 0.159 |

Source: Study SUI2001 CSR

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

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

7. Safety of Esketamine for the Treatment of TRD

7.1. Overarching Safety Issues

The review team identified sedation, dissociation, and increased blood pressure as the primary safety concerns related to this product. Cognitive function impairment, liver injury, and interstitial or ulcerative cystitis have been reported in post marketing data for ketamine. In the esketamine clinical program, there was no evidence of a higher rate of cognitive impairment or liver injury with esketamine relative to placebo. There were no reported cases of ulcerative or
interstitial cystitis, but esketamine-treated patients had a higher incidence of lower urinary tract adverse events.

Randomization for Study 3001 included two esketamine arms. Therefore, the randomization ratio was 2:1 esketamine + oral AD: placebo + oral AD. Studies 3002 and 3005 had esketamine arms with flexible dosing (which had 1:1 randomization ratios). Data are presented separately for the 56- and 84-mg fixed doses for Study 3001; the flexible dosages of 28, 56, 84 mg are combined for Studies 3002 and 3005.

7.2. Deaths, Serious Adverse Events, Adverse Events Leading to Study Withdrawal

7.2.1. Deaths

There were six deaths in the esketamine for treatment-resistant depression development program as of January 8, 2019, all in esketamine-treated subjects. Three of these deaths were by suicide—two well after the patient’s last dose of esketamine (12 and 20 days), and one 4 days after the patient’s last dose of esketamine. The patients who committed suicide 12 and 4 days after their last dose both appeared to be improving based on their MADRS scores (from baseline of 27 to 9, and 41 to 25, respectively). The patient who committed suicide 20 days after his last dose was experiencing worsening symptoms (from MADRS 7, 13 days prior to death to MADRS 21, 6 days prior to death. The patient who committed suicide 4 days after last dose was enrolled in an ongoing study; that patient’s Columbia Suicide Severity Rating Scale (C-SSRS) score was not available. The other two patients had scores of 0, both at baseline and at the visit prior to their deaths. Given the small number of cases, the severity of the patients’ underlying illness, and the lack of a consistent pattern among these cases, it is difficult to consider these deaths as drug-related.

Of the remaining three cases, one involved a motorcycle accident 26 hours after the patient’s last dose of esketamine. Given the timing of sedation-related adverse events in the clinical development program and the data from the driving studies, it seems unlikely that esketamine played a role in this accident. Another death occurred in a 60-year-old male patient with a history of hypertension and obesity who died suddenly on study day 113. At his last study visit 5 days prior to death, his blood pressure, heart rate, and pulse oximetry were all within normal limits before and after receiving esketamine. It seems unlikely that this death was drug-related. The last death was a 74-year-old woman with history of hypertension and hyperlipidemia who died of myocardial infarction 6 days after last dose of esketamine. Esketamine-induced increases in blood pressure normally last for less than 4 hours post-dose; therefore, the myocardial infarction is not likely related to elevated blood pressure.
7.2.2. Serious Adverse Events

More serious adverse events (SAEs) were reported in subjects treated with esketamine than placebo.

Table 12: SAEs in Studies 3001, 3002, and 3005

<table>
<thead>
<tr>
<th></th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>ESK</td>
<td>Placebo</td>
</tr>
<tr>
<td>N. of subjects</td>
<td>113</td>
<td>231</td>
<td>109</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Road traffic accident/Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness/Fall/Hip fracture</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

SAEs of depression and suicidal ideation were reported with higher incidence in subjects treated with esketamine than placebo in Study 3001, but not in Studies 3002 or 3005. There was no obvious difference between the esketamine and placebo groups with respect to other SAEs.

7.2.3. Adverse Events Leading to Study Withdrawal

There were more adverse events leading to study withdrawal in esketamine groups than placebo groups in Studies 3001, 3002, and 3005. However, very few cases of each AE were reported. Most adverse events were reported only once and only in one study. Blood pressure increase, depression, and nausea were reported twice in one study, all in esketamine groups, which is consistent with the common adverse events profile.

7.3. Adverse Events

The most commonly reported adverse events were dissociation, dizziness/vertigo, nausea/vomiting, sedation, paresthesia, hypoaesthesia, blood pressure increase in Studies 3001, 3002, and 3005. The distribution of adverse events was similar between age groups. However, the common AEs in esketamine groups were less frequently reported in subjects ≥65 years old than in subjects < 65 year old. Adverse events occurring in greater than two percent of esketamine-treated subjects and at least twice as frequently as in placebo-treated subjects <65 years-old, and in subjects ≥ 65 years-old are presented in Tables 13 and 14, respectively.
### Table 13: Adverse Events ≥ 2% and ≥ Twice the Rate of Placebo by Treatment Group in Studies 3001 and 3002 (subjects < 65 years old)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>3001 Placebo N=113</th>
<th>3001 Esketamine 56 mg N=115</th>
<th>3001 Esketamine 84 mg N=116</th>
<th>3002 Placebo N=109</th>
<th>3002 Esketamine N=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissociation</td>
<td>22 (19.5%) 53 (46.1%)</td>
<td>54 (46.6%)</td>
<td>20 (18.3%)</td>
<td>60 (52.2%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (9.7%) 38 (33.0%)</td>
<td>32 (27.6%)</td>
<td>7 (6.4%)</td>
<td>32 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (10.6%) 32 (27.8%)</td>
<td>37 (31.9%)</td>
<td>7 (6.4%)</td>
<td>31 (27.0%)</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>13 (11.5%) 29 (25.2%)</td>
<td>29 (25.0%)</td>
<td>9 (8.3%)</td>
<td>22 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>2 (1.8%) 24 (20.9%)</td>
<td>24 (20.7%)</td>
<td>4 (3.7%)</td>
<td>30 (26.1%)</td>
<td></td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>3 (2.7%) 19 (16.5%)</td>
<td>11 (9.5%)</td>
<td>1 (0.9%)</td>
<td>14 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Hypoaesthesia oral</td>
<td>2 (1.8%) 16 (13.9%)</td>
<td>12 (10.3%)</td>
<td>1 (0.9%)</td>
<td>9 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>2 (1.8%) 14 (12.2%)</td>
<td>17 (14.7%)</td>
<td>1 (0.9%)</td>
<td>8 (7.0%)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>5 (4.4%) 11 (9.6%)</td>
<td>14 (12.1%)</td>
<td>1 (0.9%)</td>
<td>12 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.8%) 7 (6.1%)</td>
<td>14 (12.1%)</td>
<td>2 (1.8%)</td>
<td>11 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (0.9%) 2 (1.7%)</td>
<td>3 (2.6%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer
Table 14: Adverse Events ≥ 2% and ≥ Twice the Rate of Placebo by Treatment Group in Study 3005 (subjects ≥ 65 years old)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo N=65 n (%)</th>
<th>Esketamine N=72 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>5 (7.7%)</td>
<td>17 (23.6%)</td>
</tr>
<tr>
<td>Dissociation</td>
<td>6 (9.2%)</td>
<td>15 (20.8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4.6%)</td>
<td>13 (18.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.1%)</td>
<td>10 (13.9%)</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>4 (6.2%)</td>
<td>10 (13.9%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2 (3.1%)</td>
<td>8 (11.1%)</td>
</tr>
<tr>
<td>Hypoaesthesia oral</td>
<td>0 (0%)</td>
<td>5 (6.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.1%)</td>
<td>5 (6.9%)</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>1 (1.5%)</td>
<td>4 (5.6%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (1.5%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1 (1.5%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Nasal mucosal disorder</td>
<td>1 (1.5%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>0 (0%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0 (0%)</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

Adverse events of lower urinary tract symptoms were 6 to 10% in esketamine groups compared to 1 to 3% in placebo in studies 3001 and 3002 (subjects < 65 years old), and 7% in esketamine vs. 4% in placebo in Study 3005 (subjects ≥ 65 years old). However, no cases of interstitial cystitis or ulcerative cystitis were identified during the clinical trials. Given that ketamine is associated with interstitial and ulcerative cystitis (observed in individuals who abuse ketamine), cystitis-related adverse events will likely be described in the Warnings and Precautions section of labeling if this product is approved.
Table 15: Cystitis-related Adverse Events by Treatment Group in Studies 3001, 3002, and 3005

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
</tr>
<tr>
<td>N</td>
<td>113</td>
<td>115</td>
<td>116</td>
</tr>
<tr>
<td>Lower Urinary Tract AEs</td>
<td>3 (2.7%)</td>
<td>10 (8.7%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Urinary discomfort/pain</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cystitis/UTI</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Micturition urgency</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pollakiuria/Nocturia</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Sediment/Odour abnormal</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Symptoms of cystitis could be misreported as UTI due to similar clinical symptoms*

Source: Qi Chen, MD, MPH, Safety Reviewer

The most commonly reported lower urinary tract adverse events in subjects treated with esketamine were urinary frequency and dysuria.

Most (67%) of the lower urinary tract AEs were mild and resolved without intervention or esketamine dose reduction. Only two (0.04%) of the reported lower urinary tract AEs were considered severe—both were cases of urinary frequency, both occurred in the esketamine group. Only one lower urinary tract AE (a case of urinary tract infection) resulted in esketamine interruption. No dose effect was observed on the severity of the urinary AEs. 76% of the AEs were resolved or resolving at the subject’s last assessment. No dose effect was observed on the outcome of the AEs.

Attempts to identify interstitial or ulcerative cystitis could be confounded by urinary tract infection symptoms in AE reports. However, notably higher incidences of urinary frequency and dysuria may indicate adverse effects on the bladder. In long-term observational Study 3004, lower urinary tract AEs were reported in 137 (19%) subjects, most of which (90%) were resolved at the subject’s last assessment. The cumulative prevalence of subjects with lower urinary tract AEs in study 3004 was 7 subjects per thousand esketamine treatments compared to 11 per thousand treatments in short term Studies 3001, 3002, and 3005. The observed cumulative prevalence with placebo in the short-term studies was 4 per thousand treatments. On the other hand, esketamine was administered less frequently (weekly or twice weekly for 4 to 8 weeks, then every other week) in Study 3004 as compared to twice weekly in Studies 3001, 3002, and 3005. The longer duration between esketamine use may help the urinary tract to recover from any adverse effects of esketamine. Without a comparison arm, it is difficult to conclude whether esketamine treatment results in long-term adverse effects on the urinary tract.
7.4. Laboratory Studies, Electrocardiograms (ECGs), and Vital Signs

7.4.1. Laboratory Studies

Esketamine treatment had little apparent effect on laboratory studies. Notably, esketamine was not found to produce clinically meaningful changes in liver enzymes or bilirubin. There was no increase in abnormalities in urinalysis relative to placebo.

7.4.2. ECGs

In a thorough QT study, intranasal esketamine treatment (84 mg dosage) was associated with a maximum heart-rate-adjusted reduction in QT interval relative to placebo of about 6 milliseconds at maximum effect, returning to baseline in 3 to 4 hours, a change that was not deemed to be clinically meaningful. No effects on PR or QRS intervals were found.

7.4.3. Vital Signs

7.4.3.1. Blood Pressure

The rate of potentially clinically important systolic blood pressure (SBP) increases (to ≥180 mmHg with increase of ≥20 mmHg) or diastolic blood pressure (DBP) increase (to ≥105 mmHg with increase ≥15 mmHg) was higher in the esketamine group than in the placebo group. (Table 17)
Table 16: Post-dose Highest Blood Pressure Changes in Esketamine- and Placebo-treated Patients in Studies 3001, 3002, and 3005

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
</tr>
<tr>
<td>N</td>
<td>113</td>
<td>116</td>
<td>115</td>
</tr>
<tr>
<td>SBP (mmHg) Mean change ± SD</td>
<td>12 ± 10</td>
<td>20 ± 14</td>
<td>20 ± 13</td>
</tr>
<tr>
<td>SBP ≥180 and increase ≥ 20 n (%)</td>
<td>0</td>
<td>6 (5.2%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>DBP (mmHg) Change mean ± SD</td>
<td>10 ± 8</td>
<td>15 ± 8</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>DBP ≥ 105 and increase ≥ 15 n (%)</td>
<td>2 (1.8%)</td>
<td>8 (7.0%)</td>
<td>10 (8.7%)</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

Adult subjects 18 to ≤ 65 years of age experienced greater mean increases in SBP and DBP in esketamine-treated subjects compared to placebo, and more subjects experienced potentially clinically meaningful increases of SBP to ≥180 mmHg (and change ≥ 20 mmHg) and DBP ≥ 105 mmHg (and change ≥ 15 mmHg). A similar pattern was not observed in subjects ≥ 65 years of age in Study 3005. The observed changes in blood pressure generally resolved in less than four hours without clinical intervention.

Table 17: Visits with Highest BP Measured at 1.5 hour and SBP Increase ≥10 or DBP ≥5

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo</td>
<td>ESK 56 to 84 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>N (% of visits)</td>
<td>SBP</td>
<td>83 (9%)</td>
<td>177 (10%)</td>
</tr>
<tr>
<td>DBP</td>
<td>1 (0.1%)</td>
<td>3 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

Usually the highest SBP was observed at 40 minutes. In about 10 to 20% of visits, the highest observed SBP increase of at least 10 mmHg was at 1.5 hours post dose. Clinical pharmacology data from Study 1013 also showed blood pressure effects last for about 4 hours and are likely
related to esketamine plasma levels. Longer post-dose observation would be needed to capture the full profile of esketamine-induced blood pressure increase.

7.4.3.2. Heart Rate

In most phase 1 and 2 studies, esketamine treatment was associated with increases in heart rate. This effect was not observed in Studies 3001 and 3005. In Study 3002, an increase in heart rate relative to placebo (random effects mean 4.7 bpm) was observed at 40 minutes (Figure 9). Given that the time pattern of heart rate changes seen in Study 3002 and phase 1 and 2 studies matched the time pattern of changes in blood pressure and the esketamine pharmacokinetic profile, it is likely that esketamine does cause an increase in heart rate in some patients, despite the absence of this observation in Studies 3001 and 3005.

Figure 14: Changes in Heart Rate in Study 3002

![Heart Rate Graph](image)

Source: Marc Stone, MD, Deputy Director of Safety

7.5. Other Adverse Events of Special Interest

7.5.1. Sedation

Sedation was evaluated using Modified Observer’s Alertness/Sedation scale (MOAA/S) at pre-dose, and post-dose 15, 30, 45, 60, 75, and 90 minutes. On this scale, 0 represents a patient response only to painful stimulus, 1 is patient response only after painful stimulus, and 2 corresponds to response only after mild prodding or shaking. The data describing esketamine’s sedative effects are presented in following table, lower score indicating worse sedation.
Table 18: Number of Subjects Who Experienced Sedation at Least Once in Studies 3001, 3002, and 3005

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>112</td>
<td>107</td>
<td>63</td>
</tr>
<tr>
<td>Esketamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56 mg</td>
<td>114</td>
<td>114</td>
<td>72</td>
</tr>
<tr>
<td>84 mg</td>
<td>114</td>
<td>114</td>
<td></td>
</tr>
</tbody>
</table>

All sedation (score 0-4)

<table>
<thead>
<tr>
<th></th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (10.7%)</td>
<td>57 (50.0%)</td>
<td>69 (60.5%)</td>
<td></td>
</tr>
<tr>
<td>66 (10.3%)</td>
<td>12 (19.0%)</td>
<td>35 (48.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Severe sedation (score 0-2)

<table>
<thead>
<tr>
<th></th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

There was a substantially higher incidence of sedation in esketamine-treated patients (49 to 61%) than in placebo-treated patients (10% to 19%). In Study 3001, the sedation incidence was slightly higher in the esketamine 84-mg group than in the esketamine 56-mg group. The post-dose times at which sedation began, reached peak severity, and resolved in Studies 3001, 3002, 3003, and 3005 are presented in Figures 15 and 16.
Figure 15: Sedation – Onset, Peak and Resolution time by Percentage of Study Population in Esketamine-treated Subjects <65 years-old in Studies 3001, 3002 and 3003
In subjects < 65 years old who developed sedation after esketamine use, the majority experienced sedation onset at 15 minutes, peak at 30 minutes, and resolution at 60 minutes. The latest onset, peak and resolution times were 90, 120, and 210 minutes, respectively. In subjects ≥ 65 years old who developed sedation after esketamine use, the majority experienced sedation onset and peak at 30 minutes, and resolution at 45 minutes. The latest onset, peak, and resolution times were 75, 90, and 105 minutes, respectively.

The latest onset time of any sedation among all subjects in Studies 3001, 3002, 3003, and 3005 was 90 minutes post-dose. Compared to subjects < 65 years old, sedation was not as severe in subjects ≥65 years old (minimum score=3) and was shorter in duration.

There were 24 subjects in whom severe sedation (MOAA/S score 0 to 2) occurred, with some subjects experiencing severe sedation on more than one visit (reports spanned 37 visits). All of the visits with severe sedation were after esketamine use and in subjects <65 years old.

In Studies 3001, 3002, 3003, and 3005, there were two subjects who experienced loss of consciousness (LOC) with MOAA/s score 0. One subject was transferred to the emergency room. The other subject had LOC at five different visits with onset 15 to 30 minutes after receiving esketamine; these episodes lasted between 15 and 35 minutes.
Severe sedation showed markedly fluctuating patterns in several subjects. Most notably, one subject experienced minimal sedation at 45 minutes, was alert at 1 hour, then became severely sedated at 2 hours.

Time of onset, peak, resolution, and severity varied among visits in some subjects. For example, the event just described was the first time the subject experienced sedation with severity score 1, and it occurred on study day 277. Thus, it appears that the experience of previous visits cannot accurately predict future onset, peak, resolution time, or severity, and this has with implications for monitoring and labeling.

Little data on sedation were collected after 1.5 hours in phase 3 studies; however, sedation was monitored for an extended period in the phase 1 Study 1005. In this study, sedation was assessed using the Karolinska sleepiness scale at regular intervals through 6 hours post-dose. Although most subjects reported that they were “alert” by 6 hours, there were subjects who felt “sleepy” around 4 to 6 hours post-dose in both placebo and esketamine groups.

Because of the fluctuating pattern of sedation and the potential severity of sedation events, patients will need to be monitored following administration of esketamine until sedation resolves or until they have passed the period of greatest risk for sedation. In the clinical development program, sedation resolved within 2 hours of dosing (with rare exceptions). Thus, it seems reasonable to monitor patients for 2 hours following administration of esketamine to mitigate the risk of adverse events associated with excessive sedation (e.g., falls, motor vehicle accidents).

### 7.5.2. Dissociation

Dissociation was evaluated by Clinician-Administered Dissociative States Scale (CADSS) questionnaire pre-dose, and 40 and 90 minutes post-dose. The total CADSS score ranges from 0 to 92, with a higher score representing more severe dissociation. Scores between 0 and 4 are considered to be in the normal range.

**Table 19: CADSS Median Score and Incidence of Increases in Score >4 at Any Time Post-dose in Studies 3001, 3002 and 3005**

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
</tr>
<tr>
<td>N</td>
<td>113</td>
<td>113</td>
<td>116</td>
</tr>
<tr>
<td>Median (25%, 75%)</td>
<td>0 (0, 1)</td>
<td>6 (2, 14)</td>
<td>8 (3, 16)</td>
</tr>
<tr>
<td>Dissociation change &gt;4 n (%</td>
<td>10 (9%)</td>
<td>68 (60%)</td>
<td>83 (72%)</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer
Based on analyses of CADSS data from both the short-term and long-term studies, it appears that treatment with esketamine leads to dissociation. Although the highest dissociation scores were observed, on average, following initial treatment, the dissociative effects were only partially attenuated with repeat administration. For example, across trials, the mean increase in CADSS score at 40 minutes after first-time esketamine administration was approximately 6 points. In contrast, the mean increase in CADSS at 40 minutes after placebo administration was about 1 point. After 4 weeks of treatment, the mean increase in CADSS after esketamine administration was still approximately 2.4 points; no further decrease was observed with continued treatment in patients who continued esketamine treatment in longer-term trials.

There was also evidence of dose effect: In Study 3001, the average increase in CADSS at 40 minutes relative to baseline was 1.3 points greater with 84 mg than with 56 mg. No difference between dosages on dissociation was observed at 1.5 hours.

### 7.5.3. Impaired Cognition

In the phase 3 studies, cognition was evaluated by the CogState computerized test battery, which includes assessments of multiple cognitive domains, and Hopkins Verbal Learning Test-Revised (HVLT-R), which is a measure of verbal learning and memory. There were no significant differences between esketamine groups and placebo groups in Studies 3001, 3002, 3003, and 3005. In the long-term open-label Study 3004, there was some evidence of slowing reaction time (RT) in elderly subjects; however, there was high intra-individual variability, making it difficult to distinguish drug effects from other factors. No AEs related to cognitive impairment were reported in the phase 3 trials.

### 7.5.4. Suicidal Ideation and Behavior

Treatment-emergent suicidal ideation was assessed using both adverse event reports and the Columbia-Suicide Severity Rating Scale (C-SSRS). For adverse events, AEs coded with preferred terms “Suicide attempt,” "Intentional self-injury," "Suicidal ideation," and "Suicidal behavior” were included in our analyses of suicidal ideation and behavior events; the results are summarized in Table 20.

Table 20: Subjects with AEs Related to Suicidal Ideation or Behavior (SI/B) During Double-Blind Phase

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th></th>
<th>3002</th>
<th></th>
<th>3005</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
<td>Placebo</td>
<td>ESK 56 to 84 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>n</td>
<td>113</td>
<td>115</td>
<td>113</td>
<td>109</td>
<td>112</td>
<td>65</td>
</tr>
<tr>
<td>Subjects with SI/B (%)</td>
<td>1(1%)</td>
<td>2(2%)</td>
<td>2(2%)</td>
<td>1(1%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td></td>
<td>Source: Qi Chen, MD, MPH, Safety Reviewer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The odds ratio for suicide-related AEs was calculated using exact logistic regression stratified by study. Although the odds ratio (1.52) was suggestive of a higher risk with esketamine treatment, this was not statistically significant ($p=0.71, 95\%$ confidence interval 0.24 to 16.3).

Results for the C-SSRS are summarized in Table 21.

**Table 21: Subjects with Suicidal Ideation or Behavior as Measured by C-SSRS**

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td>Suicidal Ideation (Score &gt;0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>29 (25%)</td>
<td>37 (33%)</td>
<td>40 (35%)</td>
</tr>
<tr>
<td>Clinical significant suicidal ideation or Suicidal Behavior (Score ≥4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Source: Qi Chen, MD, MPH, Safety Reviewer

The odds ratio for suicidal ideation (0.82) was suggestive of a lower risk with esketamine treatment but not statistically significant ($p=0.26, 95\%$ confidence interval 0.57 to 1.16). Suicidal behavior was reported in four esketamine-treated subjects and no placebo subjects (median unbiased estimate odds ratio 3.17) but, again, was not statistically significant ($p=0.30, 95\%$ confidence interval 0.39 to infinity).

**7.6. Other Pertinent Safety Studies**

**7.6.1. Human Factors Validation Study**

The results of the Human Factors (HF) validation study did not demonstrate that the user interface supports the safe and effective use of this product. Of particular concern were errors and confusion observed regarding strength and dosing for this product. The Applicant proposes the product be supplied in a carton containing one 28-mg nasal spray device (28-mg total dose), a carton containing two 28-mg nasal spray devices (56-mg total dose), and a carton containing three 28-mg nasal spray devices (84-mg total dose). Based on the HF data submitted, confusion occurred between the proposed packages regarding strength and dosing, and the proposed packaging may contribute to product selection medication errors and wrong dose errors. In the HF validation study, healthcare providers cited confusion regarding how much drug is available per spray, how much drug is available per device, and how many devices should be administered to achieve the correct dose. It was not clear to all study participants that the number of devices per carton is dose-specific. Thus, it may be appropriate, in light of the findings from the HF validation study, that Janssen consider marketing a single packaging configuration of one device in one carton with labeling improvements to increase clarity and decrease the risk for medication errors.
7.6.2. **Driving Studies**

The effect of intranasal esketamine on driving performance was assessed by an on-road driving test using the standard deviation of lateral position as the primary end point. The results from two individual studies (i.e., Studies 1006 and 1019) demonstrated that the driving performance after 84 mg intranasal esketamine was not different from placebo 6 hours post-dose or later (i.e., 8 and 18 hours) if they met other requirements for discharge. Two subjects from Study 1006 discontinued the driving test due to persistent and worsening of treatment-emergent adverse events. No information on the driving performance between 0 to 6 hours post-dose is available.

Neither driving study included elderly subjects (≥ 60 years); the median age was approximately 25 to 35 years. Elderly subjects have a relatively higher exposure of esketamine as compared to younger adults administered the same dose, and there may be altered ability in operating a motor vehicle with aging; therefore, it is unclear whether the same results can be applied to elderly subjects.

Patients with moderate hepatic impairment have a longer elimination half-life of esketamine as compared to those with normal hepatic function. Changes in cognitive function, upon esketamine treatment, would need to be monitored for a longer period of time in such patients.

Overall, we recommend that the patients should not drive on the day of intranasal esketamine dosing, but may drive the next day following a restful sleep.

7.7. **Ketamine Postmarketing Safety Concerns and Potential Relevance to Esketamine**

7.7.1. **Adverse Events Related to Repeated Off-label Use of Ketamine**

In recent post-market safety assessments relating to ketamine, the Division of Pharmacovigilance (DPV) has identified concerns relating to the potential risk of genitourinary, hepatobiliary and cognitive effects associated with repeated exposure to ketamine for the treatment of depression or pain. DPV prioritized these signals based upon routine surveillance of the literature; however, DPV’s review of these potential risks does not address all potential safety concerns regarding ketamine. The post-market safety data do not provide a sufficient basis to conclude whether such risks are specific to particular routes of administration or doses (examined routes of administration in off-label use were oral or parenteral). Nevertheless, findings from our review of ketamine may be considered relevant to discussions regarding the safety of esketamine.

Our assessment of data within the FDA Adverse Event Reporting System (FAERS) and the published literature suggests a likely causal relationship between repeated ketamine exposure and the onset of genitourinary (e.g., cystitis) and hepatobiliary events (e.g., cholestasis, periductal fibrosis, elevated transaminases). We also reviewed a number of small studies (i.e., randomized controlled trials and observational studies), which suggested that sub-anesthetic doses of ketamine may have negative short-term effects on memory and cognitive function, though it remains unclear whether or under what circumstances such effects persist over the long-term. Although we did not assess patients noted to be abusing ketamine in this review,
similar pathologies have been reported among patients abusing ketamine. The full DPV review is provided for reference in section 13.1 of Attachment 1.

7.7.2. Ketamine Abuse and Associated Harms

Attachment 2 contains a review of postmarketing data on ketamine abuse and associated harms, including a review of recently published literature as well as information from two national surveys (National Survey on Drug Use and Health and Monitoring the Future), U.S. poison center calls (National Poison Data System), a representative sample of emergency department visits (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance), and spontaneous adverse event reports (FAERS). A summary of the recent ketamine drug utilization analysis (conducted as part of the integrated safety review included as Attachment 1) is included to provide context for the abuse-related data. The review findings are summarized briefly here.

Based on national sales distribution patterns of ketamine vials (excluding veterinary sales), ketamine utilization appears to be largely in the hospital setting. Ketamine sales increased approximately 72% from 2013 to 2017 overall and sales to clinic settings, specifically, more than doubled during this five-year period. Numerous off-label uses of ketamine have been proposed and implemented, including treatment-resistant depression, and recent literature suggests growth in some of these off-label uses of ketamine.

National survey data and the published literature indicate that ketamine abuse is relatively uncommon in the general population, with a reported lifetime prevalence of 1.3% among persons age 12 years and older, which is lower than that for other hallucinogens such as ecstasy and LSD (Acid). Among 12th graders, the annual prevalence of ketamine use has declined from 2.5% in 2000 to 1.2% in 2017. Exposure calls to U.S. poison centers involving ketamine abuse or misuse also declined slightly from 2013 to 2017 (176 calls in 2013 to 116 calls in 2017), despite the growth in non-veterinary ketamine sales. Single-substance exposure calls involving ketamine abuse or misuse were most commonly associated with minor or moderate health effects, and there were no deaths identified among these calls. In a representative sample of approximately 60 U.S. emergency departments, there were 44 ketamine-related ED cases in 2016-2017, corresponding to an estimated 669 visits nationally. Of the 44 ketamine-related ED cases, 35 (81.5%) were classified as abuse. Only six (17.1%) of these cases resulted in hospitalization. From 2015 to 2017, FAERS received 17 reports of death involving ketamine abuse. Of note, only one of these reports listed ketamine as the only suspected drug, and the drug-event causal association has not been assessed for any of these FAERS cases.

Overall, this analysis suggests that ketamine abuse continues to occur but has remained relatively limited with modest associated harms. The available data are insufficient to determine the extent to which U.S. pharmaceutical ketamine for humans contributes to abuse, relative to ketamine that is smuggled into the country or diverted from veterinary settings. Nonetheless, the risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and post marketing surveillance for esketamine, if approved.
8. Risk Mitigation

The FDA has used a variety of strategies to minimize risks associated with drugs and therapeutic biologics. The primary risk management tool is communicating through FDA-approved product labeling, which includes a summary of the essential information needed by health care providers for the safe and effective use of the drug. Labeling is sufficient for most drugs to ensure that the benefits outweigh the risks. But in some cases, FDA may determine that a Risk Evaluation and Mitigation Strategy (REMS) will also be needed to help ensure that the benefits of the drug outweigh its risks. A REMS is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication.

REMS can communicate specific risk information, as well as information regarding safe use of the product. In addition, a REMS program can provide guidance and encourage, remind, or support adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate patients or healthcare setting where the benefits outweigh the risks. The safety concerns for esketamine for which a REMS is being considered are misuse, abuse, dissociation, and sedation.

8.1. Safety Concerns Associated with Esketamine

Sedation and dissociation are adverse events that were observed in the clinical program. We are particularly concerned that patient harm could result if patients leave the healthcare setting before these symptoms have resolved. Concerns also include the potential for misuse and abuse, known effects associated with the currently approved related product, ketamine.

If approved for TRD, patients who take esketamine are at risk for sedation and could be impaired and unable to perform certain tasks. In the clinical development program, sedation was observed at high rates in the treatment population with about 50% esketamine-treated patients experiencing sedation versus 15% in placebo-treated patients. Of the patients treated with esketamine in the phase 3 studies (n=1051), 24 participants experienced severe sedation after esketamine use. Severe sedation was defined by scores of 0-2 out of 5 total on the Modified Observer’s Alertness/Sedation scale (MOAA/S) scale. On this scale, 0 is a patient response only to painful stimulus, 1 is patient response only after painful stimulus, and 2 is a patient response only after mild prodding or shaking. The majority of patients had onset of sedation within 15-30 minutes after esketamine administration; this peaked around 30-45 minutes and in most cases resolved (MOAA/S score of 5 corresponding to fully awake) by 75 minutes after administration.

Esketamine administration was associated with dissociation. This was described in the clinical program with various terms including feeling “spacey” or a sensation of “floating.” As part of the dissociation, patients experienced visual disturbances, had trouble speaking, and experienced confusion, numbness, and feelings of dizziness/faintness. The sponsor has also stated that dissociation/perceptual changes include distortion of time and space, illusions, derealization, and depersonalization. Resolution of these symptoms generally occurred about 90 minutes after
administration. Similar to the risks with sedation discussed above, patients would be at risk for potential accidents if they experienced these dissociative effects and were allowed to leave the health care setting prior to resolution of these symptoms. In the clinical trials, patients were observed by a healthcare professional after esketamine dosing and did not leave the clinical site until they were clinically stable and symptoms had resolved.

The dissociative sensations experienced in the esketamine program are known effects of ketamine. Ketamine is classified as a Schedule III substance under the Controlled Substances Act. Ketamine is misused and abused for its dissociative and hallucinogenic effects. In the clinical program, esketamine was self-administered under medical supervision in healthcare settings; misuse and abuse were, therefore, not observed. However, the potential for misuse and abuse remains a concern, especially if the distribution of esketamine was not restricted and esketamine was available in retail pharmacies for use outside of a healthcare setting.

Therefore, because of the adverse reactions of sedation and dissociation during the immediate two hours after administration, patients should be monitored to ensure that sedation and dissociation have resolved and should be instructed not to drive or engage in other activities for the remainder of the day.

The Agency is concerned about the increased rate of excessive blood pressure increases (systolic BP ≥ 180 and increase ≥ 20; diastolic BP ≥ 105 and increase ≥ 15) observed in the clinical program (see Table 17). The peak in BP occurred approximately 40 minutes post-dose.

### 8.2. Risk Evaluation and Mitigation Strategy (REMS) Background

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical manufacturers to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A communication plan consists of FDA approved materials used to aid a sponsor’s implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, “Dear Healthcare Professional” letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

**8.3. Applicant’s REMS Proposal**

The Applicant has proposed a REMS with the following goal:

To mitigate the risk of misuse and abuse of esketamine while ensuring patient access for the approved indication, as well as to mitigate the risk of administration without appropriate monitoring as per the product label by:

- Ensuring esketamine is distributed/dispensed only to hospitals, certified outpatient pharmacies, and certified outpatient sites of care,

- Ensuring esketamine is not dispensed to a patient to take home for self-administration,

- Ensuring healthcare facilities are educated about the requirement for patient monitoring for transient dissociation and blood pressure changes after esketamine administration.

To support their proposed REMS, the Applicant plans to certify healthcare settings and outpatient pharmacies that dispense esketamine. They propose to require that the healthcare settings would have procedures in place for a healthcare professional to monitor patients when they self-administer esketamine and that patients would be monitored for transient dissociative and blood pressure changes until the patient is stable and ready to leave the healthcare setting, based on clinical judgment.

The Applicant is also proposing to identify suspicious orders and a timetable for submission of assessments of the REMS.
8.4. Agency Proposed REMS

Should esketamine be approved, the REMS will be necessary to mitigate the risk of misuse and abuse and to prevent harm that could result from the adverse events of dissociation and sedation. At this time, labeling is being developed to address the concerns with elevated blood pressure.

Consistent with study protocols in the clinical program, the current Agency thinking is that to prevent harm such as falls or other accidents resulting from sedation and dissociation, the REMS would require that esketamine be self-administered under direct medical supervision and that patients then be monitored for a minimum of 2 hours post-dose. We are also recommending that after receiving esketamine, patients should not drive or operate heavy machinery for the rest of the day.

FDA is proposing the following REMS components to mitigate the risk of misuse, abuse and serious adverse outcomes from dissociation and sedation as a result of esketamine administration:

1. Elements to assure safe use including:
   - Prescriber training on the risks of esketamine and importance of monitoring patients after their dose is administered and the need to register patients
   - Administration of esketamine only in certain health care settings that ensure patient monitoring by a healthcare provider for two hours after administration
   - Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified to ensure that esketamine is not dispensed directly to patients and that patients are monitored
   - Enrollment of patients who are treated with esketamine in a registry to better characterize the risks associated with esketamine administration and inform risk mitigation strategies

2. An implementation system

3. A timetable for submission of assessments

Administration only in certain healthcare settings
Restricting the distribution of esketamine to certain healthcare settings would ensure that the patient is monitored by a healthcare provider until the sedation and dissociation subside. In the clinical development program, sedation resolved within 2 hours of dosing (with rare exceptions). Thus, it seems reasonable to monitor patients for 2 hours following administration of esketamine (see Section 7.5.1). This would prevent patients from engaging in activities that may be dangerous given these effects. Healthcare settings would also be required to counsel patients to
refrain from driving for the remainder of the day of esketamine administration. To become certified, the healthcare setting must attest that HCPs are available to monitor patients.

**Prescriber Training**
Prescribers would be educated about the risks of esketamine and the importance of monitoring patients after the dose is self-administered. In addition, prescribers would register their patients in the REMS program (see below) and monitor their patients for adverse events.

**Enrollment of Patients in a Registry**
Enrollment of esketamine-treated patients in a registry would allow for the collection of additional data to characterize further the risks of esketamine post-administration. For example, the registry could collect adverse events that occur immediately after administration or between patient visits and provide insight into serious adverse outcomes associated with treatment. This would allow us to capture systematically information on events and potentially provide data that further characterizes adverse outcomes. Information collected from the registry may also be used to evaluate the risk mitigation strategies and determine the need for modification to the REMS or approved labeling.

As part of the enrollment process, patients would be informed of the risks and the need for patients to report adverse events to their provider between patient visits.

In conclusion, the FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. The committee will be asked if the FDA’s proposed REMS will help ensure the safe use of esketamine and what components of this REMS are necessary to ensure that the benefits outweigh the risks.
9. Attachments

9.1. Attachment 1
Pharmacovigilance and Drug Utilization Review

Date: December 21, 2018

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S. Christopher Jones, PharmD, MPH, MS, Director of DPV
DPV II

Product Name: Ketalar (ketamine hydrochloride)

Subject: Adverse Events with Repeated Off-Label Use of Ketamine

Application Type/Number: NDA 016812, ANDA 074524, ANDA 074549, ANDA 076092, NDA 211243

Applicants/Sponsors: Par Sterile, West-Ward Pharmaceuticals, Hospira, Mylan

OSE RCM #: 2018-302
TSI #: 1940 (cognitive impairment) and 1941 (hepatobiliary adverse events)

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**

We acknowledge Mark Avigan, MD, Associate Director for Critical Path Initiatives, for his invaluable clinical expertise on the hepatobiliary adverse events.
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EXECUTIVE SUMMARY

Through routine surveillance of the medical literature, the Division of Pharmacovigilance identified concerns regarding genitourinary, hepatobiliary and cognitive effects associated with off-label, repeated use of ketamine. In this review, we describe our assessment of the FDA Adverse Event Reporting System (FAERS) and the published literature for evidence of such risks. To place these potential risks into context, the Division of Epidemiology evaluated drug utilization data for trends in use of ketamine. This review presents methods and results pertaining to hepatobiliary and cognitive effects and new data on drug utilization. A previously completed memorandum regarding genitourinary effects is referenced within. Key findings from the hepatobiliary and cognitive effects review are summarized below:

- We identified several cases in FAERS and the published literature to support a probable/likely causal relationship between repeated ketamine exposure and the development of a range of hepatobiliary effects in the context of medically-supervised, off-label, repeated use (e.g., cholestasis, periductal fibrosis, elevated transaminases).
- We only identified two cases in FAERS that suggested a possible causal relationship between ketamine exposure and persistent cognitive impairment, although interpretation of these cases is complicated by the presence of confounders.
- We also identified a number of small studies (randomized controlled trials and observational studies) which evaluated short-term effects of ketamine upon memory and other cognitive function, although in these studies, ketamine was not always administered in a repeated fashion, and long-term persistence of these effects was not evaluated in the majority of studies.
- Data from proprietary drug sales distribution and utilization databases suggest increasing administration of ketamine in outpatient clinic settings. The total number of ketamine vials sold from manufacturers to all channels of distribution increased in the 5 years examined to approximately 2.1 million vials in 2017 from 1.2 million in 2013. The increase was more notable in the clinic setting, where the number of vials sold more than doubled in the past 5 years from an estimated 332,000 vials sold in 2013 to 765,500 vials sold in 2017. These findings suggest increased use of ketamine in recent years although the reasons and potential factors that may have contributed to increased use were not formally studied in this review.

Given these findings, we recommend updating ketamine product labels (Warnings) to include the potential for hepatobiliary adverse effects. In addition, we recommend consideration for updating ketamine product labels (Adverse Reactions) to include that ketamine may be associated with short-term cognitive impairment at subanesthetic doses, although the long-term cognitive effects of repeated exposure to ketamine are not well understood.
1 INTRODUCTION

The purpose of this review was to evaluate risks associated with the off-label, repeated use of ketamine. Ketamine is a schedule III agent, originally approved by the Food and Drug Administration (FDA) in 1970 for use as a dissociative anesthetic. Since the time of its approval, numerous off-label uses of ketamine have been proposed and implemented, including, but not limited to, treatment of complex-regional pain syndrome (CRPS), chronic pain, and treatment resistant depression. Emerging guidelines describing protocols for off-label use of ketamine provide some standardization, though such guidelines are neither based upon strong evidence nor strictly implemented.

Although few data are available regarding trends or patterns in off-label use of ketamine, one recently published survey of physicians advertising ketamine therapy for treatment of psychiatric disorders provides some insight, albeit with limited generalizability given the small size and sampling strategy. In this study, 85 clinicians were identified through the internet or by prior relationships with the author team, 76 were emailed a survey, and 57 clinicians responded (75% response rate). Among respondents, the number of clinicians offering such therapy increased over time, with the greatest change apparently occurring during the years 2015-2016 (Figure 1). Of the clinicians surveyed, the majority of clinicians worked in a private practice setting (73%), with a smaller proportion working in academia (14%) or a health maintenance organization (9%). Clinician specialties included Psychiatry (67%) Anesthesiology (23%), Emergency Medicine (4%) and Family Medicine (4%). The majority of clinicians surveyed administered ketamine in an office-based setting (72%) with the remainder offering treatment in a hospital-based setting or surgical/procedural suite. Clinicians reported administering ketamine primarily via the intravenous route (88%), followed by oral (23%) and intranasal routes (19%). Commonly treated psychiatric conditions included major depressive disorder (72%), bipolar disorder (15%) and post-traumatic stress disorder (6%). Respondents reported repeated administration of ketamine, ranging from every 2 weeks (12%) to monthly (30%), and over two-thirds (64%) reported receiving out-of-pocket reimbursement for treatment sessions.

Figure 1. Number of providers offering ketamine treatment for psychiatric disorders (2005-2016)

Seminal studies have suggested that for carefully selected patients, ketamine use may offer some benefits with repeated use, though such benefits are short-term. For instance, in one small (n=18) randomized, placebo-controlled clinical trial led by Zarate et al., the majority of patients with treatment resistant major depression who received intravenous ketamine demonstrated significant improvement in depression scores one day after treatment. However, only 6 out of 17 patients who received ketamine maintained a response at 1 week, and only 2 patients maintained a response at 2 weeks. In another blinded study led by Sigtermans et al., 60 patients with CRPS type I were randomized to receipt of ketamine or placebo, study findings demonstrated pain scores were significantly lower in the treatment group than in the placebo group, though this difference was no longer significant at 12 weeks. Findings from such studies as well as anecdotes from clinical practice suggest that repeat dosing of ketamine, possibly at increasing doses as drug tolerance develops, may be required to sustain a treatment response for chronic comorbidities such as pain or depression.

Recently, experts in clinical practice have voiced concern that unapproved uses of ketamine pose under-recognized risks to patients, particularly those receiving repeated exposure, with proposed risks including genitourinary, hepatobiliary and cognitive adverse effects. Analagous effects have been observed among patients abusing ketamine, with several case reports or case series describing a range of genitourinary and hepatobiliary effects associated with ketamine exposure in ketamine abusers, and some data suggesting cognitive impairment, though with fewer data on chronic than acute cognitive impairment. Risks to patients receiving ketamine repeatedly, or over prolonged periods, in the context of medical supervision at doses less than those presumably used by abuse populations, have not been as well characterized.

The Division of Pharmacovigilance (DPV), the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), and the Division of Psychiatric Products (DPP) met on December 19, 2017 and May 16, 2018 to discuss potential safety signals identified by DPV through routine surveillance of the literature. Based upon preliminary data presented by DPV, including discussion of select FAERS cases and literature reports, DPV, DAAAP and DPP made a joint decision to assess the risk of genitourinary (GU), hepatobiliary and cognitive adverse events with repeated exposure to ketamine in medically supervised settings (i.e., non-abuse). In addition, DPV consulted the Division of Epidemiology II (DEPI II, Drug Utilization) to assess recent patterns in use of ketamine, with an emphasis on use in outpatient settings where much of the off-label ketamine administration is presumed to occur.

As requested by DAAAP, DPV prioritized the review of GU adverse effects and completed the review in an expedited memorandum; our recommendation to incorporate GU adverse effects into the ketamine labeling has been endorsed by DAAAP. We also note that DPV previously completed a review relating to delayed onset/prolonged duration neuropsychiatric events occurring in the context of both on and off-label medically supervised ketamine administration and recommended labeling changes. However, for the purpose of this review, we focus on presentation of methods and results relating to potential hepatobiliary or cognitive adverse events and data relating to ketamine drug utilization.
1.1 **REGULATORY HISTORY**

Ketamine was approved for use in the United States in 1970 and is currently indicated for use as 1) the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, 2) the induction of anesthesia prior to the administration of other general anesthetic agents, and 3) as a supplement to low-potency anesthetic agents, such as nitrous oxide.\(^{22}\)

As noted above, DPV has previously completed two safety assessments relating to ketamine which are briefly summarized below:

- **September 2014: Ketamine and Delayed or Prolonged Psychiatric Reactions\(^{20}\)**
  - DAAAP consulted DPV to assess prolonged duration or delayed-onset psychiatric adverse events occurring with ketamine, after two published case reports described delayed onset suicidal ideation with ketamine administration for treatment of obsessive-compulsive disorder.
  - DPV’s safety review focused on all medically-supervised administration of ketamine, with specific examination of events occurring within 3 hours of ketamine administration, lasting for at least 3 hours OR events developing at least 3 hours after completion of ketamine administration.
  - DPV identified cases for which the duration of psychiatric reactions following ketamine exposure ranged from 3 hours to several weeks, and time to onset ranging from immediate to several weeks.
  - DPV recommended revision of labeling language in existing “Special Note” (though ideally in Warnings/Precautions of PLR format) to state that adverse psychiatric events have emerged or persisted days to weeks following ketamine exposure (including beyond the 24 hours that is currently described in product labeling).

- **July, 2018: Repeated/Prolonged Use of Ketamine and Risk of GU Events\(^{21}\)**
  - DPV conducted a self-generated safety assessment based upon routine surveillance of the literature.
  - DPV’s memorandum focused on patients receiving medically supervised, off-label use of ketamine, repeatedly, for the treatment of such conditions as chronic pain.
  - DPV recommended inclusion of risk for genitourinary events (e.g., cystitis) (ideally in Warnings/Precautions of PLR format)
  - The most recent label (8/7/2018) now includes the following language in “Adverse Reactions” though labeling remains in non-Physician Labeling Rule (PLR) format.\(^1\)

  *Genitourinary: In individuals with history of chronic ketamine use or abuse, lower urinary tract and bladder symptoms including dysuria, increased urinary frequency, urgency, urge incontinence, and hematuria have been reported (see DOSAGE AND ADMINISTRATION Section). In addition, diagnostic studies performed to assess the cause of these symptoms have reported cystitis (including
cystitis noninfective, cystitis interstitial, cystitis ulcerative, cystitis erosive and cystitis hemorrhagic) as well as hydronephrosis and reduced bladder capacity.

1.2 PRODUCT LABELING: AUGUST 7, 2018

The current label\(^1\)\(^,\)\(^2\) for KETALAR does not contain language regarding hepatobiliary or cognitive adverse effects. The label for Ketalar is currently under the non-PLR format.

**Warnings**

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Postoperative confusional states may occur during the recovery period.

Respiratory depression may occur with overdosage or too rapid a rate of administration of KETALAR, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

**Adverse Reactions**

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of KETALAR alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of KETALAR. Laryngospasms and other forms of airway obstruction have occurred during KETALAR anesthesia.

Eye: Diplopia and nystagmus have been noted following KETALAR administration. It also may cause a slight elevation in intraocular pressure measurement.

Genitourinary: In individuals with history of chronic ketamine use or abuse, lower urinary tract and bladder symptoms including dysuria, increased urinary frequency, urgency, urge incontinence, and hematuria have been reported (see DOSAGE AND ADMINISTRATION Section). In addition, diagnostic studies performed to assess the cause of these symptoms have reported cystitis (including cystitis noninfective, cystitis interstitial, cystitis ulcerative, cystitis erosive and cystitis hemorrhagic) as well as hydronephrosis and reduced bladder capacity.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see DOSAGE AND ADMINISTRATION Section).
Gastrointestinal: Anorexia, nausea and vomiting have been observed; however, this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see DOSAGE AND ADMINISTRATION Section).

General: Anaphylaxis. Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

**Drug abuse and dependence**

Ketamine has been reported being used as a drug of abuse.

Reports suggest that ketamine produces a variety of symptoms including, but not limited to anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes.

Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. Therefore, ketamine should be prescribed and administered with caution.

**SPECIAL NOTE**

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY IS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY AND THE INCIDENCE IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETALAR IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See DOSAGE AND ADMINISTRATION Section). ALSO, THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS.

IN ORDER TO TERMINATE A SEVERE EMERGENCE REACTION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA SHORT-ACTING BARBITURATE MAY BE REQUIRED.
WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

2 METHODS AND MATERIALS

For this review, we used a number of data sources: IQVIA, National Sales Perspectives™ (NSP), reports submitted through the FDA Adverse Event Reporting System (FAERS) and published case reports in the literature. The databases used are described briefly below, with more detail included in Appendices A-B.

2.1 DRUG UTILIZATION

IQVIA, National Sales Perspectives™ (NSP)
The NSP database was used to provide the nationally estimated number of vials sold for injectable ketamine from the manufacturer to all U.S. channels of distribution1 from 2013 through 2017. The sales distribution data represent the amount of product sold from manufacturers to various settings of care and does not reflect what is being sold to or administered to patients directly. The amount of product purchased by various settings of care may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel
This U.S. office-based physician survey database, was used to obtain groups of diagnoses associated with the use of ketamine in 2017 as reported by a sample of approximately 3,200 office-based physicians. Diagnoses data by number of drug use mentions2 were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence were applied to the estimates. Indications for the use of ketamine in the hospitals, clinics, and other settings were not available for this review.

2.2 FAERS/LITERATURE: CASE DEFINITION AND SIGNAL-SPECIFIC SEARCH STRATEGIES

We selected reports submitted through FAERS or published in the literature for inclusion in the review if they met all elements of the case definition constructed by the review team. The case definition below was applied to resulting reports to select relevant cases.

Case Definition

1 Various channels of distribution include retail (i.e., independent and chain pharmacies), non-retail (i.e. non-federal hospitals, federal facilities, clinics, long-term care), and mail-order (i.e., standard and specialty mail).

2 A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
Inclusion criteria:
Cases were included for review if hepatobiliary, or cognitive adverse events were reported in association with prolonged/repeated, off-label, prescribed, therapeutic ketamine exposure.

- Hepatobiliary events considered included events ranging from asymptomatic elevation in liver enzymes to irreversible structural damage to the liver or biliary system and/or clinical signs of liver failure.
- Our definition of cognitive events included events related to any aspect of cognitive functioning, including memory, language, attention and other mental processing capabilities—events that were described as primarily psychiatric in nature such as psychosis, hallucination or mania were not included in the definition for the purposes of this review and were addressed in a previous review by DPV.10

Exclusion criteria:
- Reports of abuse, misuse, and overdose with ketamine and in persons who had a past medical history of abuse and misuse of other pharmaceutical medications or illicit substances
- Ketamine administration for labeled indications including anesthesia for diagnostic and surgical procedures that do not require skeletal muscle relaxation and for the induction of anesthesia prior to the administration of other general anesthetic agents.
- The presence of the same symptoms as reported preceding the initiation of ketamine.

We then assessed cases meeting the inclusion and exclusion criteria for causality using the modified World Health Organization—Uppsala Monitoring Center (WHO-UMC) causality assessment (see Appendix D). Cases that were assessed as “unassessable” or “unlikely” to be related to ketamine were excluded from further review.

DPV signal-specific FAERS and literature search strategies to identify reports for potential events of interest are described below.

Observational studies and randomized controlled trials were also included if they evaluated or reported the signals of interest in the context of off-label, medically-supervised ketamine administration at subanesthetic doses.
### 2.2.1 Hepatobiliary Events

<table>
<thead>
<tr>
<th><strong>Table 1. FAERS Search Strategy</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Search</strong></td>
<td>May 2, 2018</td>
</tr>
<tr>
<td><strong>Time Period of Search</strong></td>
<td>All reports through April 30, 2018</td>
</tr>
<tr>
<td><strong>Search Type</strong></td>
<td>FBIS Quick Query</td>
</tr>
<tr>
<td><strong>Product Terms</strong></td>
<td>Product Active Ingredients: Norketamine, Ketamine Hydrochloride, N-ethylhorketamine, Esketamine, Ketamine, Esketamine Hydrochloride, Deschlorketamine</td>
</tr>
<tr>
<td><strong>MedDRA Search Terms</strong></td>
<td><strong>SMQ:</strong></td>
</tr>
<tr>
<td><strong>(Version 20.1)</strong></td>
<td>• Biliary Disorders (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Biliary Malignant Tumours</td>
</tr>
<tr>
<td></td>
<td>• Biliary Neoplasms</td>
</tr>
<tr>
<td></td>
<td>• Biliary Neoplasms Benign (Incl Cysts and Polyps)</td>
</tr>
<tr>
<td></td>
<td>• Biliary Neoplasms Malignant and Unspecified</td>
</tr>
<tr>
<td></td>
<td>• Biliary System Related Investigations, Signs and Symptoms (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Biliary Tract Disorders</td>
</tr>
<tr>
<td></td>
<td>• Biliary Tumours Of Unspecified Malignancy</td>
</tr>
<tr>
<td></td>
<td>• Cholestasis and Jaundice of Hepatic Origin (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Congenital Biliary Disorders</td>
</tr>
<tr>
<td></td>
<td>• Congenital, Familial, Neonatal and Genetic Disorders Of The Liver (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Drug Related Hepatic Disorders - Comprehensive Search (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Drug Related Hepatic Disorders - Severe Events Only (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Functional, Inflammatory and Gallstone Related Biliary Disorders (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Gallbladder Related Disorders</td>
</tr>
<tr>
<td></td>
<td>• Gallstone Related Disorders</td>
</tr>
<tr>
<td></td>
<td>• Hepatic Disorders Specifically Reported as Alcohol-Related</td>
</tr>
<tr>
<td></td>
<td>• Hepatic Failure, Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Infectious Biliary Disorders</td>
</tr>
<tr>
<td></td>
<td>• Liver Infections (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Liver Malignant Tumours (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Liver Neoplasms, Benign (Incl Cysts and Polyps)</td>
</tr>
<tr>
<td></td>
<td>• Liver Neoplasms, Malignant and Unspecified (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Liver Related Investigations, Signs and Symptoms (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Liver Tumours Of Unspecified Malignancy</td>
</tr>
<tr>
<td></td>
<td>• Liver-Related Coagulation and Bleeding Disturbances</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy, Labour And Delivery Complications and Risk Factors (Excl Abortions and Stillbirth) (Broad)</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy-Related Hepatic Disorders</td>
</tr>
<tr>
<td><strong>SOC:</strong></td>
<td>Hepatobiliary Disorders</td>
</tr>
<tr>
<td><strong>HLGT:</strong></td>
<td>Hepatic and Biliary Neoplasms Benign</td>
</tr>
<tr>
<td><strong>Verbatim:</strong></td>
<td><em>DILIN</em>, <em>ALFSG</em></td>
</tr>
</tbody>
</table>

* See Appendix C for a description of the FAERS database.
Table 2. Literature Search Strategy

<table>
<thead>
<tr>
<th>Date of Search 1</th>
<th>July 13, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database</td>
<td>PubMed@FDA</td>
</tr>
<tr>
<td>Search Terms</td>
<td>ketamine[tiab] and (biliary OR cholestasis OR hepatic OR hepatobiliary OR cholangitis OR hepatitis OR cholangiopathy)</td>
</tr>
<tr>
<td>Date of Search 2</td>
<td>July 16, 2018</td>
</tr>
<tr>
<td>Database</td>
<td>Embase</td>
</tr>
<tr>
<td>Search Terms</td>
<td>'ketamine'/exp AND ('hepatobiliary system'/exp OR 'biliary tract disease'/exp OR 'hyperbilirubinemia'/exp OR 'cholestasis'/exp OR 'obstructive jaundice'/exp OR 'intrahepatic cholestasis'/exp OR 'liver disease'/exp OR 'sclerosing cholangitis'/exp OR 'hepatitis'/exp OR 'toxic hepatitis'/exp OR 'bile duct disease'/exp)</td>
</tr>
<tr>
<td>Years Included in Search 1 and 2</td>
<td>All</td>
</tr>
</tbody>
</table>

*In addition to the search strategy above, we mined references from identified reports.

2.2.2 Cognitive Events

Table 3. FAERS Search Strategy*

<table>
<thead>
<tr>
<th>Date of Search</th>
<th>8/1/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period of Search</td>
<td>All dates through 8/1/2018</td>
</tr>
<tr>
<td>Search Type</td>
<td>Mercado Quick Search</td>
</tr>
<tr>
<td>Product Terms (Product Active Ingredient)</td>
<td>Esketamine, Deschloroketamine, Esketamine Hydrochloride, Ketamine, Ketamine Hydrochloride, Norketamine, N-Ethynorketamine</td>
</tr>
<tr>
<td>MedDRA Search Terms (Version 21.0)</td>
<td>High Level Group Term (HLGT): Cognitive and attention disorders and disturbances, Communication disorders and disturbances, Dementia and amnestic conditions, Disturbances in thinking and perception</td>
</tr>
</tbody>
</table>

*See Appendix C for a description of the FAERS database.

Table 4. Literature Search Strategy

<table>
<thead>
<tr>
<th>Date of Search 1</th>
<th>July 30, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database</td>
<td>PubMed</td>
</tr>
<tr>
<td>Search Terms</td>
<td>ketamine[tiab] AND &quot;cognitive function&quot;[tiab]</td>
</tr>
<tr>
<td>Years Included in Search</td>
<td>All</td>
</tr>
<tr>
<td>Date of Search 2</td>
<td>July 30, 2018*</td>
</tr>
<tr>
<td>Database</td>
<td>Google Scholar†</td>
</tr>
<tr>
<td>Search Terms</td>
<td>cognitive effects of ketamine</td>
</tr>
<tr>
<td>Years Included in Search</td>
<td>All</td>
</tr>
</tbody>
</table>

*Reviewed titles and/or abstract from 500 most relevant articles, as ranked by search tool
†Embase was initially searched but failed to capture key articles that the safety reviewer was aware of
3 RESULTS

3.1 DRUG UTILIZATION

3.1.1 Sales and Distribution Data

Figure 2 below displays the nationally estimated number of ketamine vials sold from manufacturers to various channels of distribution, from 2013 through 2017, annually. The estimated total number of ketamine vials sold increased approximately 72%, from 1.2 million vials in 2013 to 2.1 million vials in 2017.

In 2017, the largest proportion of ketamine vials were sold primarily to non-federal hospitals at approximately 54%, followed by 37% and 9% of vials sold to clinics and all other channels, respectively. Although manufacturer sales of ketamine to all channels of distribution increased; the increase was most notable in the clinic settings, where the number of vials sold more than doubled in the past 5 years from an estimated 332,000 vials sold in 2013 to 765,500 vials sold in 2017. The reasons and potential factors that may have contributed to increased use over the examined time were not formally studied in this review.

Figure 2

Nationally estimated number of ketamine vials sold from manufacturers, stratified by channels of distribution


† Clinics include but are not limited to dialysis, family planning, x-ray, oncology, emergicenters, and surgicenters. Veterinary clinics not included.

†† All other channels include but are not limited to federal facilities, long-term care, mail-order, and chain/independent pharmacies.
3.1.2 Diagnosis data: U.S. office-based physician survey data

National estimates of use based on the number of drug use mentions in office-based physician surveys was assessed to provide insight into diagnoses (ICD-10 codes) associated with the utilization of ketamine. A very low number of reports for ketamine were captured in this datasource for 2017. The only reported diagnoses mentioned in association with ketamine were for “unspecified soft tissue disorders”, “malignant neoplasm of bronchus and lung”, “open wound of elbow and forearm”, “headaches”, and “gangrene”. However, the results of office-based physician survey data were too low to derive reliable estimates of ketamine use likely due to minimal utilization in this setting of care. Although these data are not representative or generalizable across other settings of care where ketamine may be used (e.g., hospitals and clinics), the findings are reflective of the sales distribution patterns that suggest that the majority of use is largely in hospital and clinic settings.

3.2 FAERS and Medical Literature

3.2.1 Hepatobiliary Events

3.2.1.1 FAERS Case Selection

The FAERS search retrieved 395 reports. After applying the case definition in Section 2.2, we excluded duplicate reports (n=143), reports not meeting the case definition (n=213), and those that were unassessable per WHO causality assessment (n = 28), leaving a total of 11 FAERS cases in the case series of hepatobiliary events with ketamine use. Reports that did not meet the case definition were excluded for the following reasons: abuse (n=136), anesthesia/single dose/single day of therapy (n=56), not a hepatobiliary event (n=10), time to onset preceded ketamine use (n=8), and overdose (n=3).

3.2.1.2 Literature Case Selection

A total of 252 published articles or reports were identified with the first search strategy described above (Section 2.2.2, Table 4). Of these, three articles met the case definition criteria. A total of 1,256 reports were identified with the second search strategy, of which two additional articles meeting the case definition were identified. Mining references from the selected articles identified one additional article. A total of 6 published literature articles or abstracts were thus identified. From these articles, some of which included multiple reports meeting case definition criteria, a total of 12 reports met the case definition, of which 3 were also retrieved in the FAERS database search. Thus, a total of 9 reports, in addition to the FAERS cases, were relevant to this review.

Tables 6-9 summarize the 20 FAERS and literature cases of hepatobiliary events reported with ketamine for this case series.

Appendix B contains a line listing of all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 11 FAERS cases and a line listing of the 9 literature cases in this case series.
Table 6. Descriptive Characteristics of Cases Reporting Hepatobiliary Events with Ketamine in FAERS and the Published Medical Literature, Received by FDA or Published, All Dates through April 30, 2018 (FAERS) or July 30, 2018 (Literature) (N= 20)

<table>
<thead>
<tr>
<th>Case Source*</th>
<th>(11^\dagger)</th>
<th>9</th>
</tr>
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<tbody>
<tr>
<td>FAERS</td>
<td>11†</td>
<td>9</td>
</tr>
<tr>
<td>Literature</td>
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</table>

<table>
<thead>
<tr>
<th>Year Received by FDA (Initial) or Published</th>
<th>(\text{#}^\dagger)</th>
<th>(\text{#}^\ddagger)</th>
<th>(\text{#}^\dagger\ddagger)</th>
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<tbody>
<tr>
<td>1995</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2002 – 2004</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2010 – 2012</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2014 – 2017</td>
<td>6</td>
<td>6</td>
<td>6</td>
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</table>

<table>
<thead>
<tr>
<th>Sex:</th>
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<th></th>
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<tbody>
<tr>
<td>Female</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age: (yrs)</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
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<tr>
<td></td>
<td>54</td>
<td>48</td>
<td>33-72</td>
<td></td>
</tr>
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<table>
<thead>
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<tr>
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<td></td>
</tr>
<tr>
<td>Direct</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Literature only</td>
<td>9</td>
<td></td>
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<table>
<thead>
<tr>
<th>Country</th>
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<tbody>
<tr>
<td>Foreign</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Domestic</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

| Serious Regulatory Outcomes $\&. || | |
|-----------------------------------|-----|-----|
| Death                             | 1†  | |
| Hospitalization                   | 6   | |
| Other Serious                     | 4   | |
| Not Reported (literature reports) | 9   | |
| Not Serious                       | 1   | |

* Case Source - ‘FAERS’ includes any case identified in either FAERS alone or in both FAERS and the literature and ‘Literature’ includes cases only identified in the literature.
† 3 of the FAERS cases were also found in the literature (FAERS Case numbers 10398893, \(11968665, 24, 25\) and 14227949\(26\)).
‡ The one direct report was submitted by the Drug Induced Liver Injury Network (DILIN).
§ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.
|| A case may have more than one serious outcome.
† This case met our case definition for hepatobiliary event, but the patient likely died due his underlying esophageal cancer.
Table 7. Descriptive Characteristics of Ketamine Route of Administration, Reasons for Use, Risk Factors, and Time to Onset of Hepatobiliary Events with Ketamine in FAERS and the Published Medical Literature, Received by FDA or Published, All Dates through April 30, 2018 (FAERS) or July 30, 2018 (Literature) (N= 20)

<table>
<thead>
<tr>
<th>Ketamine Route</th>
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<tbody>
<tr>
<td>Parenteral*</td>
<td>16</td>
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<tr>
<td>Oral</td>
<td>3</td>
</tr>
<tr>
<td>Not Reported</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Reason for Ketamine Use</th>
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</thead>
<tbody>
<tr>
<td>Complex regional pain syndrome</td>
<td>11</td>
</tr>
<tr>
<td>Pain †</td>
<td>4</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>2</td>
</tr>
<tr>
<td>Chronic migraines</td>
<td>1</td>
</tr>
<tr>
<td>Palliative care</td>
<td>1</td>
</tr>
<tr>
<td>Fibromyositis</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th># of Reported Risk Factors ‡ for hepatobiliary event</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0 risk factors</td>
<td></td>
</tr>
<tr>
<td>1 risk factor</td>
<td>7</td>
</tr>
<tr>
<td>2 risk factors</td>
<td>3</td>
</tr>
<tr>
<td>Not Reported</td>
<td>7</td>
</tr>
</tbody>
</table>

* Parenteral route includes: infusion not otherwise specified (NOS), injection NOS, IV infusion, SC, or SC infusion.
† Pain included chronic facial pain, pain not otherwise specified, phantom limb pain, or sciatic pain.
‡ Risk factors for hepatobiliary events evaluated included: viral hepatitis A, B, C, or E, cytomegalovirus, Epstein Barr Virus, preexisting or autoimmune hepatitis, history of alcoholism, use of one or more concomitant drugs with a NIH Liver Tox Likelihood score of A, B, or C (See Appendix F), past medical history of biliary disease including, but not limited to gallstones, cholecystitis, gallbladder disease unspecified, and cholangitis.
¶ We classified cases documenting negative pertinent history for risk factors as reporting no risk factors.
Table 8 details the reported time to onset and correlating cycle for each hepatobiliary event. There were a total of 28 hepatobiliary events that occurred among the 20 cases (two cases reporting two events each and three cases experiencing three events each). A cumulative list for time to onset for each event is documented in the far right column. Time to onset following the administration of ketamine was reported for 18 of the 28 events (64%). The majority of the events (61%) with a reported time to onset occurred within 4 days following ketamine.

A cumulative list for the cycle for each event is documented in the bottom row of table 8. Sixteen events (within 12 unique cases) reported the details of the cycle number (57%). The majority of the events (75%) with a reported cycle occurred following cycle 1 or cycle 2; however, this likely indicates that once the event occurred, the ketamine was not resumed. The term “cycle” may be a bit nebulous, as each cycle is defined by the individual patient ketamine regimen, and is not standardized, though we provide this descriptive data for awareness.

| Table 8. Time to Onset of Hepatobiliary Event by Ketamine Treatment Cycle Number* (n= 28) |
|-----------------------------------------|-----|-----|-----|-----|---------------------|---------------------|
|                                        | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 Not Reported† | Total Events per Time to Onset |
| 6 hours                                | 0      | 1     | 0      | 0      | 0                  | 1                      |
| 1 day                                  | 0      | 0     | 0      | 0      | 0                  | 1                      |
| 2 – 4 days                              | 2      | 0     | 0      | 0      | 0                  | 9                      |
| 1 – 2 weeks                             | 0      | 0     | 0      | 0      | 0                  | 3                      |
| Less than 30 days                      | 0      | 0     | 0      | 0      | 0                  | 1                      |
| 1 – 2 months                            | 0      | 0     | 0      | 0      | 0                  | 1                      |
| + 4 years                               | 0      | 0     | 0      | 0      | 0                  | 1                      |
| 10 years                                | 0      | 0     | 0      | 0      | 0                  | 1                      |
| Total Time to Onset Not Reported        | 0      | 1     | 0      | 0      | 0                  | 8                      |
| Total Events per Cycle                  | 5      | 7     | 2      | 1      | 12                 | 28‡                    |

* Patients may have experienced the event following more than one cycle in positive rechallenges.
† Cycle may not have been reported for patients on repeated oral doses, as well in other cases where cycle number was not specified.
‡ There was a total of 28 events among the 20 cases in our case series, with 2 cases reporting 2 events each and three patients experiencing three events each.
### Table 9. Descriptive Characteristics of Hepatobiliary Events, Dechallenge and Rechallenge Information, Causality and Outcome with Ketamine in FAERS and the Published Medical Literature, Received by FDA or Published, All Dates through April 30, 2018 (FAERS) or July 30, 2018 (Literature) (N= 20)

<table>
<thead>
<tr>
<th>Characteristics of Hepatobiliary Event*</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ALT/SGPT</td>
<td>10</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>9</td>
</tr>
<tr>
<td>Unspecified liver enzymes increased</td>
<td>8</td>
</tr>
<tr>
<td>Increased AST/SGOT</td>
<td>9</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>8</td>
</tr>
<tr>
<td>Elevated bilirubin levels</td>
<td>3</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>2</td>
</tr>
<tr>
<td>Biliary dilation</td>
<td>2</td>
</tr>
<tr>
<td>Jaundice</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified liver disorder</td>
<td>1</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic cytolysis</td>
<td>1</td>
</tr>
<tr>
<td>Intrahepatic cholestasis</td>
<td>1</td>
</tr>
<tr>
<td>Cholangiopathy</td>
<td>1</td>
</tr>
<tr>
<td>Pericholeductal fibrosis</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dechallenge/Rechallenge Information Reports (number of patients)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rechallenge Positive†</td>
<td>9  (5)</td>
</tr>
<tr>
<td>Dechallenge Positive</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Dechallenge Negative</td>
<td>1  (1)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1  (1)</td>
</tr>
<tr>
<td>Ketamine continued</td>
<td>1  (1)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>1  (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO-UMC Causality Category</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
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<td>10</td>
</tr>
<tr>
<td>Possible</td>
<td>10</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered/Resolved</td>
<td>10</td>
</tr>
<tr>
<td>Recovering/Resolving</td>
<td>4</td>
</tr>
<tr>
<td>Not Recovered/Not Resolved</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Fatal</td>
<td>1†</td>
</tr>
</tbody>
</table>

*Cases may include more than one characteristic describing the hepatobiliary event.
† There was a total of 9 positive rechallenges among 5 patients.
‡ This case met our case definition for hepatobiliary event, but the patient likely died due his underlying esophageal cancer.
We highlight the following cases of hepatobiliary events that occurred in patients exposed to repeated, unapproved indications of ketamine that were not otherwise published in the medical literature.

- **FAERS Case # 8341142 (DILIN Case 109-0030):** A 51-year-old female with a history of Reflex Sympathetic Dystrophy (RSD) experienced elevated liver enzymes following ketamine infusions on at least three occasions. In the most recent infusion, the ALT was >5 x the upper limit of normal (ULN). The next set of labs drawn approximately one month after the date of onset had decreased below the Drug-Induced Liver Injury Network (DILIN) Prospective Study laboratory entry criteria. The entry criteria was defined as elevations in ALT or AST > 5 x baseline values times two consecutive occasions. An exemption was requested and granted and the patient was enrolled in the study. The patient had a past medical history of abnormal liver enzyme tests detected during treatment for hyperlipidemia. Following ketamine infusions, the patient experienced a pattern of "spiking" liver enzymes increasing from normal levels to several fold elevations documented on three separate occurrences in which liver enzymes reached peak elevations within 1-2 weeks. In September 2010 following the administration of ketamine, the ALT jumped from 9 to 283, and the AST from 15 to 94. Liver enzymes were normal in August 2010 prior to the ketamine infusion. The patient had a past medical history of negative serologies documented in 2005 and 2006 for antimitochondrial antibodies (AMA), antinuclear antibodies (ANA), smooth muscle antibodies (SMA), hepatitis B surface antigen (HBsAg), hepatitis A virus (HAV) total and immune globulin antibody (IgM), hepatitis C virus (HCV) antibody, Eptstein-Barr virus (EBV), and normal ceruloplasmin. AST (36) and ALT (45) were mildly elevated at the time of the 6 month follow-up visit in 2011.

**Reviewer comments:**

This directly submitted domestic FAERS case (submitted by the Drug Induced Liver Injury Network) supports a probable relationship between hepatobiliary events in a patient receiving ketamine for CRPS for elevations in ALT and AST. We note that the patient had no history of chronic liver disease, no liver transplant, occasional alcohol use and negative serologies for AMA, ANA, SMA, HBsAg, total and IgM, HAV antibody, EBV, and normal ceruloplasmin. There were no concomitant medications listed for this patient. The patient experienced two positive rechallenges one to two weeks following the administration of ketamine infusions in which there was a pattern of "spiking" enzymes (of ALT and AST) from normal levels to several fold elevations. We acknowledge and do not know the reason why the patient had several years pass between the second and third reported dose of ketamine.

**WHO causality assessment- probable**

- **FAERS Case # 10740815:** This spontaneous report from a non-clinical-study program, Pfizer Rx Pathways, is for a 49-year-old female patient with a history of reflex sympathetic dystrophy receiving ketamine infusions every month since 2008, and prior to 2008, every other month starting in 2007. She took a break from the infusions for about one year, due to an increase in liver enzymes in 2012. Ketamine infusions were restarted in 2014 for which she was hospitalized to receive a five day infusion. Ketamine was
infused into her port “every other month 2 days 5 hrs” [sic], but ketamine was stopped 'waiting for enzymes to drop which happen before they stopped ketamine for a while then they resume it.' Patient reported “I took ketamine for approx. 4 years. Ketamine is tough on liver so they stopped it. Now it is up again but not a whole lot but they want me to take a break for 3 months and test me to see if they resume it.” The patient was started on pregabalin to cover her pain while the healthcare providers were “waiting for enzymes to drop.” The patient was having trouble covering her costs of pregabalin therapy. Additional past medical history included hypothyroidism, ongoing acid reflux, thoracic outlet syndrome, ongoing asthma, and multiple shoulder surgeries. Concomitant medications included pregabalin, duloxetine hydrochloride, citalopram, omeprazole, levothyroxine, trazodone, and montelukast sodium. The patient was started on pregabalin to cover her pain while the healthcare providers were ‘waiting for enzymes to drop.’

**Reviewer comments:**
This expedited domestic FAERS case supports a possible relationship between hepatobiliary events in a patient receiving ketamine for complex regional pain syndrome for elevations in unspecified liver enzymes. We note that although general past medical history and concomitant medications were addressed, risks factors for and a history of hepatobiliary health was not addressed including viral etiologies, alcohol status, and other liver diseases. Of the reported concomitant medications, the National Institutes of Health has categorized omeprazole as liver tox B, duloxetine as liver tox B, and citalopram as liver tox C. (See Appendix F for NIH Likelihood LiverTox Categories). Despite the use of concomitant drugs that may be associated with liver toxicity, there is a strong temporal relationship to the use of ketamine and the onset of elevation in liver enzymes. The patient experienced at least one positive rechallenge following the repeat administration of ketamine for which it had been put on hold due to an increase in liver enzymes.

**WHO causality assessment- possible**

**Literature**

Case characteristics from the 12 identified literature case reports, of which 3 were also retrieved in the FAERS database search, are summarized together with other cases identified through FAERS in Tables 6,7,8 above. Narrative detail on select literature cases is also provided below.


This US based published abstract reports a case of a 58-year-old female who received a multi-day ketamine infusion (dose/rate not specified) with largely normal liver enzymes at baseline (total bilirubin 0.2 mg/dL, AST 20 IU/L, ALT 17 IU/L, alkaline phosphatase 111 IU/L), rise in liver enzymes one day following initiation of the ketamine infusion, and peak in ketamine on the third day following initiation of ketamine (total bilirubin 1.0 mg/dL, direct bilirubin 0.4 mg/dL, AST 721 IU/L, ALT 1034 IU/L, alkaline phosphatase 289 IU/L). Abdominal ultrasound revealed gallstones without gallbladder thickening and
a mildly dilated common bile duct without choledocholithiasis as well as mild hepatic steatosis. Liver function studies began declining one day following discontinuation of ketamine infusion. Similar elevation in liver function studies occurred during next two admissions with rise in liver function studies following ketamine initiation, with decline following discontinuation of ketamine. (See Appendix E for graph of Dechallenge Rechallenge Information with Ketamine Infusions and ALP, AST, ALT, and T.bili levels).

**Reviewer comments:**

The pattern of injury here appears to be slightly more hepatocellular than cholestatic. Bilirubin levels are normal suggesting no extrahepatic obstruction (i.e., choledocholithiasis). Though occult gallstones may be suggested by ultrasound findings, lack of bilirubin elevation is not supportive, and cannot explain why liver enzymes decline consistently following discontinuation of ketamine in three separate hospital admissions. The infusion dose was not specified in this case. The history appears consistent with a diagnosis of drug-induced hepatitis.

**WHO causality assessment—probable**


This was a pilot study evaluating the effect of two 5-day intravenous ketamine infusions on pain relief in CRPS type 1 patients, with a 16-day ketamine-free interval separating treatment sessions. Of the six patients randomized to the treatment arm with a short-interval between treatment episodes (i.e., 16-day interval), three patients were excluded due to elevated liver enzymes, which developed during the second treatment week. The dosing regimen for ketamine was weight dosed and dynamically titrated based on pain scales.3 Details of one of these three cases is summarized below with figures from the paper depicting the pattern of change in liver enzymes:

A 65 year-old woman with a 6 year history of CRPS in her left foot, on chronic tramadol and paracetamol/codeine, and a baseline pain score of 7/10, experienced some pain relief with ketamine infusion during the first week of treatment, though was unable to tolerate maximum titration due to side effects (i.e., psychotropic effects, nausea, dizziness) on the second treatment day. During the second week, pain was back to baseline, and similar side effects occurred upon initiation of the infusion as well as an generalized rash and fever at approximately 72 hours; liver enzymes at this time were also elevated, with ALT peaking at approximately 400, AST at 380, GGT at 340 and alkaline phosphatase at 200—though without any noted abdominal pain, jaundice or hepatic enlargement. At this point, ketamine was discontinued, with a total of 1.3 grams of ketamine that had been administered. Hematologic labs were notable for mild eosinophilia (8%). The rash

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3 “On day 1, infusion started at 8 am at 1.2 ug/kg/hr. Three times a day (at 8 am, noon, and 4 pm), the infusion rate could be increased in steps of 0.6 ug/kg/h until a maximum infusion rate of 7.2 ug/kg/hr was reached. When the patient reached a pain rating of zero, the infusion rate was not further changed. In case of severe side effects, the infusion rate was lowered in steps of 0.6 ug/kg/h and later increased again if possible.”
improved and the liver enzymes decreased following ketamine discontinuation other than GGT and alkaline phosphatase which increased for one additional day; enzymes further normalized over the course of 1 month. The patient’s pain returned to baseline 5 weeks after the second treatment.

**Reviewer comments:**
The pattern of injury appears mixed hepatocellular/cholestatic. The temporal association between onset of elevation in enzymes following ketamine initiation as well as positive dechallenge information is convincing that there was a causative relationship between ketamine exposure and elevation in liver enzymes.

**WHO causality assessment:** probable


This US study involved retrospective chart review of 33 patients in Australia who received subanesthetic intravenous infusion for CRPS with variable doses. Among these patients, 4 experienced elevation in liver enzymes which resolved upon discontinuation of ketamine. In the case of one patient, liver enzymes prevented completion of the protocol, and in two subsequent admissions for ketamine infusion, elevation of liver enzymes was observed.

**Reviewer comments:**
Although little information is provided regarding the levels of rise in liver enzymes, or pattern of injury, the temporal association between ketamine exposure and onset of elevation in liver enzymes, dechallenge and rechallenge information appear supportive. **WHO causality assessment:** probable
3.2.2 Cognitive Events

**FAERS**
We identified a total of 172 FAERS reports using the search strategy above. We excluded reports not meeting the case definition (n=128), duplicates (n=18), those that were confounded by the presence of multiple medications or comorbidity (n=9), and those with insufficient information (n=15), leaving a total of 2 cases meeting the case definition.

Details from these cases are summarized below:

- **FAERS # 8555950** (literature article, sponsor-submitted, expedited)
  A 36-year-old male with a history of CRPS and depression underwent a ketamine-midazolam induced coma for treatment of refractory pain. Ketamine was infused reportedly at a rate of 700 mg/hour intravenously and continued for 5 days. Upon awakening, the patient reported reduced levels of pain, though also reported anxiety, hallucinations and fear. Persistence of these symptoms for two days prompted a psychiatric evaluation which also identified a short-term memory deficit—the patient was able to recall only 2 out of 4 words after a 5-minute delay. The patient was initiated on quetiapine, after which time he no longer experienced hallucinations and short-term memory testing improved, with a delayed recall of 4 out of 4 words.

  **Reviewer comments:**
  *In this case, a strong temporal relationship between exposure to ketamine and the onset of a persistent memory deficit is reported. However, the apparent cognitive impairment (i.e., short-term recall) appeared to occur in the context of concomitant hallucinations, anxiety and fear. In addition, treatment with quetiapine, an antipsychotic, appeared to relieve the entire constellation of symptoms, suggesting that cognitive impairment in this case could have occurred in the context of drug-induced psychosis, in which case it would have not met the case definition specified for this review. However, we are given insufficient detail in the case to definitively diagnose the patient with psychosis. For additional detail regarding prolonged neuropsychiatric events following ketamine exposure see prior DPV review or the summary provided on page 4 of this document.**

- **FAERS # 11693064** (direct report, submitted by affected individual)
  A 58-year-old male with a history of depression and mild cognitive impairment underwent treatment with ketamine for treatment of depression symptoms. Ketamine was infused at a rate of 2 mg/kg, for a total of 5 infusions over a period of 2 weeks. It is not clear that he received more than a single series of infusions. Subsequently the patient experienced changes in behavior, which he reported to be unusual such as writing “dozens of emails of confusing and scary content” leading to a charge of email harrassment. The patient reports additional symptoms—decline in functionality, difficulty with oral communication without arguments, severe limitations in working memory, and poor control of emotions—all of which reportedly began following the infusions, and persisted for two years following the treatment, up until the time of
reporting. The report, in the patient’s own words, is copied below. We have removed select content to protect the identity of the reporter who is also the patient.

“I was administered ketamine IV for the symptoms of depression under the direction of [my physician], with a questionable diagnosis of bipolar and a recent prior diagnosis of MCI with indications of early inset[sic] dementia. [My physician] prescribed a series of 5 infusions over two weeks, each at the dosage of 2.0 mg/kg, a level I have recently found is quadruple the accepted dose for depression. I have reason to believe [my physician] used a similar protocol on three other patients suffering from neurological deficits and two of them suffered adverse events similar to mine. I have also recently found out that the prescribed dosage is in the range of abuse for ketamine, and that any unnecessary anesthesia is contraindicated in the case of neurological problems of unknown cause. After the series of infusions, I exhibited such unusual behavior (dozens of emails of confusing and scary content) that I was charged with email harassment and put under court ordered treatment for presupposed bipolar. At this point I should say that I am a retired prodpfessional [sic] with a jacket of five speeding tickets - this was all very bizarre behavior for me. I have now been diagnosed with the progressive neurological disorder called by-FTD, formally Pick's disease. Pick's patients are especially sensitive to anesthesia[sic], with marked and often permanent decline. [My physician] also has solicited and received millions of dollars in investments from me during the period I was being given IV ketsmine [sic] - I believe July 2013. My functionality has declined significantly - oral communications are almost impossible without arguments starting, especially with strangers or in environments with lots of stimulation. I am largely confined to email. Despite a graduate degree from Harvard I cannot follow a sitcom. My working memory extends back only one day. My executive control of emotions is so poor that I have to isolate for peace. All of these symptoms are new since the infusions in January [sic].”

Reviewer comments: The reporting patient in this case suggests a causal relationship between ketamine exposure and the onset of his symptoms, which include severe deficits in memory (i.e., working memory extending back only one day, loss of attention span). However, the reporter suggests the presence of baseline mild cognitive impairment, in which case it is not clear whether the condition he had would have deteriorated regardless of the ketamine exposure, whether ketamine accelerated the process, or whether the cognitive symptoms that the reporter perceived as new were solely due to the ketamine. Alternatively, some of the behavior that is described (i.e., speeding while driving, argumentativeness) may be explained by a prolonged manic episode that may have occurred in the context of ketamine exposure or the reporter’s baseline possible diagnosis of bipolar disorder, although there is not sufficient information to diagnose the patient with mania. For additional detail regarding prolonged neuropsychiatric events following ketamine exposure see prior DPV review or summary provided on page 4 of this document.21 

WHO causality assessment- possible
Literature
The PubMed search retrieved 69 articles, while the Google Scholar search resulted in greater than 500 articles. Screening of titles and abstracts resulted in 8 full-length articles that were reviewed further for relevance.30-37

Of the 8 relevant articles, 5 evaluated the effects of ketamine upon memory or other cognitive functions in healthy adults, 2 articles assessed such effects in patients with CRPS, and 1 article assessed these effects in patients with treatment resistant depression. No published case reports met our case definition. Studies were generally small, with patient sample sizes ranging from 9 (Koffler, 2007)36 to 32 (Kim, 2016)35. Study design included double-blind placebo-controlled randomized trials (n=4), prospective cohort studies (n=2), and retrospective cohort studies (n=2). Though they all included parenteral (intravenous or intramuscular) formulations, dosing protocols for ketamine were highly variable across studies—for instance, one study (Ghoneim, 1985)30 compared the effect of two doses of ketamine, 0.25 mg/kg, 0.5 mg/kg with placebo, where ketamine was provided as a one-time only intramuscular injection; another study (Newcomer, 1999)32 compared three doses of ketamine, provided as an intravenous bolus, followed by maintenance infusions. Measurements of cognition and memory were also highly variable across the studies, and included tests of attention (e.g., color-word interference test), information recall (e.g., delayed free recall), verbal fluency and recognition, among other measures of cognitive function. A subset of studies also assessed outcomes related to psychiatric adverse effects (i.e., Brief Psychiatric Rating Scale), or treatment efficacy (e.g., Beck Depression Inventory, McGill Pain Questionnaire).

Several studies identified significant negative effects of ketamine upon specific aspects of cognitive function. These studies are highlighted below:

- Ghoneim, 198530: immediate recall and delayed recall, learning performance
- Malhotra, 199631: recognition memory, free recall, attention
- Newcomer, 199932: dose-dependent decrease in learning, verbal/non-verbal declarative memory
- Krystal, 200033: Wisconsin Card Sorting Test (i.e., attention, mental shifting, information storage)
- Diamond, 201434: episodic memory, immediate and delayed recall, autobiographical memory
- Kim, 201635: digit span/symbol test (i.e., memory, attention, concentration, working memory)

One study did not detect negative effects of ketamine upon assessed measures of cognitive function, and identified potential improvement in some areas of function:

- Koffler, 200736: no change in learning/memory; attention and processing speed reported to have improved in patients with CRPS type I after treatment with ketamine
One study reported negative effects of ketamine on very specific aspects of cognitive function, while not appearing to affect the majority of cognitive functions assessed:

- Honey, 2003: negative effects on verbal working memory, manipulation only; no effects on other aspects of verbal working memory (i.e., forward/backward digit span), spatial working memory, or planning

In general, many of the studies were limited by small sample sizes, in most cases without statistical significance adjustment for multiple testing (e.g., Bonferroni adjustment). While the majority of the studies evaluated suggest that ketamine may have stronger negative effects on specific cognitive domains, such as immediate/delayed recall, which may be dose-dependent, one study (Koffler) identified potential positive effects of ketamine upon cognition. Finally, none of the studies prospectively examined long-term persistence of cognitive effects resulting from repeated exposure to ketamine. Overall, these studies suggested possible short-term effects of ketamine upon cognitive function that may be independent of neuropsychiatric changes, though there is a need for additional prospective data to better understand persistence of these effects over time.

4 DISCUSSION

Our review of FAERS and the published literature confirm that ketamine is being used off-label to treat a number of conditions, such as pain and depression. We identified a number of strong cases that appear to support a causal relationship between repeated ketamine exposure and the onset of hepatobiliary adverse events, and some data to support a possible relationship between ketamine exposure and the onset of negative cognitive effects. Although it is difficult to estimate the size of the at-risk population of patients who are receiving ketamine off-label in this manner, as such use is typically reimbursed through cash payment only, trends in outpatient sales of ketamine in recent years provides some indirect evidence to suggest growing popularity of the drug.

We also note that esketamine (the S-enantiomer of racemic ketamine) nasal spray, NDA 211243, is currently in-house. The sponsor of this product is seeking approval for induction and maintenance treatment of adults with treatment-resistant depression. If approved, esketamine would likely be dosed once or twice a week, or every other week, under the supervision of a health care professional. Consideration of the safety findings from this ketamine review, which relates to risks of repeated administration, as is proposed for NDA 211243, may be informative when considering the drug safety profile of esketamine, although some adverse events may be route-specific, a factor we have not examined in this review.

Ketamine Utilization Trends
Sales distribution data were assessed to provide a national estimate of the number of ketamine vials sold from manufacturers into all channels of distribution. Although sales data do not provide a direct measure of patient use, the amount of product purchased by various settings of care may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. Based on national sales distribution patterns of ketamine vials, the utilization appears to be largely in the hospital setting. Notably, we also found sales to clinic
settings appears to have more than doubled in the five years examined suggesting changes in utilization patterns. However, national data on diagnoses or indications directly linked with the administration of ketamine in the clinic or hospital settings were not available for review. In order to obtain some insight into reported indications for the use of ketamine, U.S. office-based physician survey data were assessed for prescriber reported use of ketamine. However, the results of office-based physician survey data were too low to derive reliable national estimates of ketamine use. Due to the low utilization of ketamine outside of hospital and clinic settings, the results from the office-based physician survey data are not generalizable nor representative of ketamine use across all settings of care.

Data on repeated use of ketamine as well as national estimates of use in the clinic or hospital settings by indication were not conducted for this review. Additional analyses are necessary to characterize off-label, repeated use of ketamine. However, our findings suggest increasing use of ketamine in recent years, although the reasons and potential factors that may have contributed to increased use were not formally studied in this review.

**Ketamine and Hepatobiliary Events**

The FAERS and literature cases support an association between hepatobiliary events and the off-label, repeated use of ketamine. Our findings are consistent with previous inferences made by the medical community regarding potential hepatotoxicity associated with chronic ketamine use. Additionally, in 2017, the French National Agency for the Safety of Medicines and Health Products (ANSM) published a Dear Healthcare Professional Communication (DHPC) letter regarding the risk of severe liver damage during repeated and/or prolonged use of high-dose ketamine. The letter reported ten cases of serious liver damage (cholestatic cholangitis), including four cases requiring liver transplantation, since 2014. ANSM stated that cases may be linked to repeated or prolonged use of ketamine and at high doses in the management of severe pain or severe burns. The letter reminded healthcare professionals to follow the recommended dosage for palliative care practice, that treatment should be initiated by a specialized team, and patients should undergo close observation and monitoring, including liver function monitoring. In response, to the ANSM letter, Malaysia’s National Pharmaceutical Regulatory Agency (NPRA) also issued an advisory to clinicians to “monitor patient’s liver function closely if repeated and/or prolonged high dose of ketamine is used.”

Although there are a limited number of cases in our case series, it is important to note that we only reviewed cases of off-label, prolonged/repeated use of ketamine. Due to the complex nature of patients and confounding that can complicate reports, we did not review cases of labeled use of ketamine (e.g. sedation) or abuse cases of ketamine. We noted the repeated off-label use cases to be less confounded than abuse cases, allowing us to evaluate a drug-event relationship.

Of the events that occurred, the majority of the cases documented liver transaminase elevations, including increases in ALT, GGT, AST, and ALP with a close temporal relationship to the ketamine administration. In addition, we identified cases with elevated transaminases further complicated by cholangitis, biliary dilation, jaundice, chronic hepatitis, hepatic fibrosis, liver cirrhosis, intrahepatic cholestasis, cholangiopathy, and pericholeductal fibrosis. Although health authorities from other countries, as noted above, have received reports of liver damage from repeated or prolonged ketamine use resulting in transplant, at the time of this review there were
no cases of fulminant hepatic necrosis or transplant identified from FAERS or the literature for the case definition applied.

Our case series had a strong positive dechallenge and rechallenge correlation of events with the administration of ketamine. Of the seventeen reports in which the ketamine was discontinued, sixteen documented a positive dechallenge (94%), and five more patients went on to develop positive rechallenges, including four cases with two positive rechallenges each. We feel the strength of the evidence lies in the number of positive dechallenges and rechallenges in our case series. Additionally, two of the probable cases (FAERS Case # 14227949 and Kato Case #1) experienced an ALT level greater than 3 times the ULN and a total bilirubin level greater than 2 times the ULN after receiving ketamine. In FAERS Case # 14227949, on day three after 2nd dose, the patient experienced epigastric pain and elevated bilirubin (90 mmol/L) and ALT (868 u/l). In Kato Case #1, it was documented that the total bilirubin (4.0 mg/dl) and ALT (204 IU/l) were elevated 53 days after starting ketamine. In summary, we reviewed several cases where liver enzymes returned to normal upon discontinuing ketamine, although in some cases, enzymes did not normalize even over a period of several months and repeat assessment of the pathology (e.g., fibrosis) was not available to characterize the extent of residual injury.28

There was one death case in our case series (FAERS case # 12801413). However, we note that at the time of the events, the patient was hospitalized for palliative care for esophageal cancer. The patient had experienced mental confusion, intrahepatic cholestasis, with cytolisis and increased levels of hepatic enzymes which were considered by the DPV reviewers (MM/SC) to be possibly related to ketamine. However, the patient was also receiving ceftriaxone, and haloperidol at the time of the events—in the literature, ceftriaxone has been associated with development of biliary sludge and biliary colic, and haloperidol is commonly associated with minor serum aminotransferase elevations and rare instances of acute liver injury, thus the case was confounded by the concomitant use of these medications.41,42 The reporter attributed the death to progression of cancer.

Ketamine has been shown to cause transient abnormalities in LFTs when used as an anaesthetic agent.43 The exact mechanism for injury is unknown, but has been hypothesized to be due to a reduction in hepatic oxygen delivery, and increased lipid peroxidation with free radical formation.44 Although the patients receiving ketamine for anesthesia were excluded from our review, a literature article from Hong Kong identified abnormal LFTs in 16% of ketamine abusers who sought care at the hospital emergency departments.45 Animal studies performed in mice treated with ketamine showed fatty degeneration of liver cells, fibrosis and a rise in liver enzymes.46 Effects were noted to be more severe if the animals were also treated with alcohol.

We note that there is a clear pattern of elevation in transaminases, temporal relationship, multiple positive rechallenges, and biologic plausibility leading us to believe that there is a probable drug-event relationship. Furthermore, early detection of drug-induced hepatic injury along with immediate discontinuation of the suspected drug may enhance the likelihood of recovery.
Ketamine and Cognitive Events

Ketamine’s activity on NMDA receptors form a potential mechanistic basis for adverse effects relating to cognitive function.\(^4^7\) NMDA antagonists, such as ketamine and phencyclidine (i.e., PCP) are known to bind with high affinity to structures in the central nervous system, such as the cortex and limbic system. Although the exact mechanism by which ketamine and PCP cause “dissociation” between sensation and higher cognitive functions is not known, ketamine’s activity on NMDA receptors are hypothesized to play a central role in its effects on cognition and memory, and both ketamine and PCP have been demonstrated to reliably induce schizophrenia-like states.

Despite the few FAERS cases reporting potential cognitive adverse effects of repeated doses of ketamine and lack of published case reports, we identified 8 studies that have attempted to assess the effects of ketamine upon memory and other aspects of cognitive function. Although findings from some of these studies are somewhat mixed, and many do not specifically assess the effects of repeated dosing, several studies of healthy adults suggest that specific aspects of cognitive function (e.g., immediate/delayed recall, working memory) appear to be negatively affected by ketamine use in the short-term, even with subanesthetic doses. It is also worth noting that these effects may be even more pronounced, or altogether distinct, among patient populations that were excluded from several of the studies who may receive ketamine in the real-world setting, such as the cases we noted from FAERS (e.g., patients with baseline cognitive impairment, dementia, substance use disorder or history of psychosis).

Underscoring the complexity of the risk-benefit assessment in deciding whether ketamine may be appropriate for use despite potential adverse effects, one study of patients with CRPS I suggested potential for improvement with ketamine treatment in certain aspects of cognitive function such as attention and processing speed, which is conceivable in the context of the impact that debilitating pain may have on baseline cognitive processes.\(^3^6\) Additional prospectively collected data are required to better understand risks of persistent cognitive changes (positive or negative) resulting from ketamine exposure in specific patient populations.

5 CONCLUSION

In conclusion, we find an association between ketamine and a range of hepatobiliary events in the context of off-label, repeated use.

In addition, available studies support a possible association between ketamine and short-term cognitive impairment with subanesthetic doses of ketamine, having potential implications for post-treatment monitoring or restrictions on activity. However, it remains to be determined whether or not the cognitive effects observed with ketamine are sustained and in which populations, and in which populations such risks are outweighed by potential benefits.

The current ketamine labeling does not convey potential for either hepatobiliary or cognitive complications in the context of subanesthetic doses, and increased awareness among clinicians may mitigate adverse outcomes, especially in the context of growing ketamine utilization.
6 RECOMMENDATIONS

Based on this review, DPV recommends the following:

- Add a statement to the Warnings section of ketamine product labels to reflect the potential risk of hepatobiliary events with ketamine, and routine monitoring of liver function studies in the context of repeated use.

Consider use or modification of the following proposed language: “In individuals with a history of prolonged/repeated off-label ketamine use, post-marketing case reports of hepatobiliary events have been reported, including positive rechallenges, that suggest a causal relationship with ketamine. These events have ranged from reversible elevation in transaminases to irreversible liver damage (e.g., fibrosis, biliary ductal changes). Routine monitoring of liver function studies may help mitigate irreversible or long-term consequences of these hepatobiliary events.”

- Consider a statement to the Adverse Reactions section of ketamine product labels to reflect that ketamine may be associated with short-term cognitive impairment at subanesthetic doses, although the long-term cognitive effects of repeated exposure to ketamine are not well understood.
7 REFERENCES


44. Sear JW. Ketamine hepato-toxicity in chronic pain management: another example of unexpected toxicity or a predicted result from previous clinical and pre-clinical data? Pain 2011;152:1946–7.


8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA’s post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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.

8.2 APPENDIX B. DRUG USE DATABASE DESCRIPTIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Syneos Health Research & Insights LLC., TreatmentAnswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month.
These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals. Data below 100,000 (mentions) do not represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level. In general, this physician survey database is most appropriate to identify the typical uses for a product in office-based physician’s clinical practice. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed.
## 8.3 Appendix C. FAERS and Literature Line Listing of Hepatobiliary Events with Ketamine Case Series (N=20)

<table>
<thead>
<tr>
<th>Initial FDA Received Date (YYYY)</th>
<th>FAERS Case #</th>
<th>Version #</th>
<th>Manufacturer Control #</th>
<th>Case Type</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Country Derived</th>
<th>Serious Outcome(s)*</th>
<th>Hepatobiliary Event</th>
<th>WHO Causality Assessment</th>
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</thead>
<tbody>
<tr>
<td>1 2002</td>
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<td>061-0945-M0200098</td>
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<td>66</td>
<td>F</td>
<td>AUS</td>
<td>increased ALP, GGT, ALT, AST</td>
<td>possible</td>
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<tr>
<td>2 2003</td>
<td>401019-5</td>
<td>3</td>
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<td>72</td>
<td>M</td>
<td>BEL</td>
<td>chronic active hepatitis, hepatic fibrosis, increased GGT, cholangitis</td>
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<td>723941-8</td>
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<td>50</td>
<td>F</td>
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<td>unsp liver disorder</td>
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<tr>
<td>5 2012</td>
<td>834114-2</td>
<td>1</td>
<td>N/A</td>
<td>Direct</td>
<td>50</td>
<td>F</td>
<td>USA</td>
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<td>F</td>
<td>GBR</td>
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<td>F</td>
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<td>Liver injury, increased AST, ALT, ALP</td>
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<td>9 2016</td>
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<td>FRA</td>
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<tr>
<td>Initial FDA Received Date (YYYY)</td>
<td>FAERS Case #</td>
<td>Version #</td>
<td>Manufacturer Control #</td>
<td>Case Type</td>
<td>Age (years)</td>
<td>Sex</td>
<td>Country Derived</td>
<td>Serious Outcome(s)*</td>
<td>Hepatobiliary Event</td>
<td>WHO Causality Assessment</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>1 0 2016 128014-13 1</td>
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<td>60</td>
<td>M</td>
<td>FRA</td>
<td>DE,HO</td>
<td>intrahepatic cholestasis, elevated t bili, d bili, GGT, ALP, AST, ALT</td>
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<td></td>
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<td>1 1 2017 142279-49 2</td>
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<td>AUS</td>
<td>HO</td>
<td>severe cholangiopathy, jaundice and cholangiitis, biliary dilation elevated bilirubin, ALP, GGT, ALT, AST</td>
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<tr>
<td>1 2 1995 Kato-Case1</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>70</td>
<td>M</td>
<td>JPN</td>
<td>NR</td>
<td>jaundice, increased ALP, GGT, tibil, dbil, AST, ALT, imaging showing deformity of the liver, and biopsy with &quot;extensive pericholeductal fibrosis compatible with drug-induced hepatitis&quot;</td>
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<td></td>
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<tr>
<td>1 3 1995 Kato-Case2</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>83</td>
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<td>JPN</td>
<td>NR</td>
<td>increased ALP, GGT, AST, ALT</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td>Initial FDA Received Date (YYYY)</td>
<td>FAERS Case #</td>
<td>Versi on #</td>
<td>Manufacturer Control #</td>
<td>Case Type</td>
<td>Age (years)</td>
<td>Sex</td>
<td>Country Derived</td>
<td>Serious Outcome(s)*</td>
<td>Hepatobiliary Event</td>
<td>WHO Causal tity Assessment</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>-----------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>1 4 2004</td>
<td>Correll - Case 1 (patient 9)</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>33</td>
<td>M</td>
<td>AUS</td>
<td>NR</td>
<td>elevated LFTs (unsp)</td>
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<tr>
<td>1 5 2004</td>
<td>Correll - Case 2 (patient 21)</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>46</td>
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<td>AUS</td>
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<tr>
<td>1 6 2004</td>
<td>Correll - Case 3 (patient 25)</td>
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<td>N/A</td>
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<td>45</td>
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<td>NR</td>
<td>elevated LFTs (unsp)</td>
<td>possible</td>
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<tr>
<td>1 7 2004</td>
<td>Correll - Case 4 (patient 30)</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>47</td>
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<td>AUS</td>
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<tr>
<td>1 8 2011</td>
<td>Nopper - Case 1 (patient A)</td>
<td>N/A</td>
<td>N/A</td>
<td>Literature</td>
<td>65</td>
<td>F</td>
<td>NLD</td>
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<tr>
<td>1 9 2011</td>
<td>Nopper - Case 2 (patient E)</td>
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<td>N/A</td>
<td>Literature</td>
<td>48</td>
<td>F</td>
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<td>NR</td>
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<td>probable</td>
</tr>
<tr>
<td>2 0 2011</td>
<td>Nopper - Case 3 (patient F)</td>
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<td>N/A</td>
<td>Literature</td>
<td>46</td>
<td>M</td>
<td>NLD</td>
<td>NR</td>
<td>elevated ALT, GGT</td>
<td>probable</td>
</tr>
</tbody>
</table>

*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. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome. Abbreviations: DE=Death, HO=Hospitalization, OT=Other medically significant, N/A = not applicable, NR = not reported, AUS = Australia, JPN = Japan, NLD = Netherlands, USA = United States of America, BEL = Belgium, FRA = France, LFTs = Liver Function Tests, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, GGT = Gamma-glutamyl transferase, tbili = total bilirubin, dbili = direct bilirubin
### World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Categories

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td><em>Due to the spontaneous nature and quality of FAERS reports, no case would be considered certain.</em></td>
</tr>
<tr>
<td>Probable/Likely</td>
<td>• Event or laboratory test abnormality, with reasonable time relationship to drug intake  &lt;br&gt; • Unlikely to be attributed to disease or other drugs  &lt;br&gt; • Response to withdrawal clinically reasonable  &lt;br&gt; • Rechallenge not required</td>
</tr>
<tr>
<td>Possible</td>
<td>• Event or laboratory test abnormality, with reasonable time relationship to drug intake  &lt;br&gt; • Could also be explained by disease or other drugs  &lt;br&gt; • Information on drug withdrawal may be lacking or unclear</td>
</tr>
<tr>
<td>Unlikely</td>
<td>• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  &lt;br&gt; • Disease or other drugs provide plausible explanations</td>
</tr>
<tr>
<td>Conditional/ Unclassified</td>
<td>• Event or laboratory test abnormality  &lt;br&gt; • More data for proper assessment needed, or  &lt;br&gt; • Additional data under examination</td>
</tr>
<tr>
<td>Unassessable/ Unclassifiable</td>
<td>• Report suggesting an adverse reaction  &lt;br&gt; • Cannot be judged because information is insufficient or contradictory  &lt;br&gt; • Data cannot be supplemented or verified</td>
</tr>
</tbody>
</table>
8.5 APPENDIX E. DECHALLENGE RECHALLENGE INFORMATION FOR LITERATURE CASE REPORT BY TOFANI C, ET AL.

8.6 APPENDIX F. NATIONAL INSTITUTES OF HEALTH LIVERTOX CATEGORIZATION OF THE LIKELIHOOD OF DRUG INDUCED LIVER INJURY SCALE

<table>
<thead>
<tr>
<th>Category A.</th>
<th>The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category B.</td>
<td>The drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described.</td>
</tr>
<tr>
<td>Category C.</td>
<td>The drug is probably linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series.</td>
</tr>
<tr>
<td>Category D.</td>
<td>Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury.</td>
</tr>
<tr>
<td>Category E.</td>
<td>Despite extensive use, no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is not believed or is unlikely to cause liver injury.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Category E.</td>
<td>The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is unproven, but suspected to cause liver injury.</td>
</tr>
<tr>
<td>Category X.</td>
<td>For medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as “unknown.”</td>
</tr>
</tbody>
</table>

9.2. Attachment 2
Drug Abuse Epidemiology Review

Date: January 7, 2019

Primary Reviewers: Amy Seitz, PhD, MPH, Epidemiologist
Division of Epidemiology II

Yulan Ding, PhD, Data Analyst
Division of Epidemiology II

Secondary reviewer: Rose Radin, PhD, MPH, Acting Team Lead
Division of Epidemiology II

Tertiary reviewer: Jana Mcaninch, MD, MPH, MS, Senior Medical Epidemiologist
Division of Epidemiology II

Subject: NDA 211243 – esketamine
Abuse and misuse of ketamine and associated harms

**This document contains proprietary drug use data and American Association of Poison Control Centers data obtained by FDA under contract. These data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. All product codes must be redacted for public release.**
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EXECUTIVE SUMMARY

Ketamine is a rapidly acting dissociative anesthetic, marketed in the U.S. since the 1970s for use in humans and animals. For many decades, ketamine has been reported as a drug of abuse, and in 1999, ketamine and its salts were designated as Schedule III substances under the Controlled Substances Act. Ketamine is abused for its dissociative and hallucinogenic effects and has been termed a “club drug” or “party drug” because of its popularity for use at nightclubs and raves. According to the DEA, most of the ketamine illegally distributed in the U.S. is diverted or stolen from legitimate sources such as veterinary clinics or smuggled from Mexico and then sold or shared at parties or nightclubs.

For this review, drug utilization data are referenced from Attachment 1 of this briefing document to provide context for recent data on ketamine abuse. Previously published literature and national estimates from National Survey on Drug Use and Health and the Monitoring the Future survey are provided to understand the prevalence of ketamine abuse. We also provide information on ketamine abuse and associated adverse outcomes, analyzing data from calls to U.S. poison centers (National Poison Data System), emergency department visits (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event), and spontaneous adverse event reports (FDA Adverse Drug Event Reporting System).

Based on national sales distribution patterns of ketamine vials (excluding veterinary sales), ketamine utilization appears to be largely in the hospital setting. Ketamine sales increased approximately 72% from 2013 to 2017 overall and sales to clinic settings, specifically, more than doubled during this five-year period. Numerous off-label uses of ketamine have been proposed and implemented, including treatment resistant depression, and recent literature suggests growth in some of these off-label uses of ketamine.

National survey data and the published literature indicate that ketamine abuse is relatively uncommon in the general population, with a reported lifetime prevalence of 1.3% among persons age 12 years and older, which is lower than that for other hallucinogens such as ecstasy and LSD (Acid). Among 12th graders, the annual prevalence of ketamine use has declined from 2.5% in 2000 to 1.2% in 2017. Exposure calls to U.S. poison centers involving ketamine abuse or misuse also declined slightly from 2013 to 2017 (176 calls in 2013 to 116 calls in 2017), despite the growth in non-veterinary ketamine sales. Single-substance exposure calls to poison control centers involving ketamine abuse or misuse were most commonly associated with minor or moderate health effects, and there were no deaths identified among these calls. In a representative sample of approximately 60 U.S. emergency departments, there were 44 ketamine-related ED cases in 2016-2017, corresponding to an estimated 669 visits nationally. Of the 44 ketamine-related ED cases, 35 (81.5%) were classified as abuse. Only six (17.1%) of these cases resulted in hospitalization. From 2015-2017, the FDA Adverse Event Reporting System (FAERS) received 17 reports of death involving ketamine abuse. Of note, only one of these reports listed ketamine as the only suspected drug, and the drug-event causal association has not been assessed for any of these FAERS cases.

Overall, this analysis suggests that ketamine abuse continues to occur but has remained relatively limited with modest associated harms. The available data are insufficient to determine the extent to which U.S. pharmaceutical ketamine for humans contributes to abuse, relative to ketamine that is smuggled into the country or diverted from veterinary settings. Nonetheless, the risks of abuse...
and associated harms are important considerations in determining appropriate risk mitigation strategies and post marketing surveillance for esketamine, if approved.

1. INTRODUCTION

The Division of Epidemiology II (DEPI) was asked by the FDA Controlled Substances Staff to provide current information on ketamine abuse and misuse and associated adverse events, for consideration at the joint meeting of the Psychopharmacologic Drugs and the Drug Safety and Risk Management Advisory Committees on February 12, 2019. The committees will discuss the New Drug Application 211243 for esketamine, an enantiomer of ketamine, for treatment resistant depression in adults.

Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor and is a rapidly acting dissociative anesthetic marketed in the U.S. since the 1970s for use in humans and animals. In humans, it is indicated for 1) diagnostic and surgical procedures that do not require skeletal muscle relaxation, as the sole anesthetic, 2) administration prior to other general anesthetic agents, and 3) supplementing low-potency agents, such as nitrous oxide.(1) In the U.S., injectable ketamine is the only approved formulation for humans. Since the time of its approval, numerous off-label uses of ketamine have been proposed and implemented, including, but not limited to, treatment of complex-regional pain syndrome (CRPS), chronic pain, and treatment resistant depression.(2-6) Emerging literature describes some of these off-label uses of ketamine,(3, 7) providing some standardization, but in practice, treatment regimens can vary.

Ketamine has been reported in the literature as a drug of abuse for many decades, and in 1999, ketamine and its salts were designated as Schedule III substances under the Controlled Substances Act. Also known as “Special K” and by multiple other slang terms, ketamine is abused for its dissociative and hallucinogenic effects and has been termed a “club drug” or “party drug” because of its popularity for use at nightclubs and raves.(8, 9) Due to its sedative and amnesic effects, ketamine has also been used for facilitating sexual assault and nonconsensual sexual intercourse.(8, 9) Powdered ketamine can be snorted or smoked, and liquid ketamine can be injected, mixed into drinks, placed on materials to be smoked, or evaporated by heating and ground into a powder.(8, 9) According to the DEA, most of the ketamine illegally distributed in the U.S. is diverted or stolen from legitimate sources such veterinary clinics or smuggled from Mexico and then sold or shared at parties or nightclubs.(8)

The purpose of this review is to provide current information on the scope and patterns of ketamine abuse and associated harms in the U.S.

2 MATERIAL AND METHODS

This review includes information from the epidemiologic literature, the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event (NEISS-CADES) database, the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), the National Survey on Drug Use and Health (NSDUH), and the Monitoring the Future (MTF) survey. Also, we considered estimates of annual U.S. sales of ketamine vials analyzed by the DEPI-Drug Use team for a previous review (October 2018, DARRTS ref ID 4367425) and
FDA Adverse Event Reporting System (FAERS) results analyzed by the Division of Pharmacovigilance for a previous memo (October 2017; DARRTS ref ID 4161583).

The purpose for including multiple data sources is to provide a robust description of ketamine abuse and misuse through complementary data sources because each of these data sources has strengths and limitations. Details on each data source are provided below. Definitions of misuse and abuse vary by data source and will be described as appropriate. The following standard regulatory definitions of misuse/abuse were applied throughout this review, unless otherwise indicated:(10, 11)

**Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

**Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

### 2.1 Drug Utilization

Drug utilization data provide context for data on misuse and abuse of pharmaceutical products. For drug utilization information, we referenced the recent integrated review by the Division of Pharmacovigilance (DPV) II and DEPI-Drug Use (DARRTS ref ID 4367425), which is included in this briefing document as Attachment 1. This review focused on the hepatobiliary and cognitive impairment adverse events associated with repeated off-label use of ketamine and also provided results of a sales and distribution analysis from the IQVIA, National Sales Perspectives (NSP) database.

### 2.2 Pharmacoepidemiology Literature Search

Using the search terms and parameters described in Table 2.2, DEPI II conducted a literature search using PubMed.gov to identify recent published observational epidemiologic studies on ketamine misuse and abuse, and their consequences (e.g., addiction/ substance use disorder, overdose).
<table>
<thead>
<tr>
<th>Table 2.2 Literature Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Search</strong></td>
</tr>
<tr>
<td><strong>Database</strong></td>
</tr>
<tr>
<td><strong>Search Terms</strong></td>
</tr>
<tr>
<td><strong>Years included in search</strong></td>
</tr>
<tr>
<td><strong>Other criteria</strong></td>
</tr>
</tbody>
</table>

Note: In addition to the search strategy above, we mined primary sources from secondary references.

### 2.3 National Survey on Drug Use and Health (NSDUH)

The National Survey on Drug Use and Health (NSDUH) is an annual survey conducted nationwide by the Substance Abuse and Mental Health Services Administration (SAMHSA). NSDUH collects information on drug use, mental health, and other health related issues with the goal of providing accurate, nationally representative data about the use of alcohol, tobacco, other drugs and substance use and misuse. NSDUH also aims to “assess the consequences of substance use and misuse.” Information is collected from civilian, noninstitutionalized participants aged 12 years and older. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2017, the interview response rate of 50.4% included 68,032 completed interviews.(12) In NSDUH, misuse is defined as “use in a way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.” However, because NSDUH categorizes ketamine as a hallucinogen and includes it in the same section with illicit drugs such as cocaine and heroin, misuse of ketamine is termed “ketamine use.”(12, 13)

A partial redesign of the NSDUH questionnaire occurred in 2015 so trends are limited for many estimates.(12) We extracted and summarized information on hallucinogens and ketamine use from the most recent publicly available reports of NSDUH results.(12, 13)
2.4 Monitoring the Future (MTF)

The Monitoring the Future survey (MTF) is an annual survey monitoring the “behaviors, attitudes, and values of American secondary school students, college students, and young adults.” The survey is supported with grants from the National Institute on Drug Abuse, National Institutes of Health.(14)

MTF uses the term “misuse” for prescription medications to mean “use outside of a doctor’s orders.” They describe ketamine abuse and misuse as the annual prevalence of use, meaning “the percent of the study sample that report using a drug once or more during a given period- i.e. past 12 months.”(15) We extracted and summarized the findings relating to ketamine from the published report of 2017 MTF survey results.

2.5 National Poison Data System (NPDS) Analysis

The NPDS database includes calls from individuals, healthcare professionals, and other interested persons regarding exposures to prescription drugs, over-the-counter medications, unapproved products, and other substances, to all poison control centers in the U.S.(16) NPDS is managed by the American Association of Poison Control Centers (AAPCC). The AAPCC Annual Report contains additional information.(17)

The NPDS calls for exposures may result in provision of information or advice regarding medical management, and AAPCC staff managing these calls undergo training to standardize documentation across centers. Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received, medical, and other variables. Reasons for exposure are categorized into groups by AAPCC, and include such categories as “intentional”, “unintentional,” the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or unknown intent. Additional detail regarding the definition of these variables is provided in Appendix A of this review. Medical outcomes are based on all information known at the conclusion of the case and coded as “No effect,” “Minor effect,” “Moderate effect,” or “Major effect.” Medical outcome was characterized for the subset of calls with a “Related” clinical effect. NPDS defines “Related” clinical effects as exposures where the following criteria are satisfied: the timing and severity of clinical effects are reasonable for the reported exposure, the clinical effect is consistent with the anticipated substance, and the clinical assessment is made by a physician. Exposures with “Related” clinical effects were identified if any listed clinical effect for a given exposure call involving the drug of interest was designated as “(R).” If not appropriate or possible to follow a case, the case is labeled as “case not followed to known outcome.” Additional detail regarding the definition of these variables is provided in Appendix B of this review. Follow-up calls to NPDS from the same exposure event are recorded as a single exposure; a person can have more than one call for an exposure to the same substance if they happen at different times.

We searched NPDS using the criteria described in Table 2.3. For the purposes of this descriptive analysis, we included all “closed cases” of human exposure to ketamine, January 1, 2013 to December 31, 2017, including cases with multiple drug exposures. Closed cases have been through quality assurance procedures by AAPCC. We identified generic and product codes for pharmaceutical preparations for ketamine, including human and veterinary products from the
U.S. and other countries (n=105 generic and product codes), using Micromedex® Solutions (Appendix C of this review).

Analysis of NPDS consisted of tabulating counts of ketamine exposure calls by year. We separated intentional exposures from unintentional exposures/adverse reactions and cross-tabulated various characteristics of the exposure--i.e., reason for exposure, related medical outcome, number of substances involved, and route of exposure--by year. These analyses were replicated by a second analyst for quality assurance.

Table 2.3. AAPCC-NPDS Search Strategy-Ketamine

<table>
<thead>
<tr>
<th>Database</th>
<th>National Poison Data System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report name</td>
<td>Case Log (Generic and Product Code)</td>
</tr>
<tr>
<td>Month/year of query</td>
<td>12/2018</td>
</tr>
<tr>
<td>Date range for query</td>
<td>01/01/2013- 12/31/2017</td>
</tr>
<tr>
<td>Call type</td>
<td>Exposure</td>
</tr>
<tr>
<td>Case status</td>
<td>Closed</td>
</tr>
<tr>
<td>Species</td>
<td>Human</td>
</tr>
<tr>
<td>Exposure reason</td>
<td>All</td>
</tr>
<tr>
<td>Age</td>
<td>0-120 years</td>
</tr>
<tr>
<td>Product codes</td>
<td>See Appendix C of this review</td>
</tr>
</tbody>
</table>

2.6 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) ANALYSIS

DEPI consulted with Centers for Disease Control and Prevention to identify ketamine-related adverse drug event (ADE) cases in the NEISS-CADES database. NEISS-CADES data comprise a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the U.S. and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the U.S. Consumer Product Safety Commission, and the U.S. Food and Drug Administration.(18-21) In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events, to report up to 4 medications implicated in each adverse event, and to record narrative descriptions of the incident.

NEISS-CADES has historically focused exclusively on ED visits due to use of medications for a therapeutic indication, or unintended medication exposures by young children. However, in 2016 NEISS-CADES surveillance activities were expanded to represent a wider spectrum of pharmaceutical-related harm, encompassing ED visits resulting from abuse, self-harm, overdoses without indication of intent, therapeutic misuse and assault, in addition to therapeutic adverse drug events.

The 2016-2017 NEISS-CADES database was searched for ADEs related to ketamine, including cases of nonmedical use (i.e., abuse, therapeutic misuse, or overdose with unknown intent), therapeutic adverse event, assault, and self-harm/suicide (search date: November 28, 2018). Definitions for these case types are provided in Appendix D of this review. National projections of ED visits for ADEs associated with ketamine were estimated using hospital-based sample weights. National projections of the number of cases can only be made when there are sufficient
number of cases (\(\geq 20\) cases in the sample and \(\geq 1,200\) cases in the national estimate) and level of variability (coefficient of variation \(\leq 0.3\)).

**2.7 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) CASE DEFINITION AND SEARCH STRATEGY**

FAERS is a database that contains spontaneously reported information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS was previously searched by DPV II for ketamine and its abuse, and the results were included in an October 2017 review memo (October 2017; DARRTS ref ID 4161583). The description of the FAERS search below is from this memo.

“For the purposes of this descriptive analysis, we included all serious U.S. reports coded to the Standardized MedDRA Query (SMQ), *Drug abuse, dependence, and withdrawal (SMQ) Broad* and listing ketamine-containing product as a suspect product.

<table>
<thead>
<tr>
<th>Table 2.7. Ketamine FAERS Search Strategy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Search</strong></td>
</tr>
<tr>
<td><strong>Time Period of Search</strong></td>
</tr>
<tr>
<td><strong>Search Type</strong></td>
</tr>
<tr>
<td><strong>Product Terms</strong></td>
</tr>
<tr>
<td><strong>MedDRA Search (Version 20.0)</strong></td>
</tr>
<tr>
<td><strong>Other Filters</strong></td>
</tr>
</tbody>
</table>

MedDRA= Medical Dictionary for Regulatory Activities, SMQ = Standardized MedDRA Query
* See Appendix E of this review for a description of the FAERS database is included in the integrated review by DPV II and DEPI Drug Use, included as an appendix to this briefing document.
† The search dates used represent recent use and were requested by the consultant – the Controlled Substance Staff.
‡ FDA data entry completion date.

a Product terms were used to encompass all potential formulations for off-label use.
3 RESULTS

3.1 DRUG UTILIZATION

As described in the recent DPV II and DEPI Drug Use review (included as Attachment 1 of this background package), (DARRTS ref ID 4367425), the estimated total number of ketamine vials sold from manufacturers to all settings of care increased approximately 72% from 2013 to 2017, from 1.2 million vials to 2.1 million vials, respectively. In 2017, the largest proportion of ketamine vials were sold to non-federal hospitals, at approximately 54%, followed by 37% and 9% of vials sold to clinics and all other channels, respectively. Although manufacturer sales of ketamine to all channels of distribution increased; the increase was most notable in the clinic settings, where the number of vials sold more than doubled, from an estimated 332,000 vials sold in 2013 to 765,500 vials sold in 2017. Veterinary sales were not included in this analysis.

Data on indication for use were not available for ketamine, however recent publications propose numerous off-label uses(2-6) and guidelines for off-label use,(3, 7) suggesting an increasing interest in ketamine for off-label uses.

3.2 PHARMACOEPIDEMIOLOGY LITERATURE SEARCH

A total of 200 articles were identified using the search strategy described in Table 2.2. Of these 200 articles, 36 were determined to be relevant to this review, and additional articles were identified by mining primary sources through these articles. Articles included reviews, observational epidemiology studies, and ecologic studies. Individual case reports and case series were identified in the search but not included as part of the epidemiologic review.

Published reviews and other studies indicate that ketamine abuse began soon after its approval as an anesthetic agent in 1970, but its popularity at dance clubs and raves rose in the 1980s and 1990s.(22-24) Ketamine is described as a drug abused as a recreational drug worldwide, often in the setting of electronic music parties and dance clubs, and has also been used for drug-facilitated sexual assault.(22-24) Illicit ketamine is available as aqueous solution, capsules, powder, crystals and tablets.(22) Adulterants are often added to the illicit formulations, especially in tablets. Ketamine is also used as an adulterant of ecstasy.(22, 25) Ketamine can be abused by insufflating powder, but ingesting, smoking or injecting are also routes of administration for abuse, depending on the form.(9, 22, 24)

Multiple articles describe harms from ketamine abuse. One review of published case studies and case series focused on people in Hong Kong who abuse ketamine, describing urological complications, neuropsychiatric complications, hepatobiliary complications, and gastrointestinal complications.(26) One study from Taiwan described sexual and bladder dysfunction associated with ketamine abuse among participants presenting at clinics and men who encountered law enforcement.(27)

Original observational epidemiology studies described patterns of illegal drug use, including ketamine abuse, in specific populations such as people who had used ecstasy in the past year, men who have sex with men and persons attending dance clubs.(28-30) The prevalence of ketamine abuse varied by the population studied. For example, in a study conducting secondary analysis of NSDUH data, 6.5% of people ages 12-34 years who had used ecstasy in the past-year
(N=332,560) reported past-year ketamine use in 2013-2014. In a cohort of Australian gay and bisexual men (N=1,710), the twelve-month incidence rate of ketamine use (i.e., abuse or misuse) was 2.1 per 100 person-years, and varied by age group from 4.1 per 100 person-years for ages 16-24 years to 0.98 per 100 person-years for persons 40 years and older. Multiple other studies report epidemiology of ketamine abuse and other illicit drugs in specific populations, many using convenience samples in non-U.S. populations.

### 3.3 National Survey on Drug Use and Health (NSDUH)

In 2017, 1.3% of NSDUH survey respondents aged 12 or older reported using ketamine during their lifetime, corresponding to an estimated 3.4 million U.S. residents (Table 3.3a). Those aged 18-25 years had the highest prevalence, with 1.8% in 2017 reporting lifetime ketamine use. This was much lower compared to lifetime use of other hallucinogens. For example, 7.0% of respondents aged 12 years and older and 12.0% of respondents aged 18-25 years reported lifetime use of ecstasy. For LSD, 9.6% of respondents aged 12 years and older and 9.1% of respondents aged 18-25 years reported lifetime use. For hallucinogens overall (including ketamine), 15.5% of respondents aged 12 years and older and 17.1% of respondents aged 18-25 years reported lifetime use. For additional context, among respondents 12 years and older 45.2% of respondents reported lifetime use of marijuana, 14.9% reported lifetime use of cocaine, and 1.9% reported lifetime use of heroin in 2017 (data not shown).

<table>
<thead>
<tr>
<th>Table 3.3a. Reported Lifetime Use of Ketamine and Related Drugs, by Age Group, National Survey on Drug Use and Health, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Ketamine</strong></td>
</tr>
<tr>
<td>Percent reporting lifetime use</td>
</tr>
<tr>
<td>Estimated number (in thousands)</td>
</tr>
<tr>
<td><strong>Ecstasy</strong></td>
</tr>
<tr>
<td>Percent reporting lifetime use</td>
</tr>
<tr>
<td>Estimated number (in thousands)</td>
</tr>
<tr>
<td><strong>LSD (Acid)</strong></td>
</tr>
<tr>
<td>Percent reporting lifetime use</td>
</tr>
<tr>
<td>Estimated number (in thousands)</td>
</tr>
<tr>
<td><strong>Hallucinogens (including ketamine)</strong></td>
</tr>
<tr>
<td>Percent reporting lifetime use</td>
</tr>
<tr>
<td>Estimated number (in thousands)</td>
</tr>
</tbody>
</table>

Source: “Table 1.96A Specific Hallucinogen, Inhalant, Needle, Heroin, and other Drug Use in Lifetime among Persons Aged 12 or Older, by Age Group: Numbers in Thousands, 2016 and 2017 and Table 1.96B Specific Hallucinogen, Inhalant, Heroin and other Drug Use in Lifetime among Persons Aged 12 or Older, by Age Group:
The 2017 NSDUH Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health does not report past month or past year ketamine use separately but describes past month hallucinogen use, a category which includes ketamine, LSD, ecstasy and others.(12) Table 3.3b shows the estimated prevalence of past month use of hallucinogens, by age group, in 2017. Not surprisingly, past month estimates are considerably lower than lifetime prevalence estimates in all age groups (Table 3.3a).

### Table 3.3b. Reported Past Month Hallucinogen Use, by Age Group, National Survey on Drug Use and Health, 2017

<table>
<thead>
<tr>
<th>Aged 12 years or older</th>
<th>Aged 12 to 17 years</th>
<th>Aged 18 to 25 years</th>
<th>Aged 26 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent using in past month</td>
<td>0.5</td>
<td>0.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Number (in thousands)</td>
<td>1,400</td>
<td>143</td>
<td>594</td>
</tr>
</tbody>
</table>

Source: “Figure 11. Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2017. and Figure 17. Past Month Hallucinogen Use Among People Aged 12 or Older, by Age Group: Percentages, 2017. SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2017.(12)

### 3.4 Monitoring the Future (MTF)

Among 12th graders, the estimated annual prevalence of ketamine use declined from 2.5% in 2000 to 1.2% in 2017 (1.4% for males and 0.7% for females), as shown in Figure 3.4.(15)

**Figure 3.4 Annual prevalence of ketamine use among 12th graders, Monitoring the Future, 2000-2017**

![Ketamine use in the last 12 months](chart)

Note: In order to maintain trends during questionnaire changes, estimates are based on varying proportions of the sampled populations in some years. See MTF documentation for details.(15)

Source: The Monitoring the Future study, the University of Michigan, Table 5-2. Long-Term Trends in Annual Prevalence of Use of Various Drugs for Grade 12(15)
Estimated annual prevalence of use for ketamine and select additional drugs from 2008 to 2017 are presented in Table 3.4 for context. The data suggest that, among 12th graders, the percentage who used ketamine in the last 12 months was generally lower than for other drugs, with the exception of heroin. In 2017, the he estimated annual prevalence of use for ketamine was most similar to that of Ritalin and inhalants. From 2007 to 2017, the percentage of 12th graders reporting past-year use of ketamine, Ritalin, OxyContin, Vicodin, heroin, inhalants, over the counter cough/cold medicines and cocaine all declined slightly.

| Table 3.4 Trends in annual prevalence of use of ketamine and other drugs in Grade 12, 2008-2017, percentage who used in the last 12 months |
|---|---|---|---|---|---|---|---|---|---|---|
| Ketamine | 1.5 | 1.7 | 1.6 | 1.7 | 1.5 | 1.4 | 1.5 | 1.4 | 1.2 | 1.2 |
| Ecstasy<sup>a</sup> | -- | -- | -- | -- | -- | -- | 5.0 | 3.6 | 2.7 | 2.6 |
| Ritalin<sup>b</sup> | 3.4 | 2.1 | 2.7 | 2.6 | 2.6 | 2.3 | 1.8 | 2.0 | 1.2 | 1.3 |
| OxyContin<sup>b</sup> | 4.7 | 4.9 | 5.1 | 4.9 | 4.3 | 3.6 | 3.3 | 3.7 | 3.4 | 2.7 |
| Vicodin<sup>b</sup> | 9.7 | 9.7 | 8.0 | 8.1 | 7.5 | 5.3 | 4.8 | 4.4 | 2.9 | 2.0 |
| Heroin | 0.7 | 0.7 | 0.9 | 0.8 | 0.6 | 0.6 | 0.6 | 0.5 | 0.3 | 0.4 |
| LSD | 2.7 | 1.9 | 2.6 | 2.7 | 2.4 | 2.2 | 2.5 | 2.9 | 3.0 | 3.3 |
| Inhalants | 3.8 | 3.4 | 3.6 | 3.2 | 2.9 | 2.5 | 2.9 | 1.9 | 1.7 | 1.5 |
| OTC Cough/ Cold Medicines<sup>c</sup> | 5.5 | 5.9 | 6.6 | 5.3 | 5.6 | 5.0 | 4.1 | 4.6 | 4.0 | 3.2 |
| Cocaine | 4.4 | 3.4 | 2.9 | 2.9 | 2.7 | 2.6 | 2.6 | 2.5 | 2.3 | 2.7 |
| Marijuana/ Hashish | 32.4 | 32.8 | 34.8 | 36.4 | 36.4 | 36.4 | 35.1 | 34.9 | 35.6 | 37.1 |

Note: In order to maintain trends during survey changes, data for multiple years and multiple drugs are based on varying proportions of the sampled populations. See MTF documentation for details.(15)

<sup>a</sup>This question was revised in 2014 and earlier years are not presented due to this change.

<sup>b</sup>Only use not under a doctor’s orders is included here.

<sup>c</sup>Only use “to get high” is included here.

Source: The Monitoring the Future study, the University of Michigan, Table 5-2. Long-Term Trends in Annual Prevalence of Use of Various Drugs for Grade 12

### 3.5 NATIONAL POISON DATA SYSTEM (NPDS) ANALYSIS

From January 1, 2013 to December 31, 2017 there were 1,454 ketamine exposure calls to U.S. poison control centers. The majority of these calls (67.8%) were due to intentional exposures, and intentional abuse and misuse contributed to more than half of all exposure calls (53.5%). Characteristics of all ketamine exposure calls and abuse and misuse exposure calls are described in Table 3.5a and 3.5b, respectively.
### Table 3.5a. Ketamine Exposure calls in the U.S. National Poison Data System, January 1, 2013 to December 31, 2017

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Exposures</strong></td>
<td>309</td>
<td>327</td>
<td>308</td>
<td>260</td>
<td>250</td>
<td>1454</td>
</tr>
<tr>
<td><strong>Intentional</strong></td>
<td>208</td>
<td>227</td>
<td>223</td>
<td>164</td>
<td>164</td>
<td>986</td>
</tr>
<tr>
<td>Suspected suicide</td>
<td>24</td>
<td>32</td>
<td>32</td>
<td>35</td>
<td>38</td>
<td>161</td>
</tr>
<tr>
<td>Abuse</td>
<td>169</td>
<td>174</td>
<td>165</td>
<td>114</td>
<td>109</td>
<td>731</td>
</tr>
<tr>
<td>Misuse</td>
<td>7</td>
<td>12</td>
<td>14</td>
<td>7</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>9</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td><strong>Unintentional</strong></td>
<td>62</td>
<td>63</td>
<td>43</td>
<td>57</td>
<td>55</td>
<td>280</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>22</td>
<td>21</td>
<td>17</td>
<td>23</td>
<td>21</td>
<td>104</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>7</td>
<td>17</td>
<td>7</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>36</td>
</tr>
</tbody>
</table>


Among the 778 intentional abuse and misuse ketamine exposure calls, a little more than half (53.4%) involved only one substance. Among cases with only one substance, moderate effect was the most frequent related clinical effect, and ingestion was the most commonly reported route of exposure. Inhalation was the second most frequent route of exposure. Multiple routes of exposure could be selected for a single case. These descriptive characteristics for intentional abuse and misuse exposures are shown below in **Table 3.5b**.
3.6 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) ANALYSIS

In 2016-2017, based on 44 surveillance cases, there were an estimated 669 (95% CI 949-3,628) ED visits nationally for adverse events related to ketamine. Of the 44 cases identified in the surveillance sample, 35 (81.5% [95% CI 61.0-100.0%]) were classified as abuse. National estimates of the number of ED visits due to ketamine abuse were not stable due to a high coefficient of variation (>0.30). Of the 35 cases involving abuse, six were hospitalized. Routes of ketamine abuse included swallowing, inhaling/snorting and IV injection; however, in most cases the route of administration was unknown. No cases were found for overdose without indication of intent or therapeutic misuse. Table 3.6 describes the NEISS-CADES cases for ketamine related ED cases.

Most (60%) of the 35 abuse cases also involved illicit drugs (cocaine, heroin, marijuana, methamphetamine, fentanyl, or other), alcohol, or both. Of all the ketamine abuse cases, 10
involved another approved medication, dietary supplement, homeopathic product, or vaccine (data not shown).

| Table 3.6 Ketamine Related Emergency Department Cases, National Electronic Injury Surveillance System- Cooperative Adverse Drug Event Surveillance Sample, 2016-2017 |
|---|---|---|---|
| | Abuse | Therapeutic Use | Assault | Total |
| Total | 35 | 8 | 1 | 44 |
| Route | | | | |
| Oral | | | 1 | 2 |
| Nasal | 6 | 1 | | 7 |
| Injection | 3 | 4 | | 7 |
| Infusion | 0 | 1 | | 1 |
| Unknown | 25 | 2 | | 27 |
| Medical disposition | | | | |
| Hospitalized | 6 | 1 | | 7 |
| Not hospitalized<sup>a</sup> | 29 | 7 | | 37 |

<sup>a</sup>Includes “left without being seen LWBS/ left against medical advice LAMA” (n=3 for abuse)


3.7 FDA Adverse Event Reporting System (FAERS)

Below is a summary of results of the FAERS search conducted by DPV II for a memo on ketamine abuse in October 2017. (DARRTS ref ID 4161583)

The FAERS search from January 1, 2015 to September 11, 2017 for serious U.S. cases of ketamine associated with drug abuse retrieved 39 reports. Abuse reports for ketamine include all reports coded under the MedDRA Drug abuse, Dependence, and Withdrawal (SMQ) Broad, including reports coded to the preferred term (PT) Intentional product misuse. These reports have not been manually reviewed and, as such, the data may contain duplicates. Further, a causal association of the reported adverse event(s) or reported outcome(s) with ketamine exposure was not determined for this assessment. The 39 cases were received by FDA from 2015 to 2017 although some of these cases had occurred in previous years. Only 13 reports included information on event year, and these years ranged from 2013 to 2017. Approximately 43.6% (17/39) of the reports reported an outcome of death, and 53.8% (21/39) of the reports involved hospitalization. Deaths and hospitalizations were not mutually exclusive case outcomes. Table 3.7 provides descriptive characteristics of the ketamine FAERS reports.
Table 3.7. Descriptive Case Characteristics of U.S. FAERS Reports of Ketamine Associated with Abuse,* Received by FDA from January 1, 2015 to September 11, 2017 (N=39)†

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1 – 12</th>
<th>13 – 18</th>
<th>19 – 40</th>
<th>41 – 60</th>
<th>61 and older</th>
<th>Unknown</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>19</td>
<td>4</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporter type</th>
<th>Health care professional‡</th>
<th>Consumer</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Report type</th>
<th>Expedited (15-Day)</th>
<th>Direct</th>
<th>Non-expedited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reported route</th>
<th>Nasal/inhalation</th>
<th>Intramuscular</th>
<th>Intravenous</th>
<th>Parenteral</th>
<th>Oral/Buccal</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA preferred terms§ (n=37)</th>
<th>Drug use disorder</th>
<th>Toxicity to various agents</th>
<th>Overdose</th>
<th>Unresponsive to stimuli</th>
<th>Sedation</th>
<th>Biliary dilatation</th>
<th>Drug withdrawal syndrome</th>
<th>Off label use</th>
<th>Accidental overdose</th>
<th>Hydronephrosis</th>
<th>Intentional product misuse</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>11</td>
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</table>

* All serious reports coded under the MedDRA Drug abuse, dependence, and withdrawal (SMQ) Broad were included.
† These reports have not been manually reviewed and, as such, may include duplicates.
‡ Healthcare professional reports include those indicating the reporter’s qualifications as a healthcare professional, physician, or a pharmacist.
§ Most frequently reported MedDRA preferred terms with n≥3. A report may include more than one preferred term.

Reports were most frequently reported in the 19 – 40 year-old age group. The majority of the reporters identified themselves as a physician, pharmacist, or a healthcare professional. The routes of suspected abuse were described in 15 reports as parenteral/intravenous/intramuscular (n=7), nasal/inhalation (n=4), oral/buccal (n=3), or transdermal (n=1).
The majority of the ketamine reports (28/39) reported one or more co-suspect drugs. These drugs included the Schedule 1 controlled substances, marijuana\(^b\) (n=3), and heroin (n=2). The co-suspect drugs also included a substance that is not scheduled at the federal level, methoxetamine (n=1) – a dissociative hallucinogen, structurally similar to ketamine and phencyclidine (PCP), and other products from various drug classes. Of the remaining eleven reports listing ketamine as the only suspect drug, only one reported an outcome of death.

4 DISCUSSION

Ketamine abuse has been reported for decades, and recent data indicate that it continues to occur, resulting in more than a hundred calls to poison control centers annually. Ketamine use also led to an estimated 669 ED visits in the U.S. in 2016-2017, with a large majority of cases being classified as abuse. National survey data indicate that ketamine abuse is relatively uncommon in the general population, with a lifetime prevalence of 1.3%, lower than other commonly abused hallucinogens, such as ecstasy and LSD (Acid). While still relatively low, lifetime ketamine abuse prevalence is highest in the 18-25 year old age group (1.8% in 2017), consistent with literature describing its use predominantly by older adolescents and young adults attending dance clubs and “raves.” Among 12th graders specifically, ketamine abuse is also relatively infrequent and has declined since 2000.

There were 35 ED cases involving abuse in the NEISS-CADES surveillance sample in 2016-2017 and 778 poison center exposure calls involving ketamine abuse or misuse (731 cases of abuse) in NPDS from 2013-2017. To help contextualize these numbers, we refer to recent FDA reviews describing abuse of propofol (another anesthetic agent with abuse potential), buprenorphine, and oxycodone (DARRTS Reference IDs: 4298560, 4361854, 4295073). The NEISS-CADES sample of EDs had no cases of propofol abuse and 751 cases of oxycodone non-medical use in 2016, and 287 cases of buprenorphine abuse in 2016-2017. NPDS contained 27 propofol and 3,233 buprenorphine abuse exposure calls from 2013-2017, 51,836 oxycodone abuse exposure calls from 2012-2016. These selected comparisons suggest that, not surprisingly, the public health burden of ketamine abuse is very low compared to that associated with prescription opioids.

When documented, the NPDS, NEISS-CADES, and FAERS data indicate that ketamine is abused via multiple routes—most commonly intranasal, ingestion/ oral, and injection (parenteral)—although the relative proportion of cases involving each of these routes varies by data source, and route is often unknown.

Clinical outcomes also varied by reporting system but, in general, suggest that ketamine abuse is infrequently associated with severe adverse outcomes, at least in the acute setting. A minority of the NEISS-CADES ED abuse visits resulted in hospitalization, even accounting for the three cases involving patients who left without being seen or against medical advice. Moderate health effects were the most commonly reported medical outcome among single-substance ketamine abuse and misuse exposure calls in NPDS, followed by minor effect, and there were no deaths.

\(^b\) Reported as cannabis sativa subsp. indica top.
identified among those cases. Reports of deaths and hospitalization were identified in FAERS in association with ketamine abuse, but only one report listed ketamine as the only suspected drug, and drug-event causal association has not been assessed for any of the FAERS cases.

Sales data from the previous FDA review are provided in Background Package Attachment 1 to provide insight into the magnitude of potential total use in the clinical setting and to provide context for the potential for diversion. Although sales data do not provide a direct measure of patient use, the amount of product purchased by various settings of care may be a possible surrogate for use if we assume the facilities purchase drugs in quantities reflective of actual patient use. Based on national sales distribution patterns of ketamine vials, the utilization appears to be largely in the hospital setting. Notably, sales to clinic settings more than doubled during 2013-2017, suggesting changes in utilization patterns. However, national data on diagnoses or indications directly linked with the administration of ketamine in the clinic or hospital settings were not available. We were not able to determine if the increasing sales are due to increases in off-label use, but literature suggests an increased interest in off-label use of ketamine. We were unable to assess off-label use as a source of diversion or abuse specifically. Despite increasing ketamine sales in recent years, and published literature suggesting growing interest in off-label therapeutic use of ketamine, the available trend data from NPDS and MTF do not suggest recent increases in ketamine abuse in the U.S. Rather, they suggest that ketamine abuse may even be declining. The U.S. DEA reports that most of the ketamine illegally distributed in the U.S. is diverted or stolen from sources such as veterinary clinics or smuggled into the U.S. from Mexico and then sold or shared among friends and acquaintances at parties or nightclubs, so it may be that increased use of ketamine in supervised medical settings has not translated to a corresponding growth in abuse.

**Limitations of the Data**

To summarize the most recent reports from epidemiologic studies on ketamine abuse, we restricted our literature review to the most recent publications (2016-2017). As a result, we identified only a subset of the many published studies on ketamine abuse since its approval. Additionally, many of the observational studies that we identified were limited to specific population subgroups or populations outside of the U.S., where abuse patterns may differ from those in the U.S.

Although NSDUH and MTF are capable of producing national estimates of drug misuse and abuse, they are subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. Additionally, individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility.

NPDS captures exposure events that are called in by someone asking for help with the exposure (public or healthcare professional), and information is limited to what is provided by the caller. These calls likely represent a small proportion of exposure events and are not likely to be representative of all abuse exposures, but it is informative for characterizing the public health burden of acute harms from ketamine abuse. AAPCC cautions that “data referenced from AAPCC should not be construed to represent the complete incidence of national exposures to
any substance(s)” (AAPCC Data Policies, October 2015). In particular, unwitnessed out-of-hospital deaths due to drug overdoses are unlikely to generate a call to poison control centers.

We did not include NEISS-CADES data prior to 2016 because abuse related ED visits were not previously captured in this database. NEISS-CADES data include reports from approximately 60 hospitals throughout the United States and are nationally representative. However, the data may be limited by low sensitivity; NEISS-CADES reports an overall sensitivity of 33% but this varies by type of adverse drug event (NEISS-CADES user’s manual, 2017).

We included FAERS data from a previous review by DPV II (October 2017; DARRTS ref ID 4161583) to add to our understanding of ketamine abuse and the nature of adverse events associated with this abuse. The FAERS assessment is a high-level overview of the reports in the database received from January 2015 to September 11, 2017. As such, individual cases have not been reviewed; therefore, the data may contain duplicates, and drug-event causal association has not been assessed. As part of the sponsor’s pharmacovigilance regulatory requirements, they are required to monitor and report medical literature case reports. The FAERS database contains case reports from the NPDS database through the published American Association of Poison Control Centers annual reports; thus, there may be overlap in the data presented in the FAERS and NPDS sections of this review.

The FAERS database is a passive reporting system and has a number of limitations, including under-reporting. In particular, cases of drug abuse are likely under reported to FAERS because people who abuse drugs are unlikely to report, as supported by the relatively low number of consumer reports received for ketamine. Missing data from these systems, and the potential for misclassification (e.g., of abuse as non-abuse) are two limitations common to both FAERS and NPDS. This hinders our ability to provide comprehensive characteristics of patients abusing these drugs, and may lead to underestimates of the true public health burden caused by the abuse of these drugs. Given the spontaneous nature of adverse event reports and limitations described, these data cannot be used to inform the rate of abuse.

5 Conclusions

The risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and postmarket surveillance for esketamine, if approved. Ketamine abuse has been recognized for decades, and it is classified as a Schedule III drug under the Controlled Substances Act. In recent years, there have been numerous cases of ketamine abuse resulting in adverse events or the need for medical attention or advice; however, most of these cases resulted in minor or moderate adverse effects and did not require hospitalization. National surveys indicate a low prevalence of ketamine use in the general population and in high school students, consistent with literature suggesting that ketamine abuse is concentrated in smaller population subgroups such as older adolescents and young adults participating in “rave” or nightclub scenes. We did not observe increasing trends in ketamine abuse calls to poison centers or in self-reported abuse despite contemporaneous increasing sales and expanding off-label use of ketamine. According to DEA reports, much of the illegally distributed ketamine in the U.S. is smuggled in from other countries or diverted from veterinary sources, and the evidence is insufficient to know whether the distribution and use of pharmaceutical ketamine in humans contribute substantially to ketamine abuse in the U.S.
<table>
<thead>
<tr>
<th>Intentional Exposure Reasons</th>
<th>NPDS Definition</th>
<th>Case Inclusions/ Exclusions examples</th>
</tr>
</thead>
</table>
| **Suspected Suicides**       | “An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons.” | “Case Inclusions: Suicides, suicide attempts, and suicide gestures, whether suspected or confirmed  
• Cases in which history indicates patient was upset or depressed  
• Patients who provide explanations for their actions such as "arguing with parents," "disturbed about poor grades," or "having marital problems"  
• Ingestions of large quantities of one or more drugs where the only likely explanation is the patient's intent to harm himself” |
| **Abuse**                    | “An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect”, including recreational use of a substance for any effect. | “Case Inclusions:  
A person who inhales helium to talk funny  
• A person who uses GHB at a dance club  
• An infant with toxic effects or withdrawal symptoms as a result of the mother’s drug abuse while the child was in utero or while breast-feeding” |
| **Misuse**                   | “An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.” | “Case Inclusions:  
A person deliberately mixes or applies a pesticide inappropriately so it will be more effective  
• A person deliberately increases the dosage of a medication to enhance its therapeutic effect  
• Overuse of caffeine to study for an exam  
Case Exclusions:  
Patients who want to get high (should be INTENTIONAL ABUSE)  
• Suspected child abuse (should be OTHER-MALICIOUS)” |
| **Unknown**                  | Exposures that are deemed to be intentional although the specific motive is undetermined. | N/A |
## APPENDIX B. NPDS DEFINITION FOR MEDICAL OUTCOME

<table>
<thead>
<tr>
<th>Medical Outcome</th>
<th>NPDS Definition</th>
</tr>
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<tbody>
<tr>
<td><strong>No Effect</strong></td>
<td>“The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.”</td>
</tr>
<tr>
<td><strong>Minor Effect</strong></td>
<td>“The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.”</td>
</tr>
<tr>
<td><strong>Moderate Effect</strong></td>
<td>“The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.”</td>
</tr>
<tr>
<td><strong>Major Effect</strong></td>
<td>“The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.”</td>
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APPENDIX C. NPDS GENERIC AND PRODUCT CODES

<table>
<thead>
<tr>
<th>NPDS Generic and Product Codes Use for NPDS Data Extraction</th>
<th>Generic Code</th>
<th>Product Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td></td>
<td>(b) (4)</td>
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</table>

Note: These product codes must be redacted for public release
APPENDIX D. NEISS-CADES DEFINITIONS OF ADVERSE DRUG EVENTS

<table>
<thead>
<tr>
<th>NEISS-CADES Definitions for Definitions of Case Type from NEISS-CADES Data Dictionary</th>
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<tbody>
<tr>
<td><strong>Analytic Category</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td><strong>ABUSE</strong></td>
</tr>
<tr>
<td><strong>UNKNOWN INTENT</strong></td>
</tr>
<tr>
<td><strong>THERAPEUTIC MISUSE</strong></td>
</tr>
<tr>
<td><strong>UNSUPERVISED PEDIATRIC EXPOSURE</strong></td>
</tr>
<tr>
<td><strong>THERAPEUTIC USE</strong></td>
</tr>
<tr>
<td><strong>SELF-HARM/SUICIDE</strong></td>
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<tr>
<td><strong>ASSAULT</strong></td>
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APPENDIX E. 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.
7 References


