NDA 211243 Esketamine
Treatment of Treatment-Resistant Depression (TRD)
CLINICAL OVERVIEW: EFFICACY

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Outline

• Overview of treatment-resistant depression
• Esketamine background
• Studies submitted for efficacy of esketamine
Treatment-Resistant Depression (TRD)

- Major depressive disorder (MDD) unresponsive to at least two antidepressants (monotherapy) of adequate dose and duration (usually at least 4 to 6 weeks) including current episode.

- TRD is an extremely serious, life-threatening condition with increased rates of suicide, hospitalization, and impairment in daily functioning (employment, relationships, self-care).
Treatment-Resistant Depression (TRD)

• 2016 NIMH data indicate 16.2 million adults in the US (121 million worldwide) have had at least one MDD episode

• Estimates of TRD range from:
  – 29 to 46% of the MDD population (Fava and Davidson, 1996)
  – 55 to 75% in a UK primary care MDD population (Wiles, 2014; Thomas, 2013)
Current Treatments for TRD

• Only FDA-approved drug for TRD is olanzapine-fluoxetine combination

• Other FDA-approved devices for TRD: ECT, VNS, TMS*

• Off-label treatments include: drugs from multiple classes (antipsychotics, lithium, thyroid hormone, ketamine), often in combination with antidepressant

*Electroconvulsive therapy (ECT); vagus nerve stimulator (VNS); transcranial magnetic stimulation (TMS)
Ketamine: Sales Data

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-termcare, mail-order, and chain/independent pharmacies.
Esketamine: Product Description

• S-enantiomer of ketamine (approved in 1970 under NDA 16812 for anesthesia)
• N-methyl-D-asparate (NMDA) receptor antagonist (non-competitive)
• Esketamine already approved in Europe and Latin America for anesthesia indication (IV/IM use)
• Proposed indication: treatment of TRD (separate IND also underway for MDD with imminent risk of suicide)
• Route of administration: intranasal (IN)
Esketamine: Proposed Use and Administration

- IN esketamine given in combination with newly initiated oral antidepressant
- 56 mg or 84 mg IN esketamine
  - Induction: two times a week for 4 weeks
  - Maintenance:
    - Weekly for next 4 weeks (“optimization” per Applicant)
    - Then weekly or every other week depending on treatment response, for ongoing maintenance
Esketamine: Proposed Use and Administration

• **Potential chronic dosing** for maintenance treatment
• Differs from anesthesia use
  – **Lower** dose
  – **Chronic** administration
• Administration at supervised settings only, with REMS certified clinician
Montgomery-Åsberg Depression Rating Scale (MADRS)

- 10-Item clinician-administered questionnaire
- Each item rated 0 to 6
- Scores range from 0 (asymptomatic) to 60 (most symptomatic)
- Items cover: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts
- Severity categories (variable): 0 to 6 = asymptomatic; 7 to 19 = mild depression; 20 to 34 = moderate depression; >34 = severe depression
- For esketamine studies, independent remote clinicians (including by phone) rated MADRS, to improve blinding
Regulatory History: TRD Definition

- May 2012: FDA and Applicant agreed to TRD regulatory definition
  - Failure of response (≤25% reduction on MADRS with minimum score ≥28 for adults, ≥24 geriatric) to treatment with at least prior two antidepressants as monotherapy, given at adequate dose and duration (at least 6 weeks)
Phase 3 Studies Submitted for Efficacy

• Parallel-group studies (adult, 4-week treatment)
  – Study 3001: fixed-dose (56 and 84 mg)
  – Study 3002: flexible-dose (56 and 84 mg)
  – Study 3005: flexible-dose (28, 56, and 84 mg), geriatric (ages 65+)

• Randomized withdrawal study 3003 (adult)
  – Doses: 56 and 84 mg

• Open-label long-term safety study 3004
  – Multi-year safety study 3008 ongoing
Short-Term Phase 3 Study Design

- Screening/observational phase (4 to 7 weeks)
- **4-week double-blind treatment phase (Induction)**
  - Both of the following are initiated simultaneously:
    - **IN** Esketamine or Placebo *Twice Weekly* PLUS
    - Newly Initiated Oral Antidepressant *Daily* (sertraline, escitalopram, venlafaxine XR, or duloxetine)
- Follow-up phase or transfer to long-term Study (3003 or 3004 or 3008)
Primary Efficacy Endpoint and Analysis for Short-Term Phase 3 Study

- **Endpoint**: change from baseline on MADRS total score at Day 28
- **Analysis**: difference in LS means between esketamine and placebo groups compared using mixed model for repeated measures (MMRM)
Intranasal Placebo + New Oral OL AD

Intranasal Esketamine 56mg + New Oral OL AD

Intranasal Esketamine 84mg + New Oral OL AD

MDD subjects with non-response to ≥ 1 but ≤ 5 oral AD treatments in current depressive episode and currently taking a different oral AD for at least the previous 2 weeks (at or above minimum therapeutic dose)

Non Responders Prior AD D/C n≈348

Continuation of oral AD treatment

Responders Ineligible for randomization

Screening/Prospective Observational Phase

4 Weeks (+ optional taper up to 3 weeks)

Double-Blind Induction Phase
Intranasal dose frequency: 2x per week

4 weeks

Source: Adapted from Applicant's Clinical Study Report
Study 3002 Design

MDD subjects with non-response to ≥1 but ≤5 oral AD treatments in current depressive episode and currently taking a different oral AD for at least the previous 2 weeks (at or above minimum therapeutic dose)

Continuation of same oral AD treatment

Non Responders Prior AD D/C n~196

Intranasal Placebo + New Oral OL AD

Intranasal Esketamine Flex 56 or 84mg + New Oral OL AD

Responders Ineligible for randomization

Screening/Prospective Observational Phase

4 Weeks (+ optional taper up to 3 weeks)

Double-Blind Induction Phase

Intranasal dose frequency: 2x per week

4 weeks

Source: Adapted from Applicant’s Clinical Study Report
**Study 3005 Design (Ages 65+)**

- **MDD**
  - Subjects with non-response to ≥ 1 but ≤ 8 oral AD in current depressive episode and currently taking a different Oral AD for at least 2 weeks (at or above minimum therapeutic dose)

- **Non Responders**
  - Intranasal Placebo + New Oral OL AD
  - Intranasal Esketamine (28mg, 56 or 84mg) + New Oral OL AD

- **Ineligible for Randomization in DB Phase**
  - Screening/prospective observational phase*
    - 4 weeks
  - DB Induction Phase
    - Intranasal Med Dose Freq 2x/wk
    - 4 wks

*Source: Adapted from Applicant’s Clinical Study Report*
Clinical Remission and Response in Esketamine Program

• **Remission**: MADRS total score ≤12

• **Response**: ≥50% reduction in MADRS total score from baseline (Day 1 of induction phase prior to first dose), without meeting criteria for remission
Study 3003 Design

Primary Analysis
Population

Source: Adapted from Applicant's Clinical Study Report
Study 3003

• Stable remitters (MADRS ≤12) or stable responders (≥50% MADRS decrease) to previous treatment are randomized to either:
  – Continued on esketamine at the same dose they were taking (56 or 84 mg)
  – Or switched to placebo

• Oral antidepressant ongoing in both arms

• Weekly or every other week esketamine/placebo treatment is continued
Study 3003: Primary Endpoint and Analysis (Stable Remitter Population)

• **Time to relapse**
  – MADRS total score (≥22 for 2 consecutive assessments separated by 5 to 15 days)
  – Clinically significant event (i.e., hospitalization, suicide attempt, etc.)

• Esketamine group versus placebo group compared using log-rank test
Phase 3 Efficacy Results

• Study 3002 (flexible-dose at ESK 56 or 84 mg) at \(0.010\) (one-sided p-value compared to 0.025)

• Study 3003 (randomized withdrawal design; stable remitters) at \(0.003\) (two-sided p-value compared to 0.05)
## Primary Efficacy Results for Esketamine: TRD Short-Term Phase 3 Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: MADRS Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESK or Placebo</td>
<td>Mean Baseline Score (SD)</td>
</tr>
<tr>
<td>3001</td>
<td>ESK 56 mg (115)</td>
<td>37.4 (4.8)</td>
</tr>
<tr>
<td></td>
<td>ESK 84 mg (114)</td>
<td>37.8 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Placebo (113)</td>
<td>37.5 (6.2)</td>
</tr>
<tr>
<td>3002</td>
<td>ESK (56 or 84 mg)* (114)</td>
<td>37.0 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo (109)</td>
<td>37.3 (5.7)</td>
</tr>
<tr>
<td>3005 (Ages 65+)</td>
<td>ESK (28, 56, or 84 mg) (72)</td>
<td>35.5 (5.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo (65)</td>
<td>34.8 (6.4)</td>
</tr>
</tbody>
</table>

*aLower dose could not be tested because the higher dose failed  
b*p-values not adjusted for multiple comparisons  
*Arm statistically significant compared to placebo
Study 3002 Primary Endpoint:
MADRS: LS Mean Change from Baseline
Study 3002 Primary Endpoint: MADRS: Distribution of Responses at Day 28
Study 3002 Efficacy Highlights

Evidence

• Statistical significance on primary endpoint
• MADRS distribution of response favors ESK arm over placebo for multiple response thresholds (not statistically compared)

Uncertainties

• No major ones
Primary Efficacy Results for Maintenance-of-Effect Study 3003 (Stable Remitters)

<table>
<thead>
<tr>
<th></th>
<th>Esketamine + Oral AD</th>
<th>Placebo + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Randomized</strong></td>
<td>90</td>
<td>86</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></td>
<td>25% percentile (95% CI)</td>
<td>153 (105 to 225)</td>
</tr>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>NE\textsuperscript{a}</td>
</tr>
<tr>
<td><strong>Hazard Ratio\textsuperscript{b} (95% CI)</strong></td>
<td>0.49 (0.3 to 0.8)</td>
<td>--</td>
</tr>
<tr>
<td><strong>2-sided P-value\textsuperscript{c} (compared to 0.05)</strong></td>
<td>0.003</td>
<td>--</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NE – not estimable
\textsuperscript{b}Hazard ratio (HR) compares esketamine arm to placebo arm.
\textsuperscript{c}P-value adjusted for interim analysis that included a sample size re-estimation
Study 3003 Primary Endpoint: Time to Relapse of Depression in Stable Remitters

![Graph showing time to relapse of depression with Placebo and Esketamine + Oral AD comparisons]

<table>
<thead>
<tr>
<th>Strata</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 54 23 8 6 1 0</td>
</tr>
<tr>
<td></td>
<td>86 35 19 5 3 2 0</td>
</tr>
</tbody>
</table>
## Secondary Efficacy Results for Maintenance-of-Effect Study 3003
### (Stable Responders)

<table>
<thead>
<tr>
<th></th>
<th>Esketamine + Oral AD</th>
<th>Placebo + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Randomized</strong></td>
<td>62</td>
<td>59</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</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days)</td>
<td><strong>25% percentile (95% CI)</strong></td>
<td><strong>24 (17 to 46)</strong></td>
</tr>
<tr>
<td></td>
<td>217 (56 to 635)</td>
<td>24 (17 to 46)</td>
</tr>
<tr>
<td></td>
<td><strong>Median (95% CI)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>635 (264 to 635)</td>
<td>88 (46 to 196)</td>
</tr>
<tr>
<td><strong>Hazard Ratioa (95% CI)</strong></td>
<td>0.30 (0.16 to 0.55)</td>
<td>--</td>
</tr>
<tr>
<td><strong>2-sided P-value (compared to 0.05)</strong></td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

*aHazard ratio (HR) compares esketamine arm to placebo arm.*

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Study 3003 Secondary Endpoint: Time to Relapse of Depression in Stable Responders

- **Placebo + Oral AD**
- **Esketamine + Oral AD**

- **Cumulative Probability of Relapse**

<table>
<thead>
<tr>
<th>Strata</th>
<th>0</th>
<th>30</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>62</td>
<td>35</td>
<td>18</td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>59</td>
<td>22</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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Changes in Perception of Treatment Assignment via Changes in Dissociative Side Effects?

• CADSS score as a proxy for changes in subject perception of treatment assignment

• Dissociation measured by Clinician-Administered Dissociative States Scale (CADSS)
  – 23 item scale with item scores 0-4
  – Total score 0-92
  – Subjects report most dissociation at 40 minutes post-dose
  – Large change in CADSS after randomization to placebo

• Do subjects notice this change?
Study 3003: Dissociative Symptoms Trajectories

Maintenance Phase

Randomization

Esketamine

Placebo

Dispostion
- No relapse observed
- Relapsed

Visit Day

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Study 3003 Primary Endpoint: Sensitivity to Exclusion of a Single Site

- **Stable remitters**: HR changes from 0.49 (95% CI: 0.3-0.8) to 0.58 (95% CI: 0.37-1.02)

- **Stable responders**: HR changes from 0.30 (95% CI: 0.16-0.55) to 0.37 (95% CI: 0.20-0.70)

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Arm</th>
<th>Number of Relapses</th>
<th>Total Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Remitters</td>
<td>ESK</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stable Responders</td>
<td>ESK</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
Study 3003 Efficacy Highlights

Evidence
• Statistically significant for:
  – Primary endpoint in stable remitter population
  – Secondary endpoint in stable responder population
• Demonstrates longer-term maintenance of effect with esketamine plus oral AD (versus oral AD alone)

Uncertainties
• Change in subjects’ perception of treatment assignment influenced by acute subjective effects?
• Log-rank test results sensitive to exclusion of a single site (stable remitter population)
• Do these results generalize to a esketamine naïve population?
Study 3002 vs. Study 3001 Primary Endpoint: MADRS: LS Mean Change from Baseline

**Study 3002**

**Study 3001**
Study 3002 vs. Study 3005 Primary Endpoint: MADRS: LS Mean Change from Baseline

Study 3002

Study 3005 (Ages 65+)

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## MADRS Score Changes in Other Antidepressant Trials

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antidepressant</th>
<th>MADRS LS&lt;sup&gt;a&lt;/sup&gt; Mean CFB&lt;sup&gt;b&lt;/sup&gt; 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</td>
<td>-8.6 to -14</td>
<td>n/a</td>
<td>23 to 30</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine (vs. OLZ+FLX)</td>
<td>-1.2 to -11</td>
<td>-1.4 to -12</td>
<td>“</td>
</tr>
<tr>
<td></td>
<td>Olanzapine (vs. OLZ+FLX)</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>

<sup>a</sup>LS – least square  
<sup>b</sup>CFB – change from baseline
Esketamine: Potential Practical Advantages Over Existing TRD Treatments

- Potentially faster onset of action
- Intranasal dosing (less invasive than IV or IM)
- Different mechanism of action and AE profile from existing ADs
- Fewer drug-drug interactions than existing ADs
- Less frequent dosing regimen
- No need for general anesthesia, surgical intervention, or exogenous electrical exposure (as with ECT, TMS, VNS)
Efficacy Summary – Evidence

• One positive parallel-group RCT (Study 3002) at p-value = 0.010 (one-sided, compared to 0.025)

• One positive randomized withdrawal study (Study 3003) in two enriched populations
  – Stable remitters at p-value = 0.003 (two-sided, compared to 0.05)
  – Stable responders at p-value <0.001 (two-sided, compared to 0.05)
Efficacy Summary – Uncertainties

• 3001 not positive with formal statistical testing
  – ESK 84 mg dose failed
  – Statistical testing stopped after testing 84 mg dose
  – Inconclusive dose response

• 3005 not positive with formal statistical testing

• Subjects’ perception of treatment assignment potentially influenced by acute subjective effects (particularly in 3003 with early placebo relapses)

• Does Study 3003 with an enriched population confirm the results of Study 3002?
CLINICAL OVERVIEW: SAFETY

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Esketamine Development Program: Safety Population

- A total of 1708 subjects in one phase 2 Study (2003) and five phase 3 Studies; 1601 in phase 3 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Esketamine flexible dose</th>
<th>Esketamine 56 mg</th>
<th>Esketamine 84 mg</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3001 (&lt; 65)</td>
<td></td>
<td>115</td>
<td>116</td>
<td>113</td>
<td>346</td>
</tr>
<tr>
<td>3002 (&lt; 65)</td>
<td></td>
<td></td>
<td></td>
<td>109</td>
<td>236</td>
</tr>
<tr>
<td>3005 (age &gt; 65)</td>
<td></td>
<td>72</td>
<td></td>
<td>65</td>
<td>139</td>
</tr>
<tr>
<td>3003 Maintenance/Randomized withdrawal</td>
<td>152</td>
<td></td>
<td></td>
<td>145</td>
<td>297</td>
</tr>
<tr>
<td>3003 Induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3003 Optimization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>779</td>
</tr>
</tbody>
</table>

[Image: Esketamine Development Program: Safety Population chart]
Esketamine Exposure and Duration

• Short-term (4-week) placebo-controlled trials: Studies 3001, 3002, and 3005: 3074 treatments in 418 subjects

• Study 3003, maintenance phase – long-term randomized withdrawal

<table>
<thead>
<tr>
<th>Number of esketamine treatments:</th>
<th>1 to 5</th>
<th>6 to 10</th>
<th>11 to 20</th>
<th>21 to 30</th>
<th>31 to 40</th>
<th>41 to 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>45</td>
<td>45</td>
<td>25</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

• Open-label subjects in Studies 3003 and 3004

<table>
<thead>
<tr>
<th>Number of esketamine treatments:</th>
<th>1 to 5</th>
<th>6 to 10</th>
<th>11 to 20</th>
<th>21 to 30</th>
<th>31 to 40</th>
<th>41 to 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>146</td>
<td>394</td>
<td>465</td>
<td>160</td>
<td>164</td>
<td>118</td>
</tr>
</tbody>
</table>
## Deaths in Esketamine Studies

- Two deaths on esketamine in RCT
- Four deaths on esketamine in uncontrolled open label studies
- No deaths on placebo

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Time after last dose</th>
<th>Cause of death</th>
<th>Study; study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 M</td>
<td>26 hours</td>
<td>Motorcycle accident</td>
<td>3002; short term RCT*</td>
</tr>
<tr>
<td>41 M</td>
<td>20 days</td>
<td>Suicide (hanging)</td>
<td>2003; short term RCT*</td>
</tr>
<tr>
<td>38 M</td>
<td>3 days</td>
<td>Suicide (gunshot)</td>
<td>3008; open-label (uncontrolled)</td>
</tr>
<tr>
<td>55 F</td>
<td>13 days</td>
<td>Suicide (multi-drug overdose)</td>
<td>3004; open-label (uncontrolled)</td>
</tr>
<tr>
<td>60 M</td>
<td>5 days</td>
<td>Sudden death</td>
<td>3004; open-label (uncontrolled)</td>
</tr>
<tr>
<td>74 F</td>
<td>6 days</td>
<td>Myocardial infarction</td>
<td>3008; open-label (uncontrolled)</td>
</tr>
</tbody>
</table>

*Randomized, double-blind, placebo-controlled trial
ADVERSE EVENTS
Approach to Adverse Event Analysis

• Adverse events are categorized using the Medical Dictionary for Regulatory Activities (MedDRA)
• Verbatim reports from subjects are coded to “preferred terms” based on standard MedDRA terms
• To capture complex phenomena like dissociation, we grouped multiple terms potentially suggestive of these adverse events of special interest
## Grouping of Adverse Event Terms

<table>
<thead>
<tr>
<th>Applicant grouped:</th>
<th>We added:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissociation</strong></td>
<td></td>
</tr>
<tr>
<td>dissociation; depersonalization/derealization disorder;</td>
<td>dysgeusia; dysmetropsia;</td>
</tr>
<tr>
<td>dissociation; depersonalization/derealization disorder;</td>
<td>feeling abnormal; feeling drunk;</td>
</tr>
<tr>
<td>dissociative disorder; flashback;</td>
<td>hyperesthesia;</td>
</tr>
<tr>
<td>hallucination; auditory hallucination;</td>
<td>hypersensitivity; illusion;</td>
</tr>
<tr>
<td>visual hallucination; illusion; somatic hallucination;</td>
<td>metamorphopsia; oral hyperesthesia; pharyngeal hypoesthesia;</td>
</tr>
<tr>
<td>hyperacusis; tinnitus; diplopia;</td>
<td>photopsia; photosensitivity reaction; synesthesia; altered</td>
</tr>
<tr>
<td>vision blurred; ocular discomfort; photophobia;</td>
<td>visual depth perception; confusional state; delirium;</td>
</tr>
<tr>
<td>visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral;</td>
<td>hypogeusia; pain threshold decreased</td>
</tr>
<tr>
<td>pharyngeal paresthesia; time perception altered; daydreaming; delusional</td>
<td></td>
</tr>
<tr>
<td>perception feeling hot; feeling cold; feeling of body temperature change</td>
<td></td>
</tr>
</tbody>
</table>
# Grouping of Adverse Event Terms

<table>
<thead>
<tr>
<th>Applicant grouped:</th>
<th>We added:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation</strong></td>
<td>loss of consciousness</td>
</tr>
<tr>
<td>sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure increased</strong></td>
<td>blood pressure fluctuation</td>
</tr>
<tr>
<td>blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis</td>
<td></td>
</tr>
<tr>
<td><strong>Lethargy</strong></td>
<td>asthenia</td>
</tr>
<tr>
<td>lethargy; fatigue; listless</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>fear of death; restlessness; morbid thoughts</td>
</tr>
<tr>
<td>anticipatory anxiety; anxiety disorder; generalized anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor; anxiety</td>
<td></td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>tension headache; procedural headache; migraine</td>
</tr>
<tr>
<td>sinus headache; headache</td>
<td></td>
</tr>
</tbody>
</table>
## Grouping of Adverse Event Terms by FDA

<table>
<thead>
<tr>
<th>FDA grouped terms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events potentially suggestive of cystitis</strong></td>
</tr>
<tr>
<td>bladder discomfort; bladder dysfunction; bladder irritation; bladder pain; dysuria;</td>
</tr>
<tr>
<td>lower urinary tract symptoms; micturition urgency; nocturia; pollakiuria; polyuria;</td>
</tr>
<tr>
<td>urinary sediment abnormal; urinary sediment present; urinary tract discomfort;</td>
</tr>
<tr>
<td>urinary tract infection; urinary tract infection bacterial; urine analysis abnormal;</td>
</tr>
<tr>
<td>urine leukocyte esterase positive; urine odor abnormal; suprapubic pain; cystitis</td>
</tr>
<tr>
<td><strong>Suicidal ideation or behavior</strong></td>
</tr>
<tr>
<td>suicide attempt; intentional self-injury; suicidal ideation; suicidal behavior</td>
</tr>
</tbody>
</table>
Adverse Events with Incidence > 5% and 2X Placebo: Placebo-controlled Studies 3001 and 3002; Patients < 65*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Esketamine N=346</th>
<th>Placebo N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness/Vertigo</td>
<td>42%</td>
<td>10%</td>
</tr>
<tr>
<td>Dissociation</td>
<td>39%</td>
<td>19%</td>
</tr>
<tr>
<td>Nausea</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Sedation</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Cystitis-suggestive</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Frequencies averaged by sample size for the two studies.
Patients Age 65 and Older: Adverse Events > 5% in Study 3005

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Esketamine (N=72)</th>
<th>Placebo (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness/Vertigo</td>
<td>29%</td>
<td>11%</td>
</tr>
<tr>
<td>Dissociation</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Cystitis-suggestive</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>
### Randomized Withdrawal Study
(Maintenance Phase 3003): Adverse Events > 5%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Esketamine N=152</th>
<th>Placebo N=145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissociation</td>
<td>41%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness/Vertigo</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>Sedation</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>18%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Viral upper respiratory tract infection</strong></td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Cystitis-suggestive</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Transient Adverse Events (up to 6 hours) after Esketamine Use

• Sedation
• Dissociation
• Increased blood pressure
• Increased heart rate
Transient Adverse Events are Correlated with Serum Esketamine Level

• Half-life of plasma esketamine: 2-3 hours
• Clinical pharmacology findings:
  – Blood pressure effects last up to 4 hours
  – Sedation and dissociation last up to 4 to 6 hours
SEDATION
# Modified Observer’s Assessment of Alertness/Sedation (MOAA/s)

<table>
<thead>
<tr>
<th>MOAA/S score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly and/or repeatedly</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
</tr>
<tr>
<td>1</td>
<td>Responds only after painful trapezius squeeze</td>
</tr>
<tr>
<td>0</td>
<td>No response after painful trapezius squeeze</td>
</tr>
</tbody>
</table>
Any Sedation (MOAA/s= 0 to 4) by Treatment

Study 3001
- Placebo
- Esketamine 56 mg
- Esketamine 84 mg

Study 3002
- Placebo
- Esketamine

Study 3005 (≥65 years)
- Placebo
- Esketamine

Study 3003 (Randomized withdrawal study)
- Placebo
- Esketamine
## Severe Sedation (MOAA/s = 0 to 2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Total subjects</th>
<th>% with severe sedation</th>
<th>Total subjects</th>
<th>% with severe sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3001</td>
<td>228</td>
<td>2.6%</td>
<td>112</td>
<td>None</td>
</tr>
<tr>
<td>3002</td>
<td>114</td>
<td>0.9%</td>
<td>107</td>
<td>None</td>
</tr>
<tr>
<td>3005 (≥65 years)</td>
<td>72</td>
<td>None</td>
<td>63</td>
<td>None</td>
</tr>
<tr>
<td>3003 (randomized withdrawal)</td>
<td>152</td>
<td>2.6%</td>
<td>145</td>
<td>None</td>
</tr>
</tbody>
</table>
Two Subjects with Score = 0

<table>
<thead>
<tr>
<th>Subject</th>
<th>Study Day</th>
<th>Time of onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>75 min</td>
<td>15 min</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>15 min</td>
<td>20 min</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>15 min</td>
<td>35 min</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>30 min</td>
<td>15 min</td>
</tr>
<tr>
<td>B</td>
<td>22</td>
<td>20 min</td>
<td>15 min</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>20 min</td>
<td>25 min</td>
</tr>
</tbody>
</table>
Time to Sedation Onset, Peak and Resolution (Patients < 65 Years Old)

![Graph showing sedation times](image)

- Onset
- Peak
- Resolution

Time to Sedation Onset, Peak and Resolution (Patients < 65 Years Old)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Majority Peak time</th>
<th>Latest onset</th>
<th>Latest peak</th>
<th>Latest resolution</th>
</tr>
</thead>
</table>
Time to Sedation Onset, Peak and Resolution (Patients ≥ 65 Years Old)
Varying Patterns of Severe Sedation

Alert

Non response to painful squeeze

MOAA/S Score

Patient 1
Patient 2
Patient 3
Patient 4

time (minutes)
Sedation and Vomiting: Risk of Aspiration

- 10 subjects out of 418 (2.4%) in the esketamine groups in Studies 3001, 3002, and 3005 experienced sedation and vomiting on the same day; 0/287 in placebo
- Sedation severity was 3-4 for these subjects
- No adverse events of aspiration
Sedation Findings from Clinical Pharmacology Study 1005

- Karolinska sleepiness scale measured through 6 hours post-dose
- Most subjects were “alert” by 6 hours
- Some were reported to be “sleepy” approximately 4 to 6 hours post-dose
Recommendations for Sedation

• Observation at least for 2 hours post-dose

• No driving until next day
DISSOCIATION
Dissociation

- Dissociation includes descriptions such as, feeling weird, spacey, loopy, floating, visual disturbances, trouble speaking, confusion, numbness

- Evaluated by CADSS (Clinician-Administered Dissociative States Scale) pre-dose, 40 and 90 minutes post-dose
Clinician-Administered Dissociative States Scale (CADSS)

- 23 items, each scored 0 (not at all) to 4 (extremely)
- Component scores for amnesia, depersonalization and derealization
- Total score 0 to 92
- Normal range 0 to 4
Dissociation (CADSS increase >4) by Treatment

Study 3001

Study 3002

Study 3005
(≥65 years)

Study 3003
(Randomized withdrawal study)

- 56 mg
- 84 mg

Placebo  
Esketamine  
Placebo  
Esketamine  
Placebo  
Esketamine  
Placebo  
Esketamine
Higher Maximum CADSS Score with Esketamine after Each Treatment

Study 3001  84 mg  Study 3002  56 mg
Study 3005 (≥ 65)

Study 3003 (Randomized withdrawal study)
Mixed Model Analysis for Dissociation

• **Significant difference**: Scores in the esketamine group were higher than in the placebo group with average increase relative to placebo of 5.8 at 40 minutes and 0.7 at 90 hours.

• **Partial attenuation with repeated treatment**: The CADSS score at 40 minutes averaged 6.0 points higher with esketamine than with placebo after the initial treatment. This difference decreased with subsequent treatments for the first 4 weeks, then plateaued at an average increase of 2.4 points relative to placebo at 40 minutes.

• **Dose effect**: In Study 3001, a dose effect was seen at 40 minutes with an average increase of 1.3 points for 84 mg relative to 56 mg. No dose effect on dissociation was observed at 90 minutes.
INCREASED BLOOD PRESSURE
Higher Maximum Blood Pressure with Esketamine after Each Treatment

Systolic Blood Pressure

Study 3001 Study 3002 Study 3005 (≥ 65)

Diastolic Blood Pressure

Study 3001 Study 3002 Study 3005 (≥ 65)
Pattern of Blood Pressure Elevation Post-dose in Study 3005

Systolic

Diastolic

esketamine

placebo

esketamine

placebo
Heart Rate Increase in Study 3002

Study 3002

![Graph showing heart rate changes over time for esketamine and placebo groups.](image-url)
Adverse Events of Special Interest Based on Repeat-dose Ketamine Use or Abuse

• Interstitial cystitis or ulcerative cystitis
  – Medical literature, published case series, reports to FDA Adverse Reporting system (FAERS).
  – Described in ketamine labeling: ADVERSE EVENTS section

• Cognitive impairment
  – Ketamine abuse population: observational studies suggesting persistent cognitive deficits on cognitive testing; MRI abnormalities
  – Rodent and non-human primate studies: increased neuronal apoptosis or neurodegeneration

• Liver injury
  – Based on medical literature, published case series, reports to FAERS
  – Some foreign regulatory agencies have issued communications to healthcare providers
Ketamine-related Urological Symptoms*

• Recreational abuse of ketamine and chronic off-label use can cause interstitial or ulcerative cystitis
• Most common symptoms: dysuria, increased urinary frequency, urgency, urge incontinence, and hematuria
• Cystitis was reversible after discontinuation of ketamine in the early course of the disease, but could be irreversible later.

*Division of Pharmacovigilance, ketamine and off label use; Office of Surveillance and Epidemiology integrated review; Baker et al. Acta Neuropathologica communications 2013, 1:64
Adverse Events Suggestive of Cystitis

More common: urinary frequency, discomfort, pain; nocturia.
Less common: cystitis or UTI, urgency, hematuria, sediment or odor abnormal
No Significant Findings in Long-term Cognition

• Evaluated by:
  - CogState computerized test battery
  - Hopkins Verbal Learning Test-Revised (HVLT-R)
• Evaluation was conducted at baseline, end of induction phase, and follow-up phase.
• By these parameters, no change or slight improvement in cognition with esketamine was observed compared to placebo in Studies 3001, 3002, 3003, and 3005.
Liver Enzymes

- Liver enzymes were tested at baseline, end of induction phase, and follow-up phase.

- In Studies 3001, 3002, and 3005, there was no clinically significant effect on liver enzymes relative to placebo.
SUICIDAL IDEATION AND BEHAVIOR
# Columbia Suicide Severity Rating Scale (C-SSRS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No suicidal ideation or behavior</td>
</tr>
<tr>
<td>1</td>
<td>Wish to be Dead</td>
</tr>
<tr>
<td>2</td>
<td>Non-Specific Suicidal Thought</td>
</tr>
<tr>
<td>3</td>
<td>Suicidal Ideation-No Intent</td>
</tr>
<tr>
<td>4</td>
<td>Ideation with Intent, No Plan</td>
</tr>
<tr>
<td>5</td>
<td>Ideation with Plan/Intent</td>
</tr>
<tr>
<td>6</td>
<td>Preparatory Acts/Behavior</td>
</tr>
<tr>
<td>7</td>
<td>Aborted Attempt</td>
</tr>
<tr>
<td>8</td>
<td>Interrupted Attempt</td>
</tr>
<tr>
<td>9</td>
<td>Actual Attempt</td>
</tr>
<tr>
<td>10</td>
<td>Suicide</td>
</tr>
</tbody>
</table>
Suicidal Ideation or Behavior by Adverse Event Report and C-SSRS Score

<table>
<thead>
<tr>
<th>Study</th>
<th>3001</th>
<th>3002</th>
<th>3005</th>
<th>3003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>ESK 56 mg</td>
<td>ESK 84 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>113</td>
<td>115</td>
<td>113</td>
<td>109</td>
</tr>
<tr>
<td>Lesser suicidal ideation (Score 1 - 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>40 (35%)</td>
<td>27 (23%)</td>
<td>36 (32%)</td>
<td>24 (22%)</td>
</tr>
<tr>
<td>Clinically significant suicidal ideation or suicidal behavior (Score ≥ 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event of suicidal ideation or behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Conclusions

Main adverse effects identified:

- sedation (REMS)
- dissociation (REMS)
- increased blood pressure (REMS)
- urinary symptoms
Conclusions

Sedation, dissociation and blood pressure increase were transient and correlated with serum esketamine level.
Conclusions

No serious urinary adverse effects were observed, but sample size and duration of observation may have not been sufficient to rule out serious or long-term effects.
Risk Management for Esketamine

February 12, 2019

Somya Dunn, MD
Commander, United States Public Health Service
Risk Management Analyst
Center for Drug Evaluation and Research
Division of Risk Management
Presentation Overview

• Risk Evaluation and Mitigation Strategies (REMS) overview
• Risks for which a REMS is being considered
• Risk management options
  – Agency proposed REMS
  – Comparison of Agency and Applicant proposed REMS
Risk Evaluation and Mitigation Strategies (REMS) Overview
A REMS is a drug safety program FDA can require for certain drugs

• REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.

• REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.

• The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require Applicants or Application holders to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.

• The FDA has authority to require a REMS pre-approval or post-approval.
A REMS can include a number of components

- Medication Guide or Patient Package Insert
- Communication plan for healthcare providers (HCPs)*
- Elements to assure safe use (ETASU)
- Implementation System
- Must include a timetable for submission of assessments*

* This requirement only applies to NDAs and BLAs.
A REMS can include any of the following ETASU if determined necessary:

| Certification and/or specialized training of **HCPs** who prescribe the drugs |
| Certified pharmacies or other dispensers of the drug |
| Dispensing/administration of drug in **limited settings**, e.g., hospitals |
| Each patient using the drug is subject to certain **monitoring** |
| Drug is dispensed/administered only with **evidence of safe-use conditions**, e.g., pregnancy test |
| Enrollment of treated patients in a **registry** |
Risks for which a REMS is being considered
Risks for which a REMS is being Considered

• Sedation
• Dissociation
• Potential for misuse and abuse
Sedation

• 50% esketamine vs. 15% in placebo

• Typical onset of sedation within 15-30 min, peak 30-45 min, for most it resolved by 1 hr 15 min
  – Fluctuates with visits and there are outliers such as 1.5 hr onset, 3.5 hour resolution

• 24/855 esketamine vs. 0/287 placebo treated in phase 3 controlled studies experienced severe sedation
  – Scores of 0-2 out of 5 total on Modified Observer’s Alertness/Sedation scale

• Patients at risk for accidents due to impaired motor activity (e.g. driving)
Dissociation

• Dissociation score in the Clinician-Administered Dissociative States Scale (CADSS) in the esketamine group was significantly higher than in placebo group
  – Normal range is 0-4
• 69% in esketamine-treated vs. 14% in placebo-treated had scores > 4
  – Visual disturbances, trouble speaking, confusion, numbness, and feelings of dizziness/faintness
  – Distortion of time and space, illusions, derealization, and depersonalization
• Typical resolution by 1 hr 30 min after administration
• Effect decreases for about 4 weeks, with plateau effect
• Patients at risk for potential accidents if they experience these dissociative effects and leave the setting prior to resolution
Ketamine Abuse

- Schedule III (1999) under CSA\(^1\)
- Abused for dissociative, hallucinogenic effects (“club” drug)
- Major sources of illicit ketamine include\(^2\)
  - diversion or theft from healthcare settings (esp. veterinary clinics)
  - smuggling from outside the U.S.
- Ketamine abuse continues to occur, but relatively uncommon\(^3\)
- Recent data do not suggest increasing ketamine abuse\(^3, 4, 5\)
- Ketamine abuse is associated with some adverse effects\(^5, 6, 7\) but hospitalization and other serious outcomes appear to be infrequent

\(^3\)National Survey on Drug Use and Health; \(^4\)Monitoring the Future; \(^5\)U.S. Poison Center, National Poison Data System;
\(^6\)National Electronic Surveillance System- Cooperative Adverse Drug Event Surveillance Project; \(^7\)FDA Adverse Event Reporting System
Potential for Misuse and Abuse of Esketamine Nasal Spray

• In the clinical program, esketamine was self-administered under medical supervision in healthcare settings; therefore, misuse and abuse were not observed

• Dissociation effects are seen with esketamine and the Agency is concerned that esketamine nasal spray could be misused and abused
Agency Proposed REMS
Agency Proposed REMS Goal

The goal of the REMS is to mitigate the risks of misuse, abuse and serious adverse outcomes from dissociation and sedation as a result of esketamine administration by:

– Ensuring that esketamine is only dispensed and administered in medically supervised healthcare settings that can provide patient monitoring

– Enrollment of patients in a registry to further characterize the risks and safe use of esketamine
Agency Proposed REMS—ETASU

- Administration of esketamine only in healthcare settings that ensure patient monitoring by a healthcare provider for at least two hours
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified and ensure that esketamine is not dispensed directly to a patient
- Enrollment of patients in a registry to better characterize the risks associated with esketamine and inform risk mitigation strategies
Rationale for Agency Proposed REMS

• Limiting esketamine administration to a medically supervised healthcare setting decreases the likelihood:
  – of potential serious adverse outcomes from sedation and dissociation
  – the medication will be misused or abused
• Patient Registry will:
  – inform patients of the risks via the enrollment process
  – provide additional long-term data to assess use, safety concerns, confirm and evaluate monitoring times
• Certifications ensure that these processes occur
Differences with REMS Proposals

• Monitoring for resolution of sedation and dissociation—at least 2 hours

• Additional elements
  – Patient registry to inform patients, further characterize risk and safe use
  – Inpatient and outpatient settings would need certification
Summary

• The Agency is concerned about misuse and abuse and serious adverse outcomes from sedation and dissociation

• We would like the committee to consider if the Agency proposed REMS with ETASU program will ensure safe use of esketamine nasal spray
BACKUP SLIDE SHOWN
Study 3001 LS Mean ΔΔ MADRS for the Primary Efficacy Endpoint over Elapsed Study Week

Interim Analysis

ESK 84 mg

Final Analysis

ESK 56 mg