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February 27, 2019

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
WO51, Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: New Drug Application for Esketamine Single-Use Nasal Spray for Treatment of Treatment-Resistant Depression

Dear Commissioner Gottlieb and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) not to approve the new drug application (NDA) for the drug-device combination of esketamine (SPRAVATO) by Janssen Pharmaceuticals Inc. for intranasal administration for the treatment of treatment-resistant depression (TRD). Esketamine was the subject of the February 12, 2019, Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting.

Public Citizen strongly opposes approval of esketamine because the data from the clinical trials presented in the NDA failed to provide substantial evidence that the drug is effective for its proposed indication for use. In particular, two of the four pivotal clinical trials of esketamine failed to meet their pre-specified primary efficacy endpoints, and a third study likely was biased because of unblinding of the subjects. In addition to the lack of substantial evidence of benefit, there is clear evidence that the drug has serious risks of harm.

The applicant has failed to demonstrate that esketamine has a favorable benefit-risk profile for the treatment of TRD, and we therefore urge the agency to reject the PDAC and DSaRM's recommendation for approval and issue a complete response letter. FDA approval of esketamine

based on the available data would essentially undermine the integrity and meaningfulness of FDA's standard for approving drugs.

I. Background – Drug overview and regulatory history

Esketamine for intranasal administration was developed to treat patients with Major Depressive Disorder (MDD), a major life-threatening disease. Janssen Pharmaceuticals is specifically seeking approval for patients who exhibit TRD. From a regulatory standpoint, TRD has been defined as:

> [A] lack of clinically meaningful improvement in depressive symptoms after treatment with at least two different oral antidepressant medications as monotherapy, taken adequate doses for adequate duration (at least six weeks) for their current episode of depression.[1]

Spravato is a combination drug-device product that consists of a single-use nasal spray device that administers two sprays, each containing a 14-milligram (mg) dose of esketamine HCl. Esketamine is the S-enantiomer of ketamine, a drug that was approved by the FDA in 1970 (under NDA 16812 as KETALAR) for use as a rapid-acting general anesthetic administered either intravenously (IV) or intramuscularly. Like ketamine, esketamine is an N-methyl-D-aspartate glutamate receptor antagonist and enhances the release of glutamine in the brain.[2] Ketamine has never been approved for the treatment of any psychiatric disorders, and its use for these conditions is strictly off-label.

In this NDA, the applicant is seeking approval for the use of esketamine nasal spray for the treatment of TRD via intranasal administration twice a week for four weeks at a dose of 28 to 56 mg, which can be increased to 84 mg by week 2. The applicant also proposes that treatment be continued for an additional four weeks and then weekly or every other week for ongoing maintenance.[3]

The esketamine development program received a breakthrough therapy designation (BTD) in November 2013, as TRD is a serious condition with an unmet clinical need.[4] This BTD status designation was based on the preliminary results of the phase 2 trial Study 2001, which investigated the effects of IV esketamine in patients who failed to demonstrate adequate responses to other antidepressants. Importantly, however, the definition of TRD in Study 2001 did not require the failure of trials of two antidepressant drugs in the current major depression episode.[5]

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[1] Food and Drug Administration. FDA briefing document for the Psycopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting on February 12, 2019. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM630970.pdf. Accessed February 22, 2019. PDF page 14.

[2] *Ibid*. PDF page 14.

[3] *Ibid*. PDF pages 14-15.

[4] *Ibid.* PDF page 15.

[5] *Ibid.* PDF pages 7-8.

II. Summary of clinical efficacy data submitted with the NDA

There were four phase 3 randomized placebo-controlled trials that investigated the effects of esketamine. All studies were international, with about one-third of the subjects enrolled in the U.S. Most of the subjects were white women in their 40s and 50s with a high body mass index (>24). Depending on the study, 33 to 40 percent of the enrolled subjects had failed three or more antidepressant treatments prior to screening, and 12 to 17 percent had failed four treatments or more.[6] To be eligible for the phase 3 trials, subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition diagnostic criteria for recurrent MDD or single-episode MDD (duration ≥2 years) without psychotic features, as well as the previously noted regulatory definition of TRD.[7]

Primary efficacy endpoint for three of the trials (Studies 3002, 3001, and 3005) was the change from baseline (CFB) on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 28 days.[8] MADRS is an instrument that measures the following 10 depression-related items: sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The score ranges from 0 to 60, with a higher score indicating more severe depression. Independent, remote (via telephone) blinded raters performed the MADRS evaluations to decrease bias. Scales were administered prior to esketamine or placebo dosing. The subjects enrolled in the esketamine trials had higher baseline mean MADRS scores than those in other clinical trials of previously approved FDA antidepressants, indicating greater disease severity.[9]

The primary efficacy endpoint for the other trial (Study 3003) was time to relapse during the maintenance phase for stable remitters as assessed by the MADRS total score.[10]

Studies 3001 and 3002 also had prespecified key secondary endpoints, including the following: CFB of 50 percent or more on the MADRS Sustained Response starting Day 2 and maintained through Day 28 with a CFB less than 25 percent and only one deviation day allowed, a Sheehan Disability Scale total score change from baseline at Day 28, and a Patient Health Questionnaire-9 total score change from baseline at Day 28.[11]

Importantly, only two of the four pivotal phase 3 clinical trials (Studies 3002 and 3003) demonstrated statistically significant improvements with esketamine on the primary outcome measure.

a. Study 3002 (TRANSFORM-2)

Study 3002 was a flexible-dose, randomized, parallel group trial that compared intranasal esketamine (N=109) with intranasal placebo (N=114), each of which was added to a newly

[6] Ibid. PDF page 17.
[7] *Ibid.* PDF page 20.
[8] *Ibid*. PDF pages 17 and 19.
[9] *Ibid*. PDF pages 17-18.
[10] *Ibid*. PDF page 19.
[11] *Ibid*. PDF page 34.

initiated oral antidepressant.[12] All subjects in the esketamine arm were initiated on a dose of 56 mg, which was then titrated to 84 mg based on investigator discretion regarding the subject's response and tolerability.[13] About two-thirds of the subjects ultimately received the 84-mg dose of esketamine twice weekly and one-third received the 54-mg dose twice weekly.[14] Subjects receiving placebo followed the same protocol. Both treatment groups demonstrated similar baseline illness severity.

The esketamine-treatment group exhibited statistically significantly greater improvements in depressive symptoms, as assessed by the CFB to endpoint on the MADRS, than those in the placebo group.[15] The least squares mean difference (±standard error) between the placebo and esketamine groups at 28 days was only −4.0±1.7,[16] a relatively small difference overall for a 60-point scale.

b. Study 3003 (SUSTAIN-1)

This study enrolled subjects directly from an open-label esketamine treatment protocol or from Studies 3001 or 3002.[17] All subjects who demonstrated a ≥50 percent reduction from baseline in MADRS total score by the end of the 4 weeks of esketamine exposure were eligible to enter an optimization phase, in which they received at least 12 weeks of open-label esketamine in addition to an oral antidepressant.[18]

Subjects who met the criteria for either stable remission or stable response were subsequently randomized from the optimization phase into a double-blind maintenance phase, which lasted for an additional 500 days in which subjects either continued esketamine or were switched to placebo.[19] Stable remission and stable response were defined as the following:

- 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 [intranasal] dose) in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission[20]

The primary efficacy endpoint was time to relapse during the maintenance phase for stable remitters as assessed by the MADRS total score, and a secondary endpoint analysis was

[12] *Ibid*. PDF page 22.
[13] *Ibid*. PDF page 22.
[14] *Ibid*. PDF page 22.
[15] *Ibid*. PDF pages 22-23.
[16] *Ibid*. PDF page 23.
[17] *Ibid*. PDF page 23.
[18] *Ibid*. PDF pages 23-24.
[19] *Ibid*. PDF page 24.
[20] *Ibid*. PDF page 24.

determined in the stable response cohort.[21] Relapse was defined as a MADRS score of ≥22 for two consecutive assessments, undergoing hospitalization or another serious clinical event (as adjudicated by investigators), or both.[22]

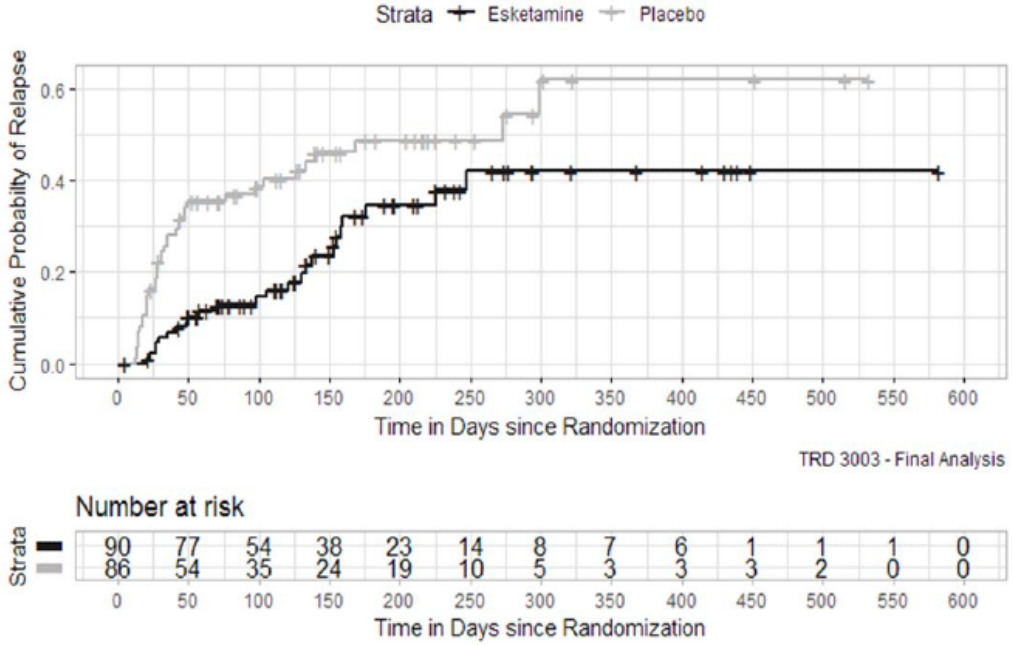
Data from Study 3003 showed a statistically significant longer time to relapse in subjects randomized to continue esketamine (N=90) compared with those randomized to placebo (N=86) in stable remitters (see Table 4 and Figure 4 below).[23]

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

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

Source: Study 3003 CSR, NE=not estimable

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



[21] *Ibid*. PDF page 24.
[22] *Ibid.* PDF page 24.
[23] *Ibid.* PDF pages 25-26.

Data from Study 3003 also showed a statistically significant longer time to relapse in subjects randomized to continue esketamine (N=62) compared with those randomized to placebo (N=59) in stable remitters (see Table 5 below).[24]

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

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

Source: Study 3003 CSR, NE=not estimable

However, as the FDA highlighted in its review, the results of Study 3003 may have been biased because the study likely was not truly blinded for the subjects. In particular, the FDA noted the following:

> 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. …
>
> 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**

[24] *Ibid.* PDF pages 25-26.

> **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**. …
>
> 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.**[25]
>
> [Emphasis added]

The likely unblinding of the subjects in Study 3003 raises serious doubts about the reliability of the study results.

c. Study 3001 (TRANSFORM-1)

This study was a fixed-dose randomized parallel group placebo-control trial.[26] Subjects randomized to receive esketamine were administered the drug at a dose of either 56 mg or 84 mg twice weekly for 28 days.[27] All subjects also received a newly initiated oral antidepressant. Under the prespecified statistical analysis plan, the esketamine 84-mg arm was the first experimental group to be tested (see Table 6 below).[28] The analysis failed to show a statistically significant difference between the 84-mg esketamine group and the control group for the change from baseline on the MADRS. Due to this result, subjects receiving the 56-mg dose could not be formally analyzed under the prespecified statistical analysis plan.[29]

[25] *Ibid.* PDF pages 27-29.
[26] *Ibid.* PDF page 29.
[27] *Ibid.* PDF page 29.
[28] *Ibid.* PDF page 29.
[29] *Ibid.* PDF page 29.

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

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

Source: Study 3001 CSR and Andrew Potter, PhD, Statistical Reviewer

Furthermore, Study 3001 also failed to demonstrate that the esketamine 84-mg dose had superior efficacy over the 56-mg dose, thus failing to confirm the results of the positive dose-response relationship determined by the phase 2 trial, Study 2002. The FDA expressed the following important concerns about this finding:

> 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.[30]

d. Study 3005 (TRANSFORM-3)

Study 3005 was a flexible-dose, randomized, parallel group trial in geriatric patients that compared intranasal esketamine (N=72) with intranasal placebo (N=65), each of which was added to a newly initiated oral antidepressant.[31] The study investigated flexible dosing of 28 mg to 84 mg of esketamine. The mean subject age for this study was 70, which was higher than in the other clinical trials.[32] Furthermore, a larger proportion of subjects had a previous diagnosis of hypertension.[33]

Patients with MDD who demonstrated no response to between one and eight oral antidepressants and who currently were taking an oral antidepressant for at least two weeks at or above the minimum therapeutic dose were initially enrolled in the study.[34] These subjects were then prospectively observed for four weeks to assess for a response. Non-responders were then

[30] *Ibid.* PDF page 30.
[31] *Ibid.* PDF pages 31-33.
[32] *Ibid.* PDF page 32.
[33] *Ibid.* PDF page 32.
[34] *Ibid.* PDF page 32.

randomly assigned to receive intranasal placebo or intranasal esketamine (flexible dose at 28 mg, 56 mg, or 84 mg). About two-thirds of the subjects in the esketamine group received the 84-mg dose and one-third received a 56-mg dose.[35]

Results showed no statistically significant difference between the esketamine group and the placebo group on the primary efficacy outcome, which was the change from baseline at Day 28 on the MADRS total score (see Table 7 below).

Table 7: Study 3005 Primary Endpoint MADRS Total Score Change from Baseline at Day 28 Using MMRM (Full Analysis Population)

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

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

In addition to the failure of the trial to meet the prespecified primary efficacy outcome, the FDA noted the following major concerns:

> 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.**[36] [Emphasis added]

III. Serious safety concerns that outweigh esketamine's purported benefits

In addition to the clinical trials failing to demonstrate substantial evidence of esketamine efficacy, safety data demonstrate that esketamine does have risks of serious harm.

a. Subject deaths occurred only in subjects who received esketamine

The FDA reported that six subjects died during the esketamine for treatment-resistant depression development program, all of whom received esketamine.[37] Three of the deaths were by suicide at 4, 12, and 20 days after the patient's last dose of esketamine.[38] Disturbingly, the FDA appears to inappropriately discount the possibility that these suicides were linked to esketamine exposure.

[35] *Ibid.* PDF page 32.
[36] *Ibid.* PDF page 32.
[37] *Ibid.* PDF page 42.
[38] *Ibid.* PDF page 42.

Of the remaining three deaths, one involved a motorcycle accident 26 hours after the subject's last dose of esketamine.[39] Another death occurred in a 60-year-old male subject with a history of hypertension and obesity who died suddenly on study day 113.[40] The last death occurred in a 74-year-old woman with history of hypertension and hyperlipidemia who died of myocardial infarction six days after her last dose of esketamine.[41] As with the deaths by suicide, the FDA downplays the possibility that esketamine played a role in these deaths.

b. Serious adverse events and adverse events leading to study withdrawal

More serious adverse events (SAE) were reported in the esketamine-group subjects than in the placebo-group subjects. SAEs that were reported with higher frequency in the esketamine treatment group included suicidal ideation and depression (see Table 12).[42]

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

	3001		3002		3005	
	Placebo	ESK	Placebo	ESK	Placebo	ESK
N. of subjects	113	231	109	115	65	72
Depression	1	6	0	0	0	1
Suicidal ideation	1	4	0	0	0	0
Road traffic accident/Death	0	0	0	1	0	0
Dizziness/Fall/Hip fracture	0	0	0	0	0	1
Cerebral hemorrhage	0	0	0	1	0	0
Headache	0	1	0	0	0	0
Blood pressure increased	0	0	0	0	0	1

Source: Qi Chen, MD, MPH, Safety Reviewer

Furthermore, there were more adverse events that led to the withdrawal from the esketamine groups than from the placebo groups in Studies 3001, 3002, and 3005.[43]

c. Other important adverse events associated with esketamine use

Other important adverse events that occurred twice as often in esketamine-group subjects than in placebo-group subjects included dissociation, dizziness/vertigo, nausea/vomiting, sedation,

[39] *Ibid.* PDF page 42.
[40] *Ibid.* PDF page 42.
[41] *Ibid.* PDF page 42.
[42] *Ibid.* PDF page 43.
[43] *Ibid.* PDF page 43.

paresthesia, hypoaethesia, and increased blood pressure. These were the most commonly reported adverse events with esketamine use (see Tables 13 and 14 below).[44]

Table 13: Adverse Events ≥ 2% and ≥ Twice the Rate of Placebo by Treatment Group in Studies 3001 and 3002 (subjects < 65 years old)

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

Source: Qi Chen, MD, MPH, Safety Reviewer

[44] *Ibid.* PDF pages 43-45.

Table 14: Adverse Events ≥ 2% and ≥ Twice the Rate of Placebo by Treatment Group in Study 3005 (subjects ≥ 65 years old)

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

Source: Qi Chen, MD, MPH, Safety Reviewer

There were more cardiac-related adverse events associated with the esketamine-treatment group than in the placebo group. Of particular concern, the rate of potentially clinically important systolic blood pressure increases (to ≥180 mmHg with an increase of ≥20 mmHg) or diastolic blood pressure increases (to ≥105 mmHg with an increase of ≥15 mmHg) was higher in the esketamine group than in the placebo group.[45]

The highest systolic blood pressure usually was observed at 40 minutes after esketamine administration.[46] In approximately 10 to 20 percent of visits, the highest observed systolic blood pressure increase of at least 10 mmHg occurred at 1.5 hours after administration of esketamine.[47] Clinical pharmacology data from Study 1013 showed that esketamine's effects on blood pressure lasted about four hours and were likely related to drug-plasma levels.[48] These effects on blood pressure have been documented previously for ketamine.

In addition to pronounced effects on blood pressure, clinical studies also confirmed that esketamine can increase heart rate.[49]

[45] *Ibid.* PDF page 47.
[46] *Ibid.* PDF page 48.
[47] *Ibid.* PDF page 48.
[48] *Ibid.* PDF pages 48-49.
[49] *Ibid.* PDF page 49.

There is a dearth of information regarding the clinical implications of esketamine's effects on blood pressure and heart rate with long-term use, but there is concern that these effects could increase the risk of major adverse cardiovascular events.

Esketamine also causes sedation and dissociation.[50] Additionally, there are concerns that the drug may impair cognitive function. For example, in the long-term, open-label Study 3004, there was some evidence of slowing reaction times in elderly subjects.[51]

Finally, esketamine is a controlled substance that is subject to abuse and diversion.

IV. Concerns raised by Human Factor validation study

The FDA also found that the applicant has failed to produce an interface that supports the safe and effective use of their product. In particular, the agency noted the following:

> **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…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.[52] [Emphasis added]

V. Summary and Conclusions

In summary, only two of the four pivotal clinical trials that tested esketamine for treatment of TRD found statistically significant improvements on the primary efficacy outcome compared with placebo, and the results of one of these two trials likely were biased because of unblinding of the subjects. Thus, the efficacy data from the four trials overall is tenuous at best and fails to provide substantial evidence that the drug is effective.

In addition, there is clear evidence showing that esketamine causes an increased risk of serious adverse events and numerous other clinically important adverse effects. Particularly worrisome were the deaths seen only in esketamine-group subjects and the ability of esketamine to raise blood pressure and heart rate. The FDA itself has suggested that more studies should be completed to further elucidate the effect of long-term esketamine use on important cardiovascular endpoints.

[50] *Ibid.* PDF pages 49-54.
[51] *Ibid.* PDF page 54.
[52] *Ibid.* PDF page 55.

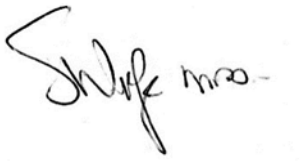
Given the uncertainty of the benefits of esketamine for treating TRD and the drug's serious risks, FDA approval of esketamine based on the available data would essentially undermine the integrity and meaningfulness of the FDA's standards for approving drugs. We therefore urge the FDA to reject the PDAC and DSaRM's recommendation for approval the NDA for esketamine and issue a complete response letter.

Thank you for considering our comments on this important matter.

Sincerely,

Meena M. Aladdin, M.S., Ph.D.
Health Researcher
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group