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APPLICATION NUMBER:

211243Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Integrated Review

NDA	211243
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Submission Date	September 04, 2018
Submission Type	505(b)(1)
Proposed Brand Name	SPRAVATO™
Generic Name	Esketamine
Dosage Form and Strength	28 mg single-use nasal spray device
Route of Administration	Intranasal
Proposed Indication	For the treatment of treatment-resistant-depression (TRD) in adults.
Applicant	JANSSEN PHARMACEUTICALS INC
Associated IND	114345
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1. EXECUTIVE SUMMARY

This clinical pharmacology review is for an original 505 (b)(1) NME NDA submitted by Janssen on September 04, 2018. The applicant is seeking approval of SPRAVATO (esketamine), a single-use unit-dose nasal spray device that delivers 28 mg esketamine in two sprays, for the treatment of treatment-resistant depression (TRD). Esketamine is the S-enantiomer of ketamine. Ketamine is marketed in the United States as a general anesthetic for intravenous or intramuscular use. In addition, ketamine is placed into a schedule III-controlled substance by the Drug Enforcement Administration (DEA) due to its illegal use as a recreational drug. Esketamine is a nonselective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is claimed to be responsible for its analgesic-anesthetic effects and/or antidepressant effect. The affinity for the NMDA receptor is approximately 3- to 4-fold greater for esketamine than for arketamine (R-ketamine, the R-enantiomer of ketamine).

The clinical development program includes 19 Phase 1 clinical pharmacology trials (i.e., single- and multiple-ascending dose, absolute bioavailability, food effect, mass balance, drug interaction, renal and hepatic impairment, abuse potential, TQT studies, etc.), 4 Phase 2 trials, and 4 Phase 3 efficacy/safety trials. The applicant is relying on two positive Phase 3 trials—the flexible-dose trial in adults younger than 65 years of age (Study 3002) and a randomized withdrawal study (Study 3003) along with supportive evidence from dose-response studies (Study 3001 and Study 2003). In addition, the submission contains 17 in vitro studies evaluating distribution, metabolism, protein binding, in vitro metabolic/transporter-based drug interactions, etc. The submission also includes 1 report for the development of population pharmacokinetic (PopPK) models for esketamine, and 3 physiologically-based pharmacokinetic (PBPK) modeling and simulation reports to assess drug-drug interaction (DDI) potential of esketamine as a ‘victim’ or a ‘perpetrator’.

In addition, most of the clinical studies evaluated the known adverse events associated with ketamine use as intended and with ketamine misuse and abuse, including transient blood pressure increase, sedation, dissociation, cognitive impairment and driving performance.

Key issues addressed in this review are:

- (1) Appropriateness of the proposed dose in non-elderly subjects (i.e., initial and maintenance dose, re-dosing guidelines and flexibility of dosing for missed doses)
- (2) Appropriateness of the proposed dose in specific patient populations (i.e., hepatic impairment)
- (3) Management of treatment-emergent adverse effects post-dose (i.e., increased blood pressure, sedation, dissociation, and decreased cognitive function)

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in NDA 211243 to support an approval of esketamine. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comments
Overall	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pending labeling
General dosing instructions	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	<p>Induction Phase (weeks 1 to 4): Two treatment sessions/week: Starting day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg</p> <p>Maintenance Phase: Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly</p>
Dosing in patient subgroups (intrinsic and extrinsic factors)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	<p>Findings:</p> <ol style="list-style-type: none"> 1. In general, no dose adjustment is necessary in patients based on gender, body weight, race and ethnicity. 2. No dose adjustment is necessary in patients with mild, moderate and severe renal impairment. 3. No dose adjustment is necessary in patients with mild and moderate hepatic impairment. Patients with moderate hepatic impairment may need to be monitored for changes in adverse events such as blood pressure, sedative and cognitive effects for a longer period of time upon esketamine treatment. Use of esketamine nasal spray in patients with severe hepatic impairment is not recommended.

		4. No dose adjustment is necessary with other concomitant medications.
Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pending satisfactory agreement with sponsor

1.2 Post-Marketing Requirements and Commitments

NA

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Clinical Pharmacology Findings

In the current submission, the sponsor has submitted 27 clinical pharmacology studies (22 in healthy subjects and 6 in patients), and 27 in vitro studies. The submitted studies include 6 PK studies (2 single dose PK studies in healthy volunteers, 1 multiple dose PK study in healthy volunteers, and 1 mass balance study in healthy volunteers), 5 intrinsic factor studies evaluating the impact of hepatic impairment, renal impairment, race and age, 7 extrinsic factor studies evaluating drug interactions with ticlopidine, clarithromycin, rifampin, and other nasal drugs, effects of esketamine on bupropion, and midazolam PK, 1 thorough QT study, 4 pharmacodynamic studies, and 4 efficacy studies. Population pharmacokinetic analysis was performed to evaluate the effect of body weight and gender on esketamine pharmacokinetics. Summarized below are the key clinical pharmacology findings from the submitted studies:

Absorption

- Esketamine exposure increases with dose from 28 mg to 112 mg. The increase in C_{max} and AUC was less than dose-proportional between 28 mg and 56 mg or 84 mg, but it was nearly dose proportional between 56 mg and 84 mg.
- Following intranasal administration of esketamine, the time to reach peak plasma concentration (C_{max}) is approximately 20 to 40 minutes post-dose. The mean absolute bioavailability is approximately 48% following intranasal route of administration.
- Esketamine does not accumulate in plasma when administered intranasally twice weekly.
- The inter-subject variability of esketamine across studies, ranges from 27 to 66% for C_{max} and 18 to 45% for AUC_{last} . The intra-subject variability of esketamine is approximately 15% for C_{max} and 10% for AUC_{last} .

Distribution

- Esketamine is extensively distributed into tissues (steady-state volume of distribution 709 L) following intravenous administration.
- Esketamine exhibits low protein binding to albumin and α_1 -acid-glycoprotein (< 50%).

Elimination

- After C_{\max} is reached following intranasal administration, the decline in plasma esketamine concentrations is multiphasic, with rapid decline in the initial 2 to 4 hours, and a mean terminal half-life ($t_{1/2}$) ranging from 7 to 12 hours.
- Esketamine is extensively metabolized in the liver. The primary metabolic pathway of esketamine in human liver is via N-demethylation to form active metabolite noresketamine. The main CYP enzymes responsible for esketamine metabolism are CYP2B6 and CYP3A4. Other enzymes, including CYP2C19 and CYP2C9, contribute to a smaller extent. The C_{\max} of noresketamine is approximately 1.2-fold higher than esketamine, and the AUC_{last} is approximately 2.7-fold higher than esketamine. The elimination of noresketamine from plasma is slower than esketamine, with an effective half-life of approximately 4 hours and the terminal half-life of noresketamine is approximately 8 hours.
- Noresketamine is 3- to 6- times less potent than esketamine as a NMDA receptor antagonist, and the brain-to-plasma ratio of noresketamine is 6-times lower than that of esketamine.

Intrinsic Factors:

- Sex, body weight and race: Clearance and volume of distribution of intranasal esketamine is not influenced by sex, body weight and race.
- Age: the mean esketamine C_{\max} and AUC_{∞} values of intranasal esketamine were 21 to 67% and 18 to 38% higher in elderly subjects (≥ 65 years) compared to younger adult subjects (< 55 years), respectively.
- Pharmacokinetics of esketamine following intranasal administration in subjects with mild hepatic impairment was similar to healthy volunteers. For subjects with moderate hepatic impairment (Child-Pugh Class B), the C_{\max} , AUC_{last} , AUC_{∞} and effective $t_{1/2}$ of esketamine were 8%, 114%, 103% and 100% higher as compared to normal subjects. The PK of esketamine in subjects with severe hepatic impairment was not investigated.
- Renal Impairment: For patients with mild, moderate or severe renal impairment, the C_{\max} , AUC_{last} and AUC_{∞} were 20 to 26%, 14 to 32% and 13 to 36% higher as compared to subjects with normal renal function.

Drug Interactions:

- Esketamine has modest induction effects on CYP3A4 and CYP2B6 in vitro in human hepatocytes, but did not translate into a clinically relevant induction of CYP3A4 and CYP2B6 probe substrates in healthy volunteers.
- Esketamine and its major circulating metabolites have a low inhibition potential against CYPs and UGTs, except for a weak reversible inhibition of noresketamine on CYP3A4 that is not likely to translate into a clinically relevant inhibition for CYP3A4 probe substrate.
- Esketamine and its active metabolite noresketamine are not substrates of transporters (P-gp, BCRP, OATP1B1, OATP1B3 for esketamine, and P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 for noresketamine), and esketamine and none of its major circulating phase-1 metabolites were found to be a clinically relevant inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters.
- Esketamine has a low potential for PK drug interaction with antidepressants that were concomitantly administered in Phase 3 trials (e.g., duloxetine, escitalopram, sertraline, and

venlafaxine) based on their PK properties and the interaction liability with metabolizing enzymes and transporters.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosage recommendations for SPRAVATO are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability to the previous dose to optimize therapeutic benefit in the induction and subsequent long-term maintenance phase.

Esketamine must be administered under the supervision of a healthcare professional. A treatment session consists of nasal administration of esketamine and post administration observation under supervision.

Table 1. Recommended Dosing for SPRAVATO

		Adults (< 65 years of age)
Induction Phase*	Weeks 1-4 Administer twice per week*	Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg
Maintenance Phase**	Weeks 5-8: Administer once weekly	56 mg or 84 mg
	Week 9 and after: Administer once weekly or every 2 weeks***	56 mg or 84 mg

* Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment

** Periodically reexamine the need for continued treatment.

*** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

(b) (4)

2.2.2 Therapeutic individualization

Dosing of esketamine will be individualized based on (A) efficacy after induction phase (B) efficacy and tolerability in the maintenance phase that would determine once-weekly or every 2-week dosing regimen.

Geriatric Patients: In dedicated PK studies with geriatric patients, C_{max} and AUC_{inf} were 67% and 38% higher, respectively in elderly subjects (≥ 65 years) compared to younger adult subjects (24 to 54 years) following intranasal spray administration of 84 mg esketamine. Per sponsor, elderly patients may exhibit greater sensitivity as compared to younger subjects. Thus, an efficacy trial (Study 3005) was conducted in geriatric patients (≥ 65 years) with a reduced initial dose of 28 mg. However, since the study in geriatric patients (Study 3005) did not achieve its primary endpoint, dosing recommendation for these patients cannot be provided.

Patients with Hepatic Impairment: Esketamine is extensively metabolized. A dedicated hepatic impairment study demonstrated that the mean C_{max} and AUC_{∞} were 8% and 103% higher for esketamine, and 44% lower and 25% higher for noresketamine, respectively, in subjects with

moderate hepatic impairment (Child-Pugh class B) as compared to healthy subjects. No dose adjustment is recommended for patients with moderate hepatic impairment. However, due to longer elimination half-life ($t_{1/2}$), patients with moderate hepatic impairment are recommended to be monitored for a longer period of time for evaluation of blood pressure increase, changes in sedative, cognitive function and dissociative effects.

The effect of severe (Child-Pugh class C) hepatic impairment on esketamine pharmacokinetics has not been evaluated. The use of esketamine in patients with severe hepatic impairment should be avoided.

Patients Concomitantly Receiving CYP2B6 Inhibitor: In a dedicated drug-interaction study, pretreatment with oral ticlopidine (250 mg twice daily for 9 days prior to and on the day of esketamine administration) had no effect on the mean C_{max} of esketamine, and AUC_{∞} was increased by 29%. The terminal $t_{1/2}$ of esketamine was not affected by ticlopidine. This difference is not likely to be clinically significant, and no dose adjustment of esketamine is recommended for co-administration with ticlopidine or other CYP2B6 inhibitors.

Patients Concomitantly Receiving CYP3A Inducer: In a dedicated drug-interaction study, concomitant use of rifampicin (a strong CYP3A4 inducer) decreased esketamine C_{max} and AUC_{∞} by about 17% and 28%, respectively. This interaction is not considered to be clinically relevant, and thus no dose adjustment is recommended for using esketamine in concomitant with strong CYP3A4 inducers.

2.3 Outstanding Issues

NA

2.4 Summary of Labeling Recommendations

Base on the review, the Office of Clinical Pharmacology addresses the following issues in the package insert:

- To prevent loss of medication, the nasal spray is recommended to be administered in a semi-reclined position with instruction for sniffing. This is based on the results of Study 1001 showing that the absorption of drug following intranasal administration is improved in a semi-reclined position with instructions for sniffing. C_{max} , AUC_{last} and AUC_{∞} were increased by 63%, 20% and 13%, respectively, in subjects who were administered esketamine in a semi-reclined position with instruction to sniff the solution relative to administration in an upright position and prohibiting sniffing. The white powder or formation of residue on the external nares was no longer present following self-administration of esketamine in a semi-reclined position with instructions for sniffing. In addition, the clinical studies other than Study 1001 all followed the modified intranasal administration in a semi-reclined position.
- The increase in blood pressure peaked at 40 min and lasted approximately 4 hours post-dose in healthy adult subjects. The effect of esketamine on blood pressure is likely related to esketamine concentrations. Please refer to Section 3.3.2 for details.

- The sedation and dissociation symptoms peaked at 40 min and were resolved by 1.5 hours post-dose in most but not all patients. Please refer to Section 3.3.2 for details.
- Patients with moderate hepatic impairment may require longer period of monitoring for changes in blood pressure, sedative, cognitive and dissociative effects. Please refer to Section 3.3.3 for details.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

SPRAVATO is a single use nasal spray containing 28 mg esketamine indicated for the treatment of TRD. Esketamine is a new molecular entity. The development of nasal esketamine was under IND 114,345. The development of esketamine for patients with TRD was granted Fast Track designation in July 2012 and Breakthrough Therapy designation in November 2013 by the US FDA. The applicant filed this NDA via the 505(b)(1) regulatory pathway on September 04, 2018. The evidence in support of esketamine’s effectiveness for TRD is derived primarily from two Phase 3 trials — the flexible-dose trial in adults younger than 65 years of age (Study 3002) and the randomized withdrawal study (Study 3003). Supportive evidence from dose-response studies (Study 3001 and Study 2003) is also being considered for labeling purposes.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Esketamine is a NMDA receptor antagonist. The efficacy of esketamine for the treatment of TRD is mediated through antagonism of NMDA receptor, which produces a transient increase in glutamate release leading to increases in postsynaptic α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function in these brain regions.
QT Prolongation	Treatment with esketamine did not prolong the QTc interval as evaluated in a randomized, double blind, placebo-, and positive-controlled cross-over thorough QTc study in 60 healthy subjects under both intranasal (84 mg) and intravenous infusion (0.8 mg/kg as a 40 min). Maximum esketamine concentrations in plasma produced following intravenous infusion were approximately 3-times higher than the maximum concentrations produced by the intranasal dose. The maximal upper bound of the 90% confidence interval for the placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the Fridericia’s correction (QTcF).
General Information	

Bioanalysis	LC-MS/MS methods using racemic ketamine and norketamine as reference compounds were used for the quantitation of esketamine and noresketamine after esketamine administration. This bioanalytical method is considered acceptable, considering similar mass spectrometry response for esketamine and arketamine, as well as no inversion between esketamine and arketamine across various preclinical species and human.	
Healthy Volunteers vs. Patients	PK is similar between TRD patients and healthy subjects.	
Drug exposure at steady state following the therapeutic dosing regimen	The AUC_{∞} and C_{max} of esketamine following 84 mg dose of esketamine (84 mg) are 310 to 489 ng·h/ mL and 95 to 164 ng/mL, respectively.	
Maximum tolerated dose or exposure	Single Dose	112 mg esketamine was the highest dose tested; and maximum tolerated dose (MTD) was not achieved.
	Multiple Dose	84 mg twice a week dosing of esketamine was the highest dose tested; and MTD was not achieved.
Dose Proportionality	Approximately linear over the dose range of 28 mg to 84 mg	
Variability	The inter-subject variability of esketamine, across studies, ranges from 27 to 66% for C_{max} and 18 to 45% for AUC_{last} . The intra-subject variability of esketamine is approximately 15% for C_{max} and 10% for AUC_{last} .	
Accumulation	There was no accumulation of esketamine in plasma following repeated administration (twice weekly).	
Absorption		
T_{max}	20 to 40 minutes after intranasal administration	
Absolute bioavailability	Approximately 48% (intranasal administration)	
Distribution		
V_d	709 L following IV administration	
Protein Binding	42.7% and 37.9% for esketamine and noresketamine, respectively.	
Substrate of transporter systems	Esketamine is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or organic anion transport proteins OATP1B1 or OATP1B3	
Elimination		

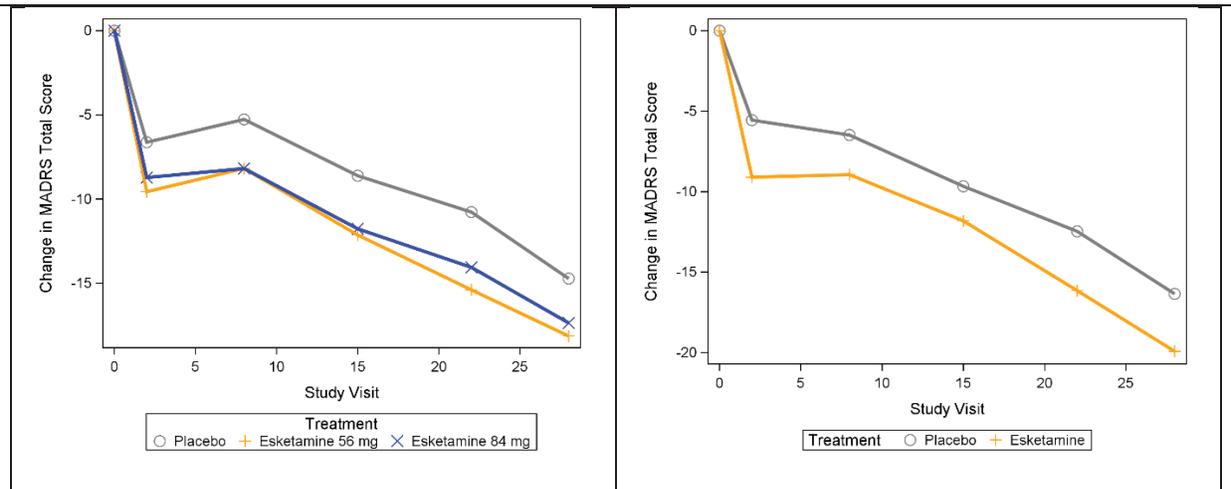
T _{1/2}	The decline of esketamine concentrations in plasma is biphasic, with rapid decline in the initial 2 to 4 hours, and the mean terminal t _{1/2} ranging from 7 to 12 hours.
Metabolism	
Primary Metabolizing enzymes	CYP2B6 and CYP3A4
Inhibitor/Inducer	Esketamine is a moderate inducer for CYP3A4 and CYP2B6, and noresketamine is a weak inhibitor for CYP3A4.
Excretion	
Primary excretion pathways	Esketamine is predominately (i.e., >80%) eliminated by hepatic metabolism followed by excretion of numerous metabolites in urine.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence in support of esketamine's effectiveness for TRD is derived primarily from two successful Phase 3 trials — the flexible-dose trial in adults younger than 65 years of age (Study 3002) and the randomized withdrawal study (Study 3003). The primary efficacy endpoint for Study 3002 was the change in the MADRS total score as measured by the change from baseline to the end of the 4-week double-blind induction phase. The primary endpoint for Study 3003 was the time from randomization to the first relapse during the maintenance phase in esketamine-treated subjects who achieved stable remission at the end of the optimization phase, and this study lasted approximate 2 years. Please refer to clinical and statistical reviews by Drs. Jean Kim and Andrew Potter for more information. In the fixed-dose study of adults younger than 65 years of age (Study 3001), the 84 mg treatment group did not show statistical significance compared to placebo, and the 56 mg treatment group could not be formally evaluated in accordance with the predefined testing sequence at Week 4 to account for multiple comparisons (Figure 1). However, 56-mg dose arm was nominally statistically significant ($p = 0.0114$) as compared to placebo, which could be considered supportive evidence of effectiveness for the 56-mg dose. The geriatric study (Study 3005) included flexible doses ranging from 28 to 84 mg; the effect of esketamine in the combined dose group was not statistically significant compared to placebo.

Figure 1. Change from baseline in MADRS Total Score by study visit (Day) in (Left) Study 3001 and (Right) Study 3002.

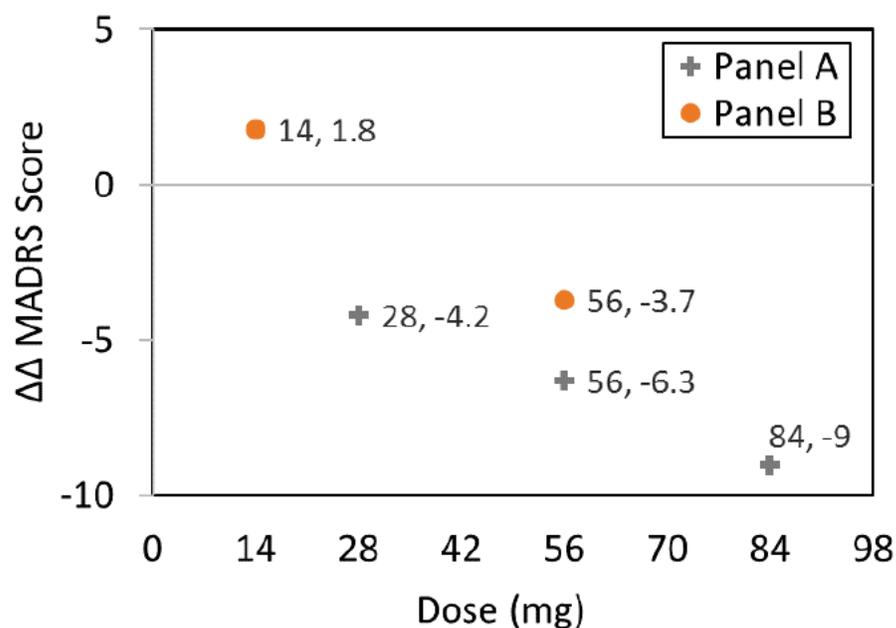


Source: Reviewer's Analysis

A Phase 2 dose-finding (Study 2003) can also be used to support evidence of effectiveness of intranasal esketamine. This Phase 2 randomized, placebo-controlled, dose-response study consisted of two panels (A and B), each testing different dose levels, and two 1-week double-blind treatment periods (1 and 2). Panel A studied 28-, 56-, and 84-mg doses of esketamine and Panel B studied 14- and 56-mg doses. Background oral antidepressant may or may not have been ongoing from previous treatment. The primary efficacy endpoint was the difference between intranasal esketamine and placebo for the change from baseline in MADRS total score for the combined double-blind treatment periods. The results show that there was a statistically significant difference in mean change of MADRS total score in esketamine dose groups (28 mg, 56 mg and 84 mg) versus placebo, with numerically greater benefit at higher doses (Figure 2). Intranasal 14 mg esketamine did not show a significant change in mean MADRS total score, and intranasal 28 mg esketamine failed consistency between Periods 1 and 2 in Panel A. Thus, a dose greater than 28 mg may be necessary to achieve meaningful clinical improvement in TRD patients.

However, the dose-response relationship between 28 mg and 84 mg for intranasal esketamine found in Study 2003 could not be confirmed in a larger scale, fixed-dose Phase 3 Study 3001 (as described earlier). It is noted that Study 2003 differs from the Phase 3 studies in its lack of consistency for background oral antidepressants and psychiatric history (Table 2). Majority (64.2%) of the patients in Panel A of Study 2003 were on 1 antidepressant in the current major depressive episode; whereas more than 80% of the patients in Phase 3 trials were on 2 or more antidepressants in the current episode. The background oral antidepressants and psychiatric history also differ between Panel A and Panel B in Study 2003, with a higher percentage of patients having more than 1 antidepressant in the current episode and a lower baseline MADRS score in Panel B as compared to subjects in Panel A. These differences in baseline characteristics may, at least partially, account for the differences in efficacy response between Study 2003 and Study 3001, or between Panel A and Panel B in Study 2003 at the same esketamine dose.

Figure 2. Dose-response for placebo corrected change of total MADRS scores from baseline ($\Delta\Delta$ MADRS) in Period 1 from Study 2003. For example, the legend in the graph, (14, 1.8) refers to Dose of 14 mg and corresponding $\Delta\Delta$ MADRS.



Source: Reviewer's analysis

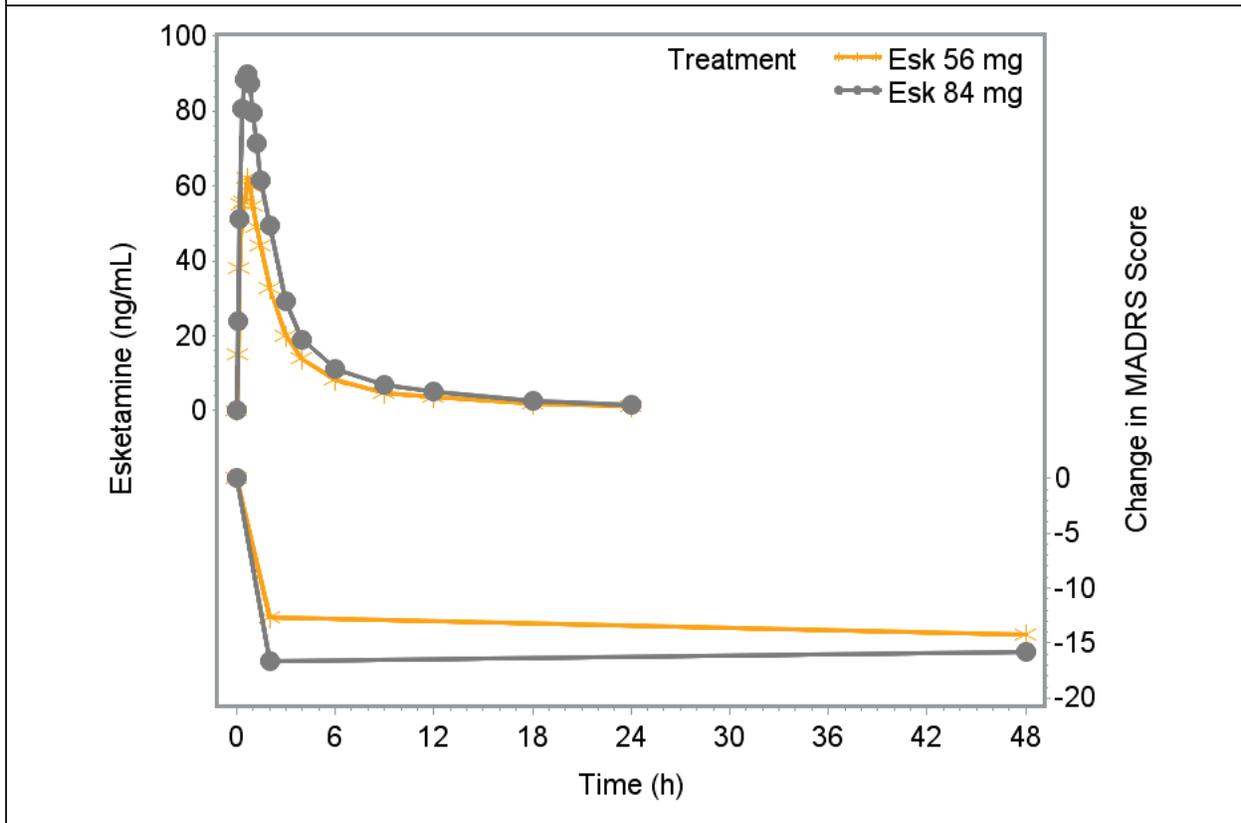
Table 2. Summary of baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores and background oral antidepressants in Phase 2 and Phase 3 Studies.

Study	Panel	No. of Antidepressants in Current Depressive Episode			Baseline MADRS Score
		1	2	3 or more	
2003	A	64.2%	22.4%	13.4%	35.2
	B	9.8%	48.8%	41.5%	30.5
3001		9.1%	51.2%	42.2%	37.6
3002		12%	55.2%	32.8%	37.1
3005		15.3%	46.0%	38.4%	35.2

Source: data from Study reports 2003, 3001, 3002, and 3005.

In addition, data from Study 2003 shows that decrease in MADRS total score was as early as 2 hours post-dose and reasonably correlated with the time to achieve peak plasma concentration, suggesting a rapid onset of effect (Figure 3). The treatment effect is sustained up to 48 hours post-dose and beyond (up to 4 days post-dose) suggesting that the effect lasts beyond the time of decline in the plasma concentration of esketamine.

Figure 3. (Top panel) PK profile of esketamine following a single intranasal dose of 56 mg and 84 mg esketamine in healthy subjects in Study 1002 (Bottom panel) Change in mean Montgomery-Asberg depression rating scale (MADRS) following a single intranasal dose of 56 mg and 84 mg esketamine in the treatment resistant depressive patients in Study 2003.



Source: Reviewer's analysis

3.3.2 Is the proposed general dosing regimen appropriate?

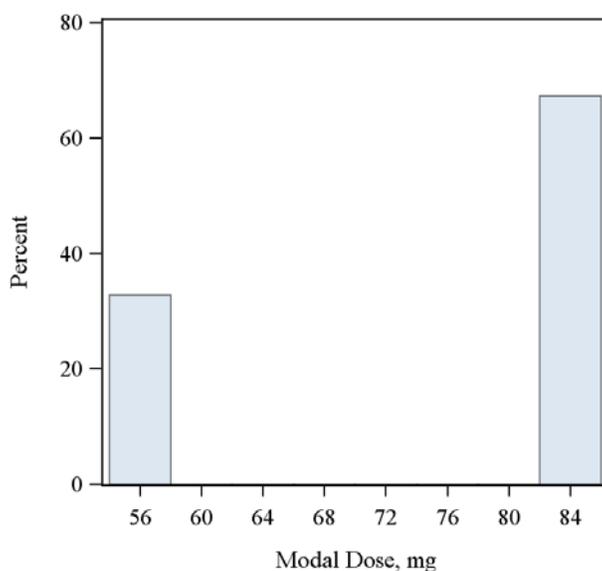
Yes, (b) (4) The following aspects were evaluated by the review team to conclude that the proposed general dosing regimen, as shown in Table 1, is appropriate.

56 mg as a starting dose on Day 1 (b) (4)

56 mg as a starting dose (b) (4) is reasonable. This is based on the following observations:

- The mean changes in MADRS total scores were reasonably similar between 56 and 84 mg in Study 3001 (fixed-dose study).
- In Study 3002 (flexible-dose study), at least 30% of the patients remained stabilized at 56 mg at the end of the study suggesting the need for 56 mg dose option.
- A Phase 2 dose-response study (Study 2003) suggests that a lower dose (28 mg) might not be an efficacious dose.
- There were dose-dependent increases in changes in blood pressure and safety endpoints such as CADSS and MOAA/S between 56 mg and 84 mg.
- There was greater occurrence of tolerability events such as vomiting, nausea, dizziness on Day 1 which led to some patients treated with 56 mg discontinuing from Study 3001. Starting patients at higher dose of 84 mg could potentially lead to more treatment discontinuations.

Figure 4. Proportion of patients taking various doses of esketamine in Study 3002



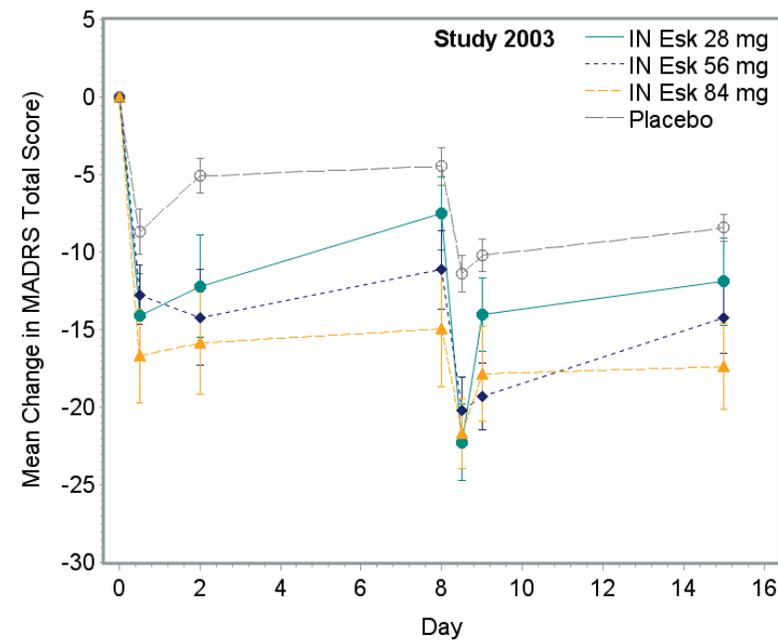
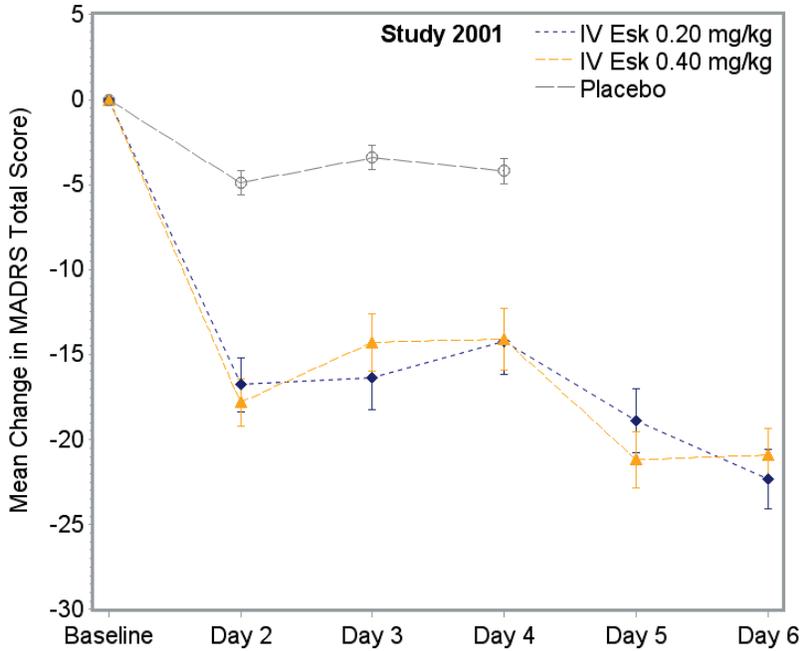
Source: Reviewer's analysis

Frequency of Induction and Maintenance doses of 56 or 84 mg

The proposed dose/dosing regimen as shown in Table 1 has been evaluated in clinical trials. Support for evaluating these doses and dosing regimens was obtained from Studies 2001 and 2003 conducted prior to Phase 3 studies. In Study 2001, patients received 0.20 mg/kg, 0.40 mg/kg IV esketamine, or placebo on Day 1 and Day 4 during a 7-day double-blind treatment phase. The results show that after intravenous administration, a reduction in MADRS total scores are seen by 2 hours post-dose followed by stabilization for at least 4 days (Figure 5). Subsequent dose on Day 4 led to further reductions in total MADRS score. Similar results were observed after administration of twice weekly 28 mg, 56mg and 84 mg intranasal esketamine in Study 2003, with a reduction in MADRS total scores seen as early as 2 hours post-dose and sustained for at least 3 days (Figure 5). These Phase 2 study results, along with the successful efficacy Study 3002, suggest that the antidepressant effect of esketamine can be sustained for at least 4 days, and thus twice per week dosing frequency is adequate for intranasal esketamine for induction phase (week 1 to week 4).

The supportive evidence for maintenance dosing regimen and frequency comes from the long-term randomized withdraw Study 3003. In Study 3003, frequency of intranasal treatment sessions was reduced from twice weekly in the induction phase to weekly for the first 4 weeks of this phase. After the first 4 weeks, the frequency of intranasal treatment sessions was individualized to either once weekly or once every other week based on the severity of depressive symptoms according to the MADRS total score. The results show a statistically significant longer time to relapse in those randomized to continue esketamine compared with those randomized to placebo, among patients who were in stable remission after 16 weeks of treatment with intranasal esketamine. Thus, weekly or bi-weekly dosing frequency is adequate for intranasal esketamine during the maintenance phase.

Figure 5. Mean change of MADRS Total Score Over Time. Upper Panel: the patients received IV esketamine (0.20 and 0.40 mg/kg) or placebo twice per week in Study 2001; Lower Panel: the patients received intranasal esketamine (28 mg, 56mg, or 84 mg) or placebo twice per week in Study 2003.

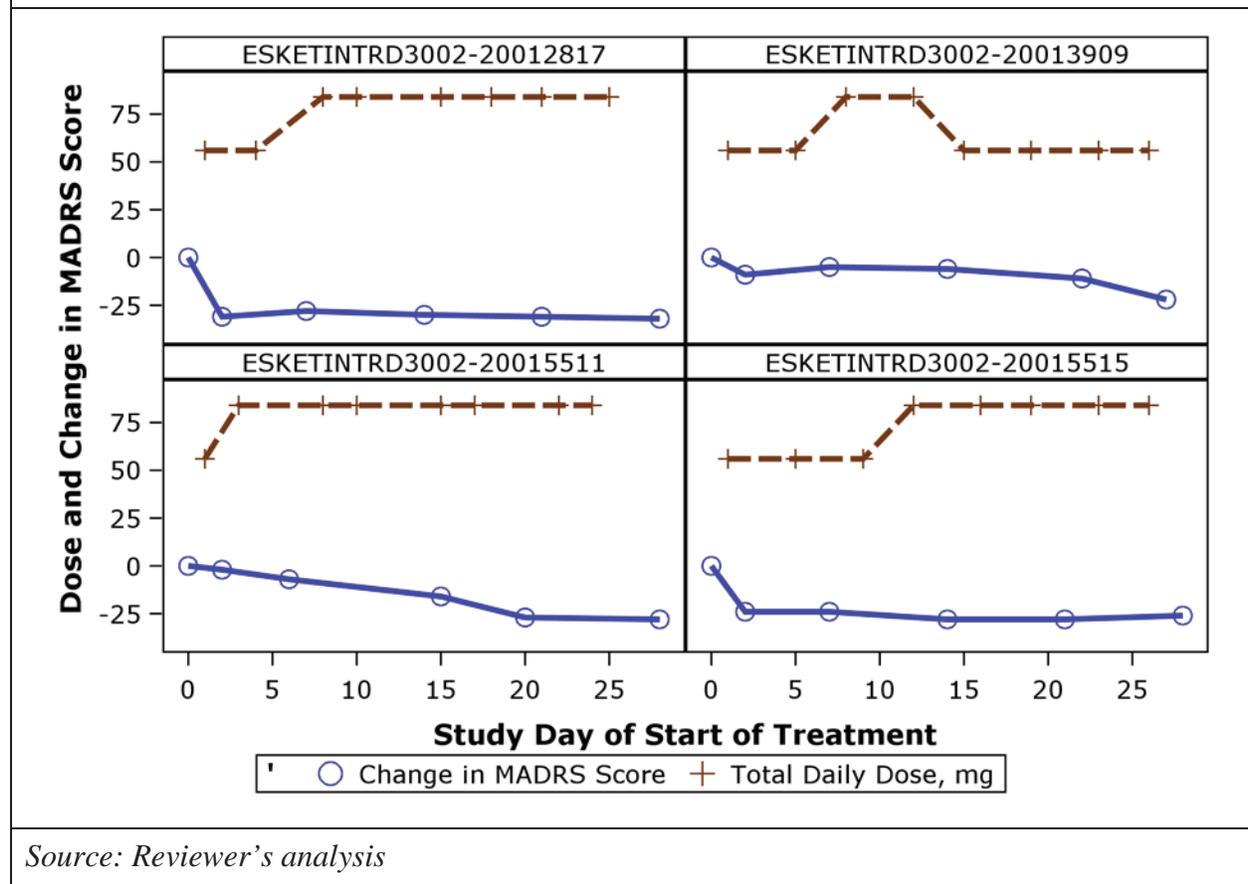


Source: Reviewer's analysis

84 mg as a maintenance dose option

There is no clear evidence from clinical trials that an individual patient would have a greater benefit from 84 mg after being initially treated with 56 mg. The study design did not allow for adequate time for patients to respond to a dose prior to dose escalation. For example, Figure 6 shows the time course of MADRS score and esketamine dose from representative patients who had their dose up titrated in Study 3002. Figure 6 shows that some patients probably did not need dose escalation to 84 mg. In these patients, the changes in MADRS scores were maintained after the first dose of 56 mg. Due to the lack of adequate data on dose-response from various clinical studies, it is recommended that esketamine dose/dosing regimen in label reflect how esketamine was dosed in the clinical trials.

Figure 6. Change in MADRS score and total daily dose in flexible-dose titration Study 3002. Shown are data from representative patients.



Source: Reviewer's analysis

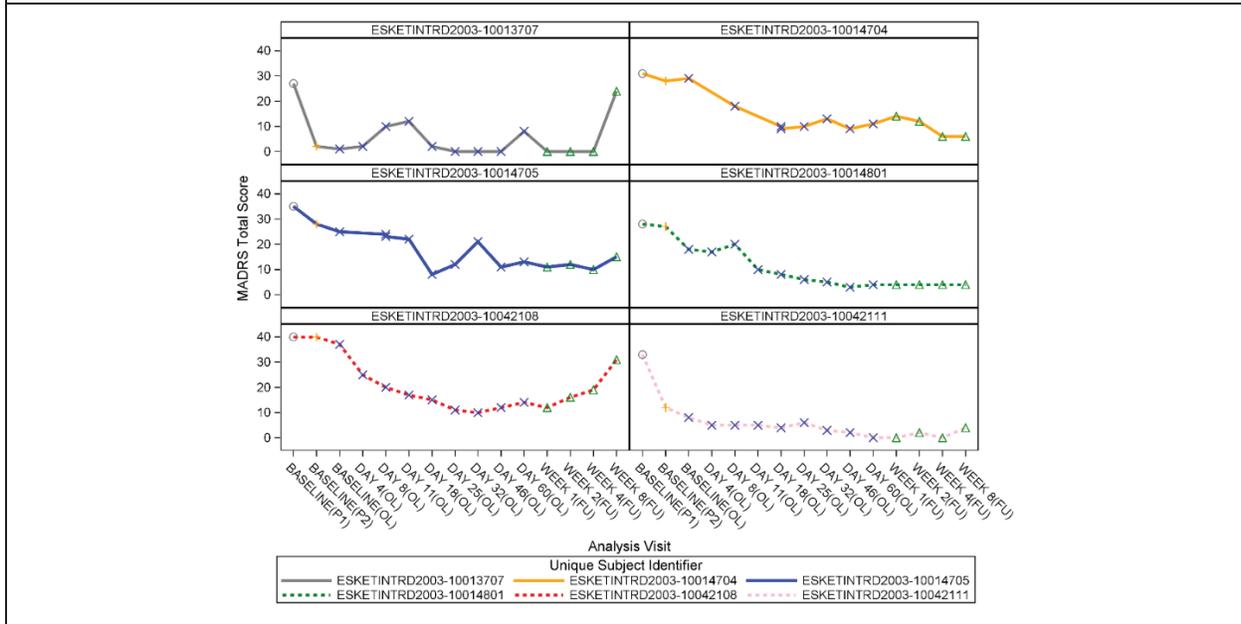
Re-dosing guidelines and Flexibility of dosing for missed doses

The *re-dosing guidelines* states:

“In case one or two treatment sessions are missed, schedule the next session when the next dosage session was scheduled to occur based on current treatment frequency. If more than 2 treatment sessions have been missed, per clinical judgement, adjustment of the dose or frequency of SPRAVATO may be clinically appropriate.”

To evaluate this aspect, the data from Study 2003 was assessed. Figure 7 shows the MADRS total score throughout the course of the study in selected patients. Figure 7 shows that there are patients (ESKETINTRD2003-10013707, ESKETINTRD2003-10042108) whose MADRS score trend towards the baseline beyond 2 weeks of treatment discontinuation. Data from other patients in Figure 7 suggests maintenance of benefit up to 4 weeks even after treatment discontinuation. These findings can also be interpreted in a setting where patients miss taking one or more doses of esketamine. Since the treatment benefit is sustained at least up to 2 weeks in all patients, the re-dosing guidelines proposed by the sponsor (in the setting of one or two missed doses) may be reasonable at least for patients who are on a once-weekly regimen.

Figure 7. Time course of MADRS total score in select patients from Study 2003. Shown are data in double-blind phase, open-label phase and during follow-up (after stopping treatment).



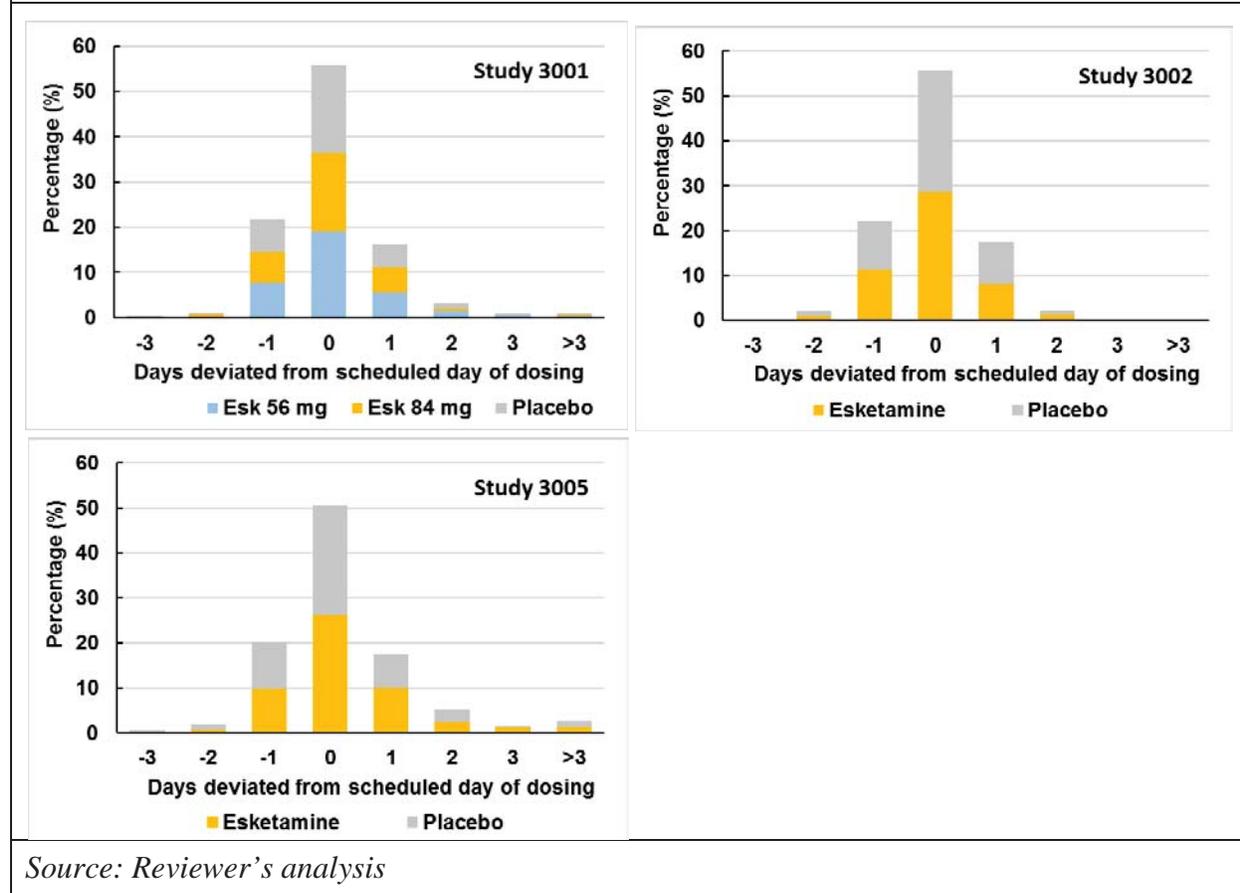
Source: Reviewer’s analysis

Flexibility of dosing

In Studies 3001, 3002 and 3005, patients were scheduled to be administered esketamine twice weekly for 4 weeks on Day 1, 4, 8, 11, 15, 18, 22, 25. However, approximately 40% of the patients deviated from the scheduled day of dosing by at least 1 day, and approximately 2% - 10% of the patients deviated from the scheduled day of dosing by 2-4 days (**Figure 8**). There was no

significant rebound in MADRS score observed in those patients with delayed dosing. This data supports flexibility in the twice per week dosing in the induction phase.

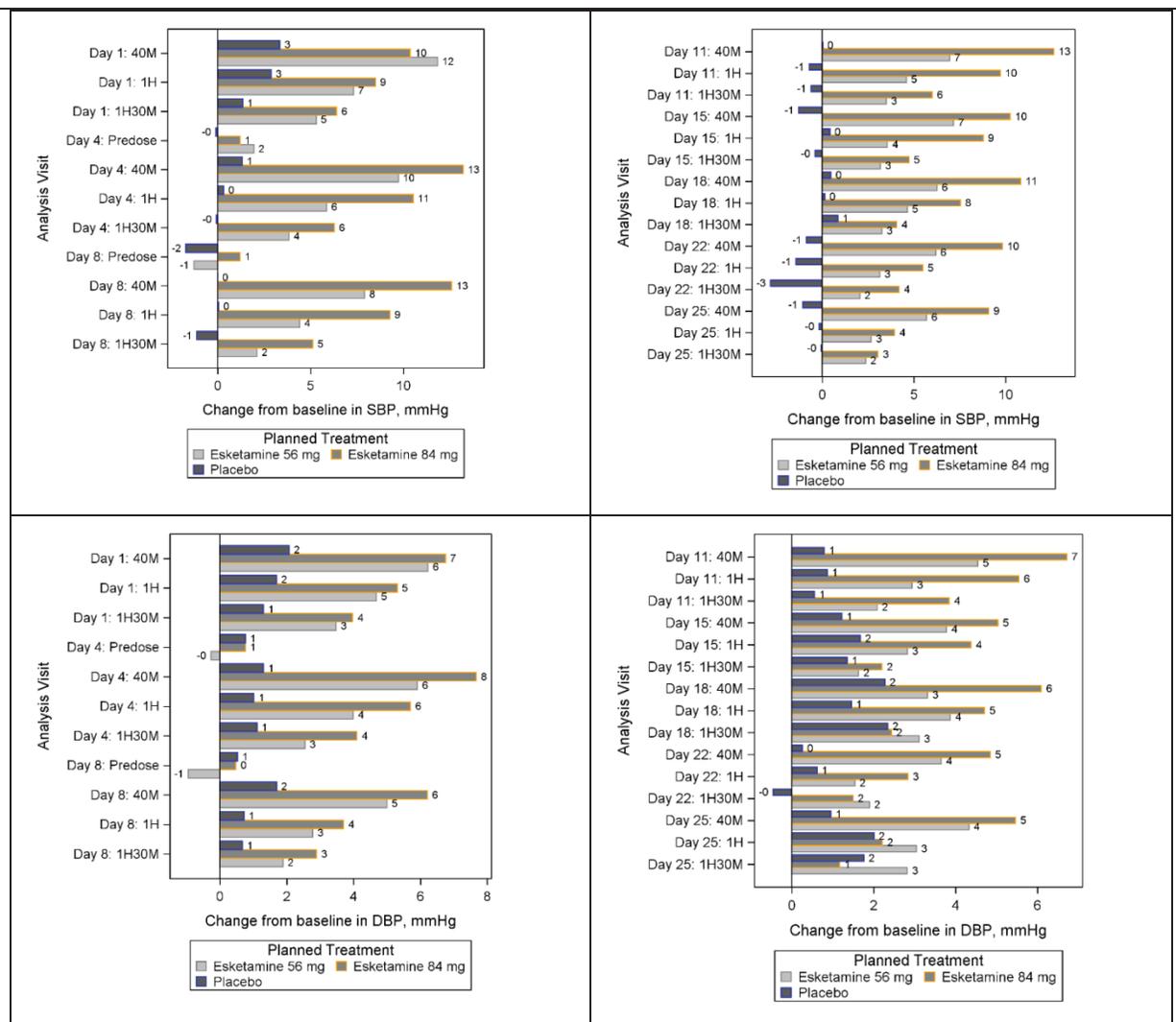
Figure 8. Doses deviated from scheduled day of dosing in Study 3001, 3002 and 3005.



Increase in systolic, diastolic blood pressure relative to plasma levels of esketamine. Implications for individual patient care.

Maximum mean increase in blood pressure is dependent on dose (For example: 84 vs 56 mg on Day 4) and was observed at 40 min post-dose, corresponding to the t_{max} of esketamine in Study 3001 (Figure 9). It should be noted that all patients received 56 mg on Day 1.

Figure 9. Time course of changes in SBP and DBP on various study days in Study 3001. Data post 40 min, 1h and 1h30 min in placebo, 56 mg and 84 mg dose groups are shown.

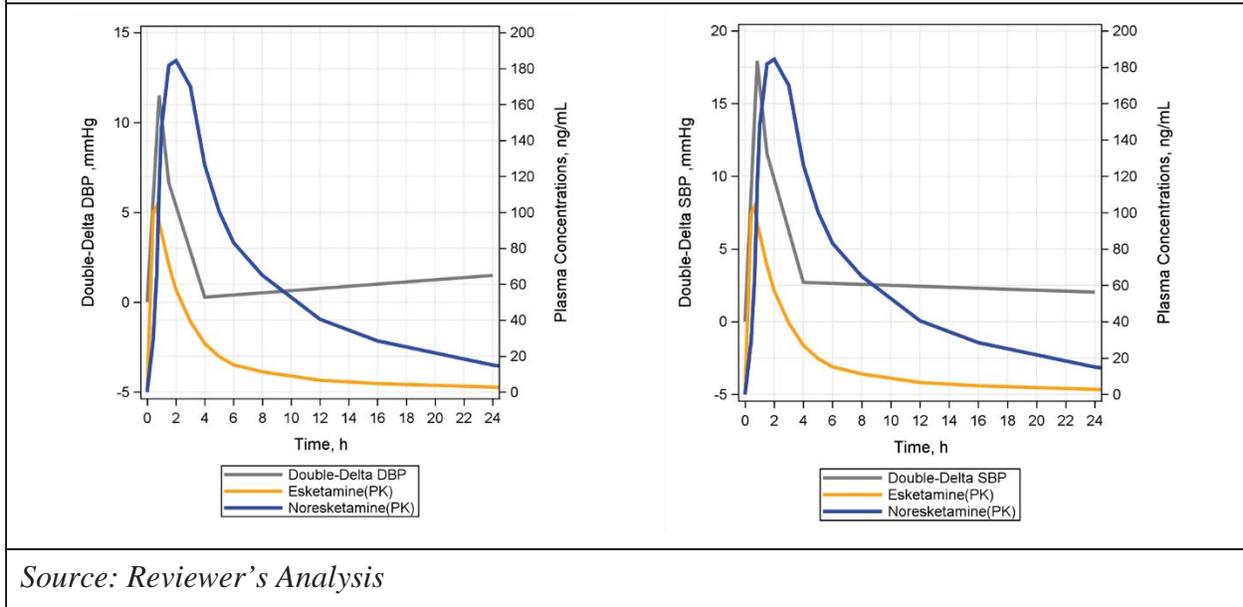


Source: Reviewer's analysis

In Study 3001, SBP and DBP were only measured until 1.5h post-dose.

To understand the effects of esketamine on SBP and DBP beyond 1.5 hours, the reviewer conducted analyses of the blood pressure data from Study 1013. The maximum mean changes in SBP and DBP occurs at the T_{max} of esketamine (Figure 10). By 4h post-dose, esketamine concentrations are about 20% of the C_{max} . However, noresketamine concentrations are about 50% of the C_{max} . The increase in SBP and DBP resolve by approximately 4 hours (Figure 10) indicating that these changes are likely related to esketamine concentrations.

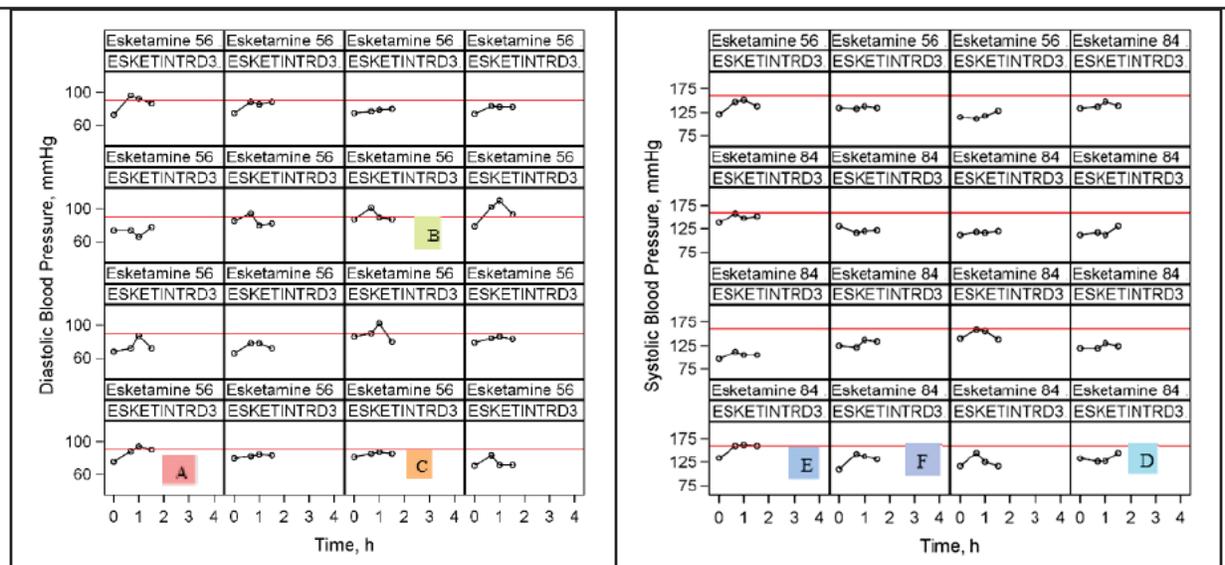
Figure 10. Mean time course of esketamine, noresketamine plasma concentrations (Right Y axis) and placebo-corrected SBP and DBP changes (Left Y-axis) in Study 1013.



Source: Reviewer's Analysis

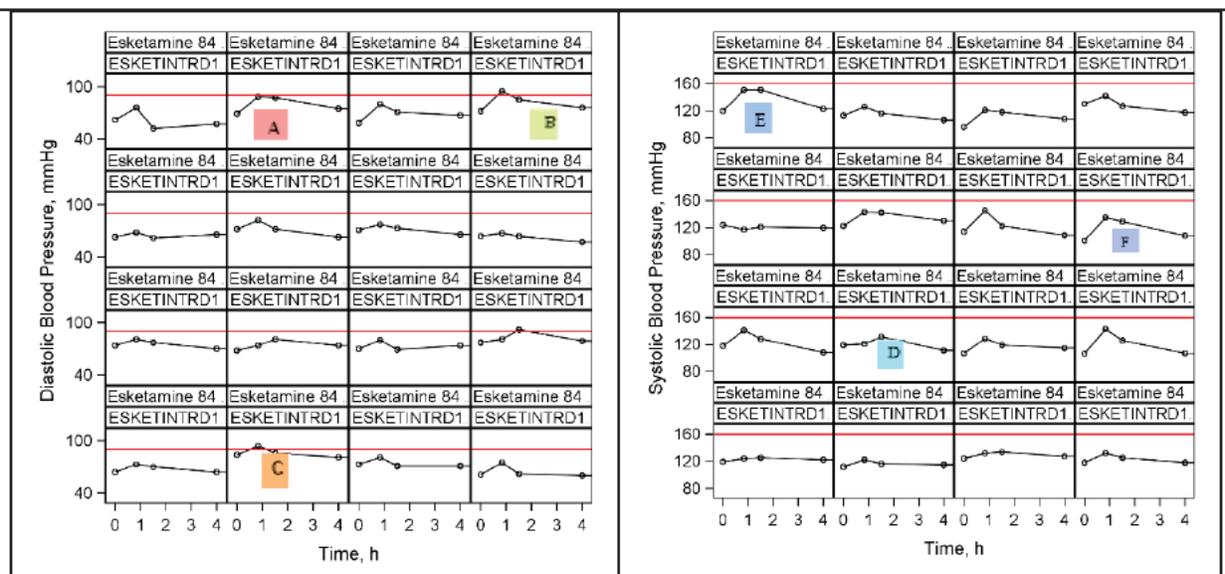
Analysis was also conducted to relate the patterns in SBP, DBP changes in Study 3001 and Study 1013. The intent of this analysis was to identify patterns like those observed in Study 3001 until 1.5 hours and understand how the changes post 1.5 hours can be projected based on the findings from Study 1013. If similar patterns exist in subjects from Study 1013 until 1.5 hours and the changes in SBP and DBP return to baseline at 4h, then these findings can inform the duration of blood pressure monitoring needed in these patients. Comparison of findings from Figure 11 and Figure 12 suggest that there are similar patterns of SBP, DBP changes (A, B, C, D, E, F represent chosen patients and healthy subjects by the reviewer) between healthy subjects and patients.

Figure 11. Time Course of SBP and DBP in Study 3001. Selected SBP, DBP profiles in patients for comparison with those in healthy subjects are referenced by “A”, “B”, “C”, “D”, “E” and “F”. Reference line at 90 mmHg for DBP and 160 mmHg for SBP is shown.



Source: Reviewer’s analysis

Figure 12. Time Course of SBP and DBP in Study 1013. Selected SBP, DBP profiles in healthy subjects for comparison with those in patients are referenced by “A”, “B”, “C”, “D”, “E” and “F”. Reference line at 90 mmHg for DBP and 160 mmHg for SBP is shown



Source: Reviewer’s analysis

Taken together, the analysis suggests that blood pressure effects last for about 4 hours and are likely related to esketamine plasma exposure. SBP and DBP increases are seen only on the day of dosing.

Decrease in short-term cognitive function, sedation and dissociation relative to plasma levels of esketamine. Implications for individual patient care.

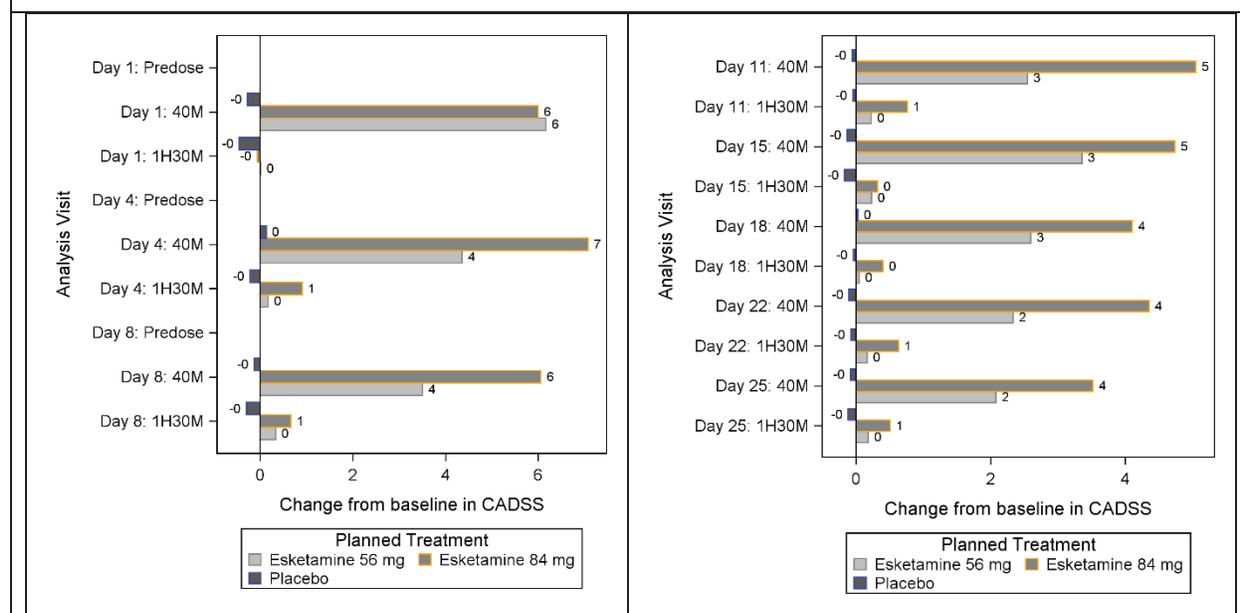
Short term cognitive function

A single dose of 84 mg esketamine nasal spray produced a transient decline in cognitive function. The difference between esketamine and placebo was statistically significant at 40 minutes post-dose. Cognitive function returned to baseline measurements by 2 hours post-dose as measured by the effort required to complete the Cogstate[®] computerized test battery. The effect of esketamine on increased sleepiness was more sustained, returning to near baseline levels by 4 hours post-dose. In addition, it is observed that in Study 1005 and Phase 3 studies that there was a dose- and esketamine exposure-related changes in dissociative state (CADSS) and alertness (Day 4 MOAA/S) after intranasal dose of esketamine (see Section 3.3.2).

Sedation and Dissociation

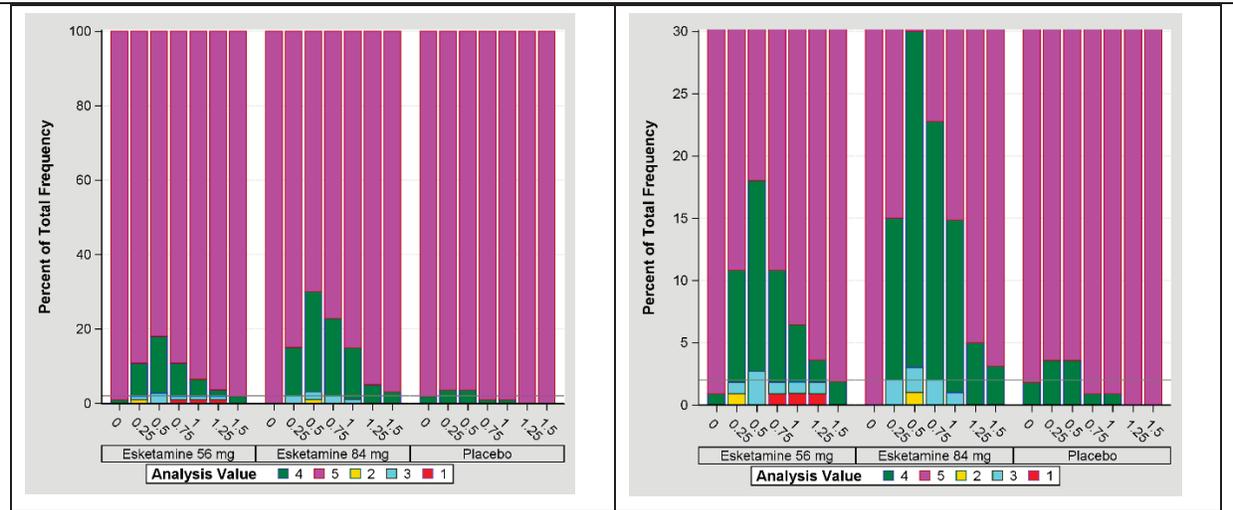
Dose related changes in dissociative state (CADSS, Clinician administered dissociative states scale) and alertness (Day 4 MOAA/S, Modified observer’s assessment of alertness/sedation) are shown in Figure 13 and Figure 14. Maximum mean increase in dissociative score is dependent on the dose (For example: 84 vs 56 mg on Day 4) and observed at 40 min post-dose, corresponding to the t_{max} of esketamine in Study 3001 (Figure 13). Maximum mean decrease in MOAA/S is dependent on the dose (For example: 84 vs 56 mg on Day 4) and observed at 40 min post-dose, corresponding to the t_{max} of esketamine in Study 3001(Figure 14). It should be noted that all patients received 56 mg on Day 1.

Figure 13. Time course of changes in CADSS on various days in Study 3001



Source: Reviewer’s analysis

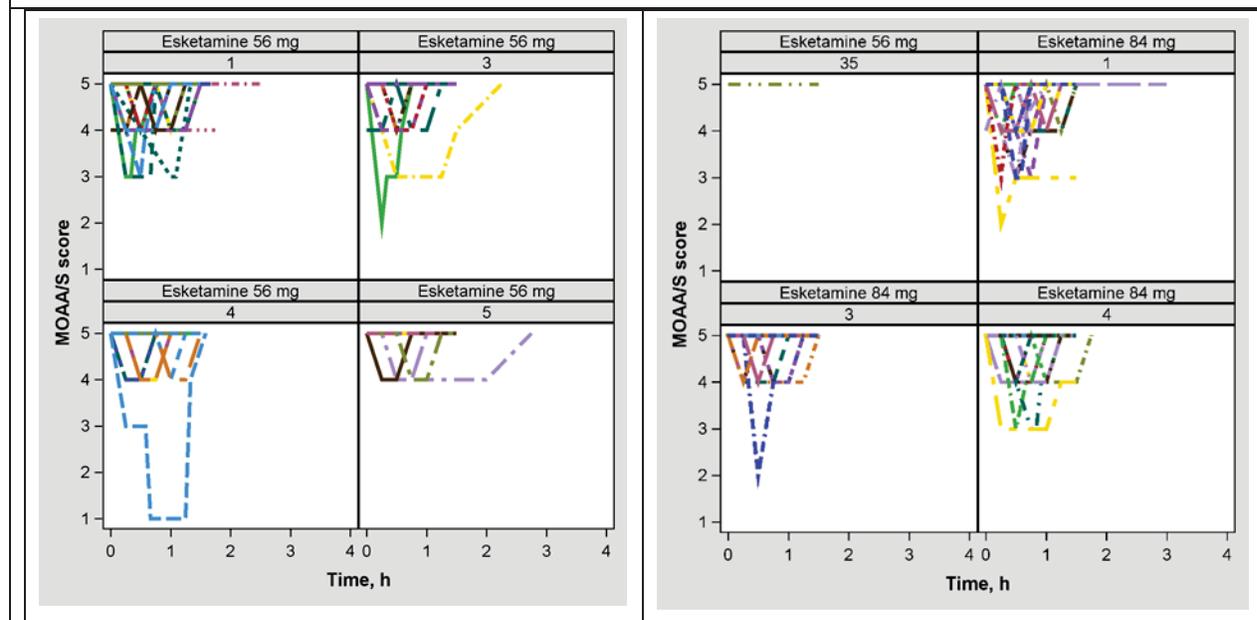
Figure 14. (Left) Percentage of patients with various MOAA/S score by time on Day 4 in Study 3001 (Right) Same graph as shown on left but Y-axis limited to 30 percent to show scores that were seen in less than 5% of the patients.



Source: Reviewer's analysis

Figure 15 shows the time course of MOAA/S score in 56 mg and 84 mg dose groups on select days. It also shows the variability in MOAA/S score changes including data from a patient whose MOAA/S score decreased from a score of 5 to 1 and reversed to a score of 5 by 2 hours.

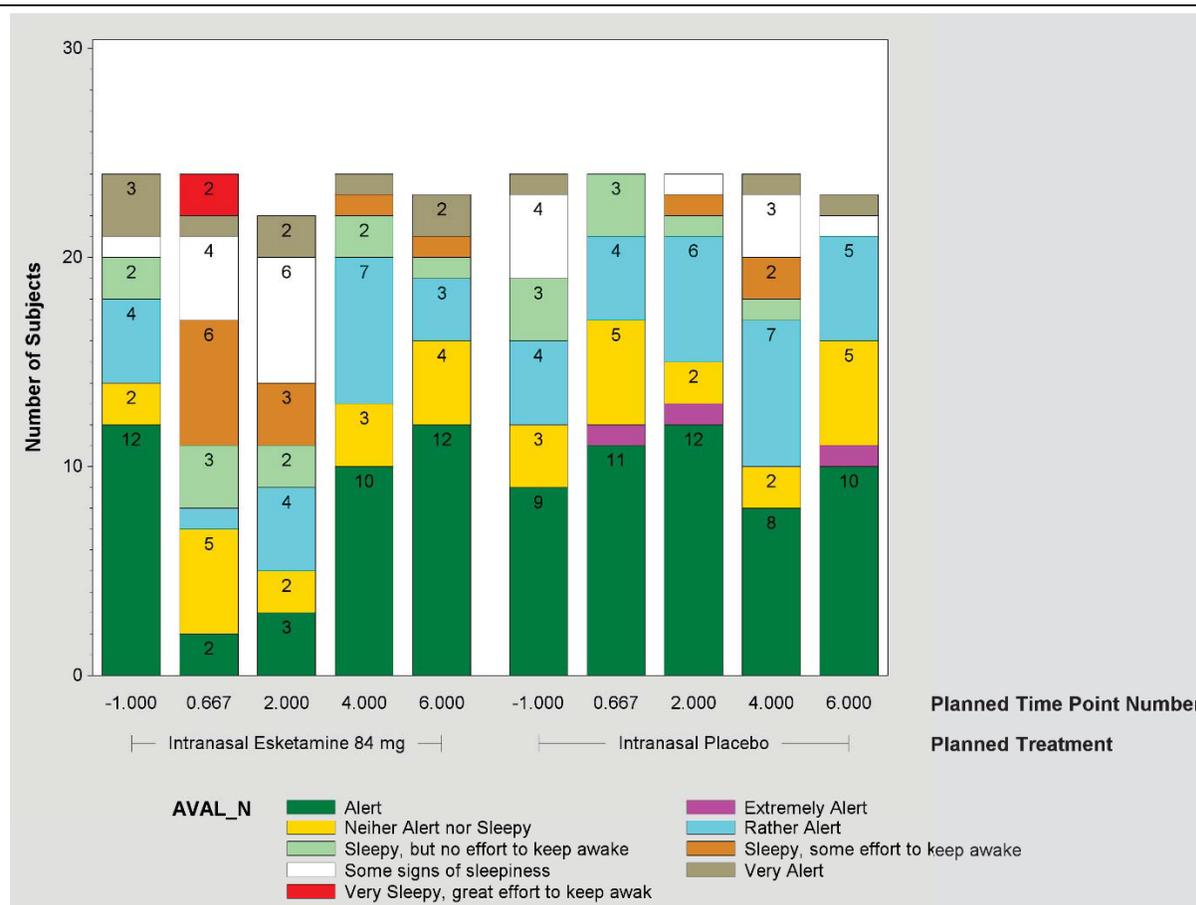
Figure 15. Time course of MOAA/S score in TRD3001.



Source: Reviewer's analysis

Since no data on sedation/alertness was available after 1.5 hours in Study 3001, the reviewer assessed the findings from Study 1005 in which data on “Sleepiness” was obtained through 6 hours post-dose. In Study 1005, sleepiness was assessed using the Karolinska Sleepiness Scale (KSS). Figure 16 shows that 2 out of 21 subjects felt “very sleepy” around t_{max} of esketamine. While all subjects reported that they were “Alert” by 6 hours, majority of the subjects reported that they were “Alert” by 2-3 hours. There are subjects who felt “sleepy” around 4-6 hours in both placebo and esketamine group.

Figure 16. Number of subjects with various degrees of sleepiness/alertness at various time points after esketamine dose in Study 1005. Segments in bars without numbers should be inferred as having 1 subject.



Source: Reviewer’s analysis

Effect on driving performance

Since transient decreased cognitive function and sedation were observed in the first few hours following intranasal dosing, it is expected that esketamine would impair driving performance in the initial few hours post-dosing.

The driving performance of healthy subjects and major depressive disorder (MDD) patients following intranasal dosing of esketamine was evaluated in two clinical Studies 1006 and 1019 by assessment of the mean standard deviation of the lateral position (SDLP).

Study 1006: this study evaluated the effect of 84 mg esketamine nasal spray on the same day (8 hours post-dose) driving performance in healthy subjects. The on-road driving performance was not different relative to when they administered placebo based on SDLP if they met other requirements for discharge. However, it is noted that two subjects from Study 1006 discontinued the driving test due to persistent and worsening of treatment-emergent adverse events, indicating potential outliers for driving performance 8 hours post-dose.

Study 1019: this study evaluated the effects of a single esketamine nasal spray (84 mg) on next-day driving performance (18 hours post-dose) and effects of twice weekly esketamine nasal spray (84 mg) on same-day driving performance (6 hours post-dose) in subjects with MDD. The results showed that the driving performance after multiple dose of esketamine was not inferior to placebo 6 hours post-dose in MDD patients. The driving performance after a single dose of esketamine was also not inferior to placebo 18 hours post-dose in MDD patients). There was also no difference in secondary measures of driving performance (i.e. standard deviation of speed, mean lateral position, or mean speed) or in subjective assessment of driving ability or perceived effort scale following both single or repeated administration of esketamine.

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 who are 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 $t_{1/2}$ 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.

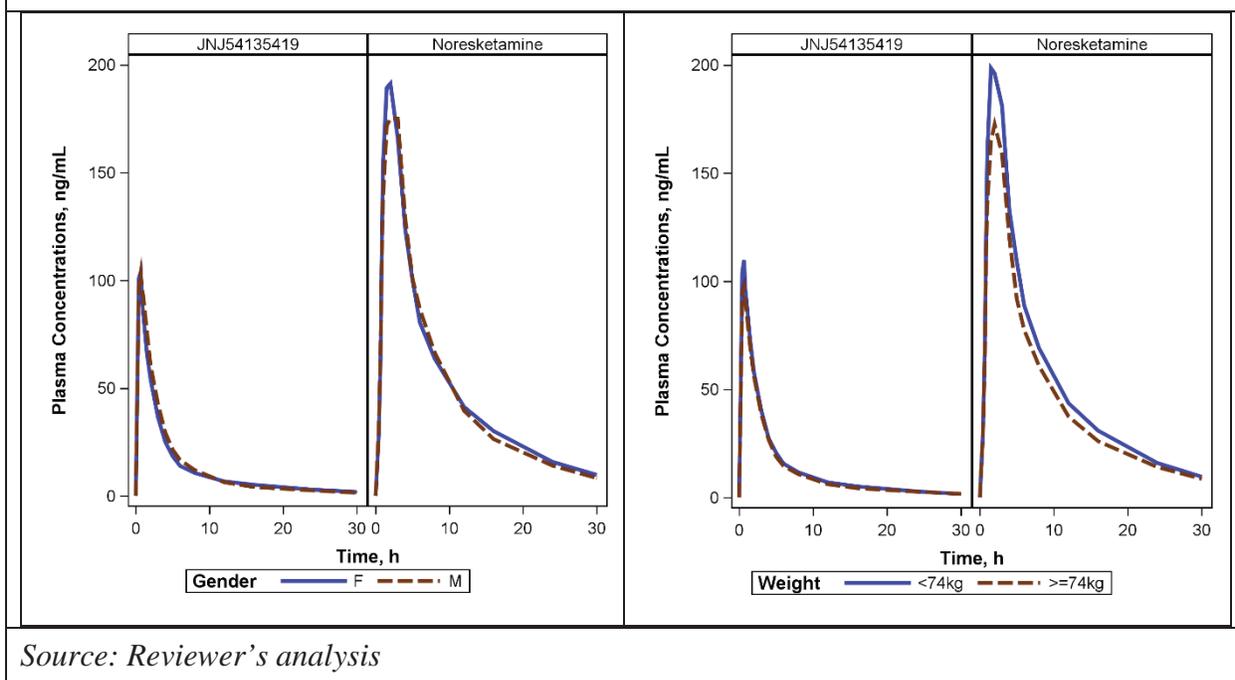
Based on these findings, we recommend that the patients should not drive on the day of intranasal esketamine dosing, but may drive the next day following a restful sleep.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Body Weight, Gender, Race: Alternative dosing regimen is not required based on body weight, gender or race.

Figure 17 shows the concentration-time profile based on gender and body weight (<74 kg vs ≥ 74 kg; Median body weight=74kg) in Study 1013. The influence of gender and body weight on pharmacokinetics of esketamine was evaluated using data from multiple studies and concluded as being not important for dose adjustment using population pharmacokinetic analysis. (See Appendix).

Figure 17. Mean concentration-time profile for esketamine (JNJ54135419) and noresketamine by (Left) gender and (Right) body weight category in Study 1013.



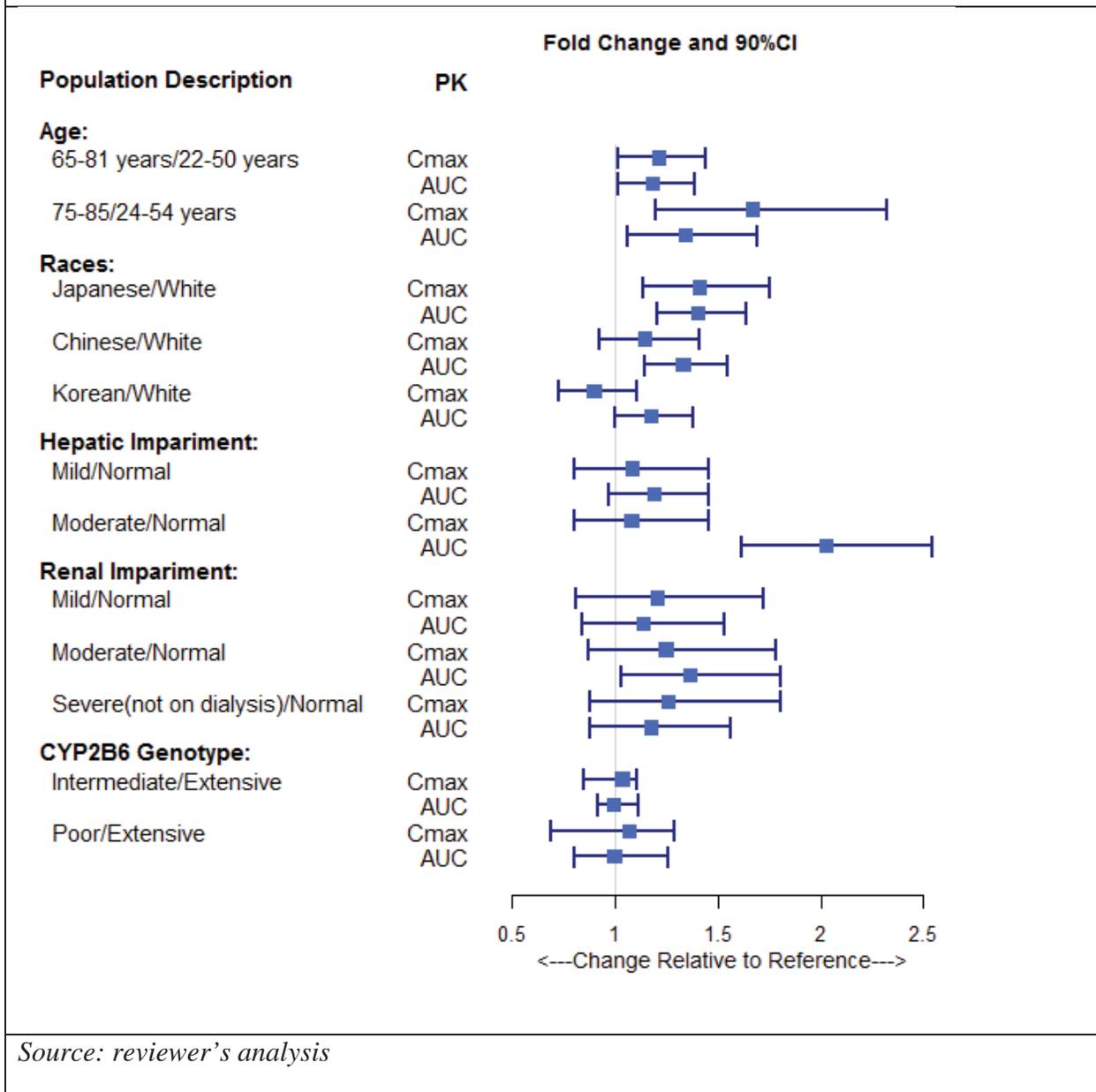
Source: Reviewer's analysis

Age

The means of C_{max} and AUC_{∞} for esketamine were approximately 21% and 17% higher in elderly subjects ≥ 65 years of age and 67% and 38% higher in elderly subjects ≥ 75 years of age compared to younger adults (18 to ≤ 55 years of age) following single intranasal dose of 28 mg esketamine (Studies 1003 and 1012). A similar trend for higher C_{max} (8 – 27%) and AUC_{∞} (36 – 52%) values were observed in elderly Japanese subjects (≥ 65 years of age) as compared to younger adults (20 to 55 years of age) (Figure 18).

Because the study in geriatric patients (Study 3005) did not achieve its primary endpoint, a dosing recommendation for these patients cannot be provided.

Figure 18. Effect of Intrinsic Factors on the Pharmacokinetics of Esketamine



Source: reviewer's analysis

Effect of Renal Impairment

The effect of renal impairment on the PK of esketamine and noresketamine was evaluated in subjects with mild, moderate and severe (not on dialysis) renal dysfunction after 28 mg single dose administration of esketamine. The results show that the exposure of esketamine was only minimally increased in subjects with mild, moderate, or severe renal impairment as compared to subjects with normal renal function. Subjects with mild, moderate or severe renal impairment had slightly higher noresketamine C_{max} (20% to 26%), AUC_{last} (14% - 32%) and AUC_∞ (13% - 36%) compared to subjects with normal renal function (Figure 18). Urinary excretion of esketamine was

low in all cohorts. The mean amount of esketamine excreted unchanged expressed as percentage of the administered dose ranged between 0.6% to 1.3% across the renal function groups.

In general, there was no clear correlation between plasma esketamine and noresketamine concentration and individual renal function. Adjustment of the dose of esketamine nasal spray in patients with renal impairment is not warranted.

Effect of Hepatic Impairment

The effect of hepatic impairment on the PK of esketamine was evaluated in mild (Child-Pugh Class A) and moderate hepatic impairment (Child-Pugh Class B) patients self-administered 28 mg of esketamine nasal spray. The PK of esketamine in subjects with severe hepatic impairment (Child-Pugh Class C) was not investigated.

The mean C_{max} and AUC_{∞} were similar in subjects with mild hepatic impairment relative to subjects with normal hepatic function. However, the mean esketamine C_{max} and AUC_{∞} were 8% and 103% higher, respectively, in subjects with moderate hepatic impairment than in the healthy subjects. The fraction of unbound esketamine (56.2% - 60.7%) was similar for the 3 cohorts (Figure 19). Urinary excretion of unchanged drug was low in all cohorts (mean, 2.41% of the administered dose in subjects with moderate impairment and <1% of the dose in subjects with mild impairment and healthy subjects).

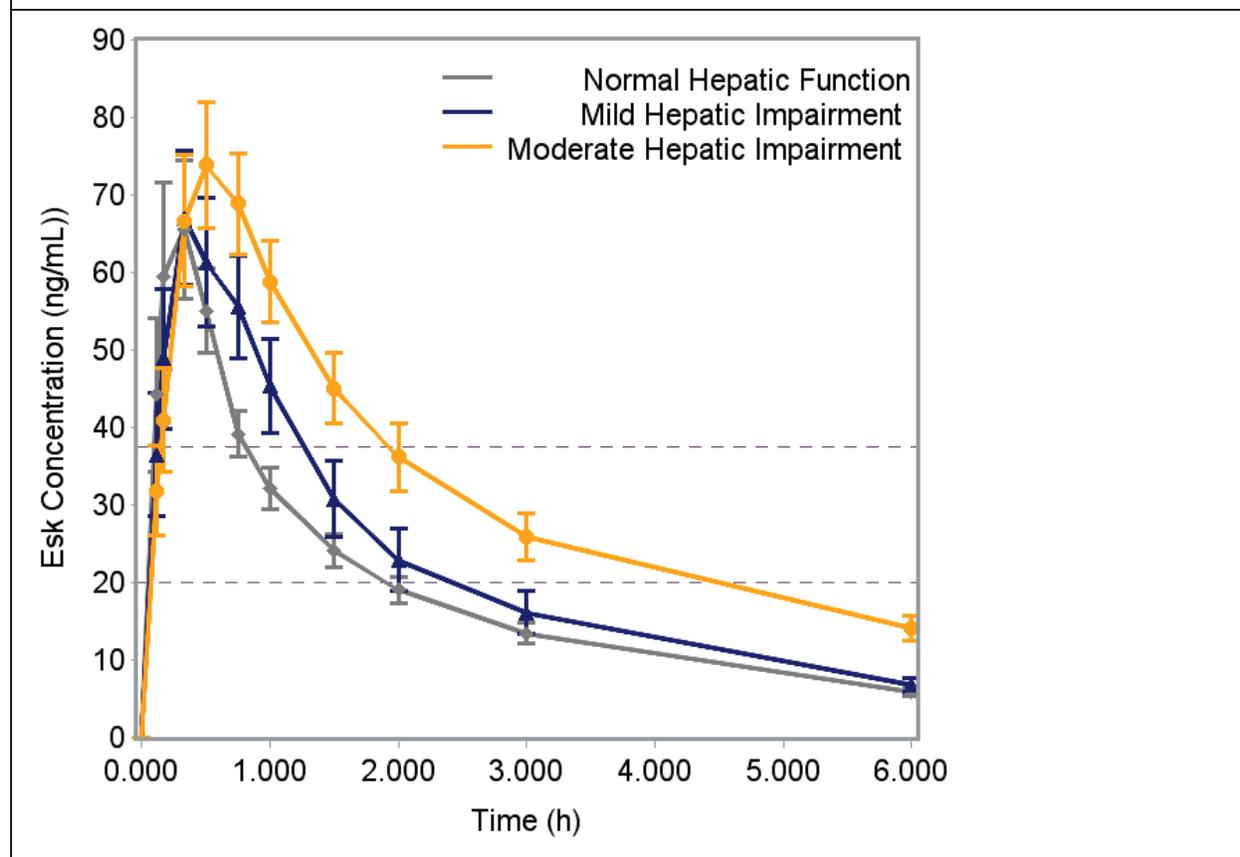
Given the increased esketamine exposure in AUC for moderate hepatic impairment group, dose adjustment is not recommended for patients with hepatic impairment given the following considerations:

- Intranasal esketamine was well tolerated in normal subjects, subjects with mild and moderate hepatic impairment. Most of the observed TEAEs were mild and were reported to be resolved by the end-of-the study.
- Blood pressure: due to limited number of subjects (n =24) and large variability of blood pressure measurement, the trend of changes in blood pressure (SBP and DBP) over time is not very clear in Study 1011. However, no observation of treatment emergent acute hypertension (elevations of SBP to ≥ 180 mm Hg or DBP to ≥ 110 mm Hg) was reported in this study. In addition, based on the review team's analysis (see Section 3.3.2), the change in blood pressure is dose-dependent and likely related with esketamine concentration-time course. Since C_{max} of esketamine was similar among three hepatic function groups, it is expected that the magnitude of increase in blood pressure following esketamine dosing would be similar between patients with hepatic impairment and subjects with normal hepatic function. In addition, the elimination of esketamine was slower for subjects with hepatic impairment as compared to those with normal hepatic function. Thus, it is expected that the effects on blood pressure would be more persistent in patients with moderate hepatic impairment function, as compared to subjects with normal hepatic function. By 2 hours post-dose, esketamine concentrations decreased to 29%, 34% and 49% of the C_{max} values for normal subjects, mild and moderate hepatic impairment groups, respectively. By 6 hours post-dose, esketamine concentrations decreased to 19%, 10% and 9% of the C_{max} values in normal subjects, mild and moderate hepatic impairment groups. Thus, the increase in blood pressure following esketamine dose would mostly likely return to baseline levels 6 hours post-dose for patients with moderate hepatic impairment.

- Sedation/alertness effects: the sedative and alertness effects of esketamine were measured by MOAA/S score in Study 1011. In general, none of the subjects experienced deep sedation and the majority of the subjects remained alert after dosing with 28 mg esketamine (MOAA/S score ≥ 4). As discussed in Section 3.3.2, the sedation/alertness effect of esketamine is likely to be related with esketamine concentration-time profile. Based on PK profiles of esketamine in subjects with hepatic impairment, subjects with moderate hepatic impairment may require a longer period to recover from decrease of cognitive function.

In summary, intranasal esketamine was well tolerated in normal subjects, subjects with mild and moderate hepatic impairment. The safety profile in subjects with hepatic impairment was similar to subjects with normal hepatic function. The magnitude of change blood pressure and cognitive function following intranasal esketamine dose are expected to be similar between subjects with hepatic impairment and normal hepatic function. However, it may take longer for blood pressure and cognitive function return to baseline levels in patients with moderate hepatic impairment, which may require a longer period of monitoring.

Figure 19. Mean (SD) Plasma Concentration-Time Curves of Esketamine After Single Intranasal Administration of 28 mg Esketamine in Subjects with Moderate or Mild Hepatic Impairment and in Subjects with Normal Hepatic Function



Source: reviewer's analysis.

Cytochrome 2B6 Genotype

The contribution of CYP2B6 to the total microsomal P450 pool in the liver is expected to be approximately 60%. Due to extensive interindividual variability in the expression of CYP2B6, the impact of genetic polymorphism of CYP2B6 on the PK of esketamine was studied by pooled PK data from Phase 1 studies.

The results showed that there is no difference in PK parameter values for esketamine and noresketamine between CYP2B6 extensive (n=211 subjects), intermediate (n=133 subjects), and poor (n=19 subjects) metabolizers for each age and ethnicity pool investigated. Some variability was observed, but there was no consistent trend suggesting an association with CYP2B6 phenotype. There was only limited data available for CYP2B6 poor metabolizers, but the available data did not show large deviations from the intermediate or extensive metabolizer results and no specific trends. Thus, the PK of esketamine does not appear to be influenced by CYP2B6 status. Adjustment of the dose of esketamine nasal spray based on CYP2B6 pharmacogenomics is not warranted.

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

Food

The effect of concomitant food intake on the PK of esketamine was not evaluated. In addition, during esketamine clinical studies, consumption of food prior to esketamine administration was restricted. Since the intended route of administration is intranasal, it is expected that the majority of the drug is quickly absorbed through vascularized mucosa, (b) (4)

DDI liability from in vitro studies

- In vitro metabolism studies indicated that CYP2B6 and CYP3A4 appear to be the two major enzymes involved in the metabolism of esketamine, so there is a potential for drug interaction between esketamine and inhibitors and/or inducers of CYP3A4 and CYP2B6.
- Esketamine has modest induction effects on CYP3A4 and CYP2B6 in vitro in human hepatocytes, so there is a potential for drug interaction between esketamine and major CYP3A4 and/or CYP2B6 substrates.
- Noresketamine has a reversible inhibition for CYP3A (IC₅₀ = 1.92 μM, 74.3 μM, and 62.4 μM with testosterone, nifedipine, and midazolam as substrates), so there is a potential for drug interaction between esketamine and major CYP3A substrate due to noresketamine inhibition on CYP3A4.
- Esketamine and its major circulating metabolites did not inhibit major CYPs and UGTs (except noresketamine on CYP3A4).
- Esketamine and its active metabolite noresketamine are not substrates of transporters (P-gp, BCRP, OATP1B1, OATP1B3 for esketamine, and P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 for noresketamine), and esketamine and none of its major circulating phase-1 metabolites were found to be a clinically relevant inhibitor of

P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters.

DDI liability from clinical studies

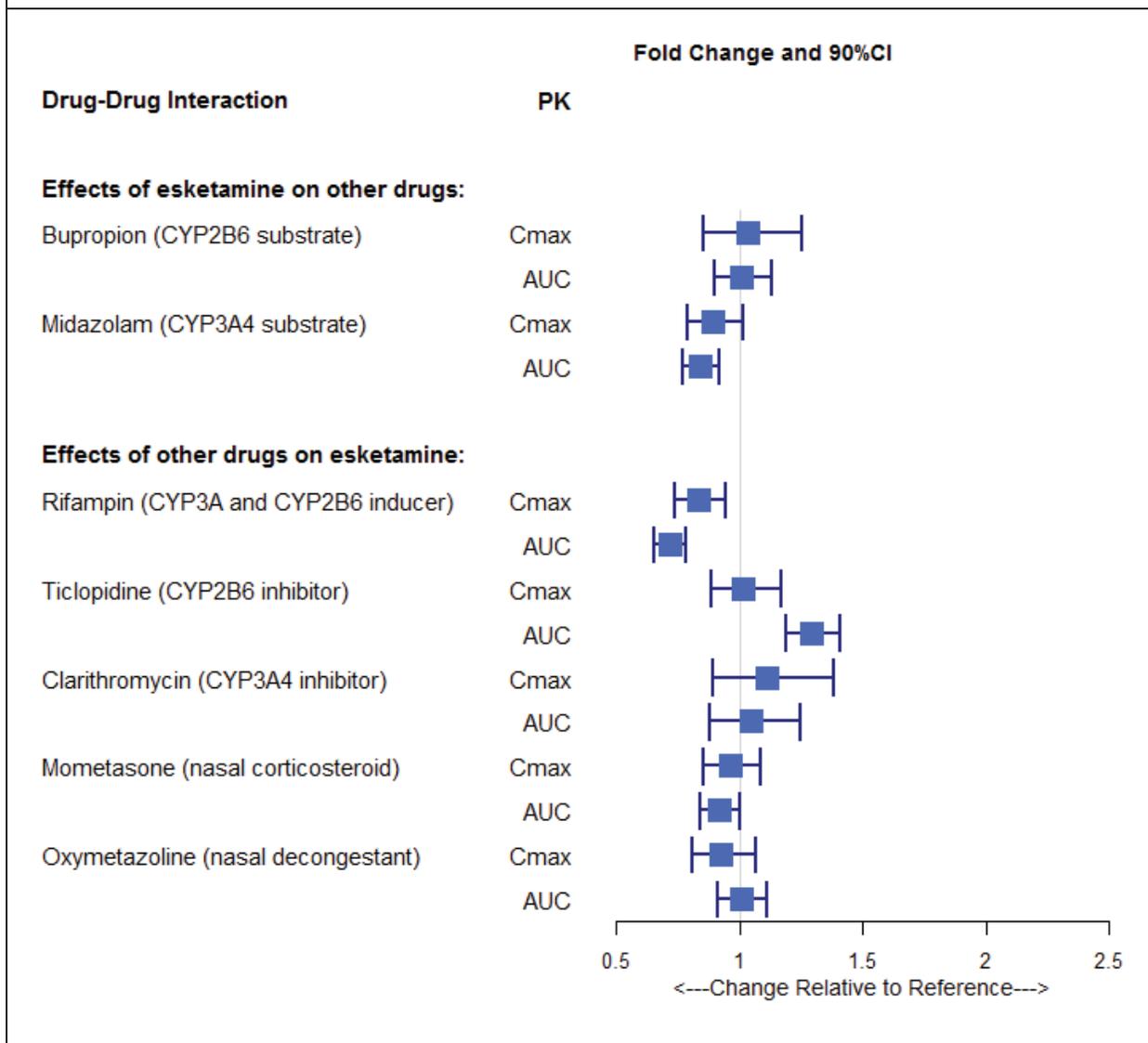
Based on the potential for drug interactions assessed from in vitro studies, the applicant conducted the following clinical drug interaction studies to further evaluate the drug interaction liability of esketamine.

Effects of esketamine on other drugs.

- Induction effect of esketamine on probe CYP2B6 substrate

Bupropion: the induction effects of twice-a-week administration of 84 mg nasal esketamine on the PK of probe CYP2B6 substrate (i.e., bupropion) activity was determined in Study 1010. The results show that the activity of hepatic CYP2B6 was not altered by 84 mg of esketamine nasal spray administered every 3 or 4 days for 5 doses (Figure 20). No changes were observed in the plasma concentrations of bupropion or hydroxybupropion or renal excretion of bupropion or hydroxybupropion. In addition, the metabolite C_{max} to parent C_{max} ratio and metabolite AUC to parent AUC ratios were similar following each administration of bupropion. Thus, dose adjustment for bupropion or any other CYP2B6 substrate when coadministered with esketamine is not warranted.

Figure 20. Effect of Coadministered Drugs on the Pharmacokinetics of Esketamine and Effect of Esketamine on the Pharmacokinetics of Coadministered Drugs



Source: Reviewer's analysis

- Induction effect of esketamine and inhibition effect of noresketamine on probe CYP3A substrate

Midazolam:

In a clinical drug interaction study (Study 1010), the effect of multiple intranasal dose (twice weekly) of esketamine on the PK of midazolam was studied. The subjects received a single oral dose of midazolam in the morning of Day 1 and Day 17, and they self-administered 5 doses of esketamine over a 15 day period. The results show that twice-a-week dosing of nasal esketamine (84 mg) reduced the AUC_{last} and AUC_{∞} of probe CYP3A substrate

midazolam by a mean of 18% and 16%, respectively, with esketamine (Day 16) and midazolam (Day 17) administered on separate days before and after induction (Figure 20). Due to the very low plasma level of noresketamine 24 hours after the last dose of esketamine, CYP3A inhibitory potential of noresketamine was expected to have no influence on midazolam PK. In addition, the high IC_{50} of esketamine on CYP3A leads to a minor inhibition potential. Therefore, the clinical DDI study (Study 1010) was conducted to evaluate the effect of CYP3A induction potential of esketamine on midazolam PK. The 18% or 16% decrease in AUC indicated a lower effect than the effects of drugs considered to be “weak” inducers of CYP3A activity (i.e., 20 to 50% decrease in CYP probe substrate AUC, per the 2017 US FDA draft guidance). In addition, the PBPK analysis was used to evaluate both induction and inhibitory effect of esketamine on midazolam when midazolam was dosed together with the last dose of esketamine. FDA’s analyses showed when the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 16 a single oral dose of midazolam (6 mg) was administered, the midazolam AUC ratios are predicted to be within a range of 0.90-1.00. A range of 1.23-1.41 for midazolam AUC ratios was also predicted under a worst-case scenario. This interaction is not considered to be clinically relevant, and thus dose adjustment for midazolam or any other CYP3A substrate when coadministered with esketamine is not warranted.

Ethinyl Estradiol: Ethinyl estradiol is an FDA approved oral contraceptive drug. Ethinyl estradiol is primarily eliminated by sulfate conjugation (60% of the first-pass metabolism) and to a less extent by glucuronidation and CYP3A-mediated 2 hydroxylation. Since esketamine is not expected to cause clinically significant changes for the PK of sensitive CYP3A substrate midazolam, a single or repeated dosing of 84 mg nasal esketamine is not expected to cause significant changes in the systemic exposure to ethinyl estradiol.

- **Effect of other drugs on the PK of esketamine.**

- Inhibitor of CYP2B6 enzyme activity

The effects of pretreatment with an inhibitor of CYP2B6 (i.e., ticlopidine) activity on the PK of nasal esketamine was assessed in Study 1020. The results showed that pretreatment with oral ticlopidine (250 mg twice daily for 9 days prior to and on the day of esketamine administration) had no effect on the mean esketamine C_{max} following a 56-mg nasal dose, whereas the AUC of esketamine was increased by 29% (Figure 20). The terminal $t_{1/2}$ of esketamine was not affected by ticlopidine pretreatment. This interaction is not considered to be clinically significant, and thus dose adjustment for esketamine when coadministered with inhibitors of CYP2B6 is not warranted.

- Inhibitor of CYP3A enzyme activity

The effects of pretreatment with an inhibitor of CYP3A4 (clarithromycin) activity on the PK of nasal esketamine was assessed in Study 1009. Healthy subjects were self-administered 84 mg of nasal esketamine before and after pretreatment with 500 mg clarithromycin twice daily for 4 days. Treatment with clarithromycin continued for an additional 24 hours (i.e., 5-day regimen in total) as esketamine PK samples were being collected. The results showed that esketamine C_{max} and AUC_{∞} were increased by 11% and 4%, respectively, when coadministered with clarithromycin (Figure 20). The terminal $t_{1/2}$ of

esketamine was not influenced by coadministration with clarithromycin. This interaction is not considered to be clinical relevant, and thus dose adjustment for esketamine when coadministered with inhibitors of CYP3A is not warranted.

- Inducers of CYP3A and CYP2B6 Enzyme Activity

The effect of pretreatment with rifampicin on the PK of nasal esketamine was evaluated in Study 1008. Healthy subjects were self-administered a dose of 56 mg nasal esketamine prior to and after administration of 600 mg rifampicin daily in the evening for 6 days. The second dose of esketamine was administered on the following morning after the last rifampicin dose. The C_{max} , AUC_{last} , and AUC_{∞} of esketamine were approximately 17%, 31%, and 28% lower, respectively, when subjects were pretreated with rifampicin, relative to esketamine administration without rifampicin pretreatment (Figure 20). This interaction is not considered to be clinical relevant, and thus dose adjustment for esketamine when coadministered with inducers of CYP3A and CYP2B6 is not warranted.

- Other nasal drugs

Symptoms of allergic rhinitis include rhinorrhea and inflammation of nasal mucosa. Subjects with allergic rhinitis may use medications that are available as nasal spray, such as corticosteroids and vasoconstrictors, for the treatment of such symptoms. Therefore, the effects of a nasal corticosteroid and a nasal decongestant on the PK of nasally administered esketamine was assessed in Study 1007. The results showed that the appearance of acute rhinitis does not impact the pharmacokinetics of intranasally administered esketamine nor is the pharmacokinetics significantly impacted by use of an intranasal corticosteroid (i.e., mometasone) or intranasal decongestant (i.e., oxymetazoline) (Figure 20). Thus, dose adjustment for esketamine is not warranted for patients with allergic rhinitis. Intranasal esketamine dose is not required to be altered when using intranasal corticosteroid or intranasal decongestant.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes, the to-be-marketed formulation is the same as the clinical trial formulation.

4. APPENDICES

Appendix 4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Esketamine and norketamine concentrations in human plasma, urine and nasal residue were measured by a validated non-chiral LC-MS/MS method using racemic ketamine and norketamine as reference compounds.

Although non-chiral LC-MS/MS method would not be able to differentiate R- and S-enantiomer of esketamine, this bioanalytical method is considered an adequately and acceptable approach, given the following evidence:

1. No significant difference between the mass spectrometry (MS) response for the esketamine enantiomer and racemic ketamine (≤ 1.0 % difference), and norketamine enantiomer and racemic norketamine (≤ 2.1 % difference) as observed in sodium rat and human plasma, respectively.
 - A non-chiral LC-MS/MS method (BTM-1521) was developed and validated for quantitation of ketamine and norketamine in heparin rat plasma (Study BTM-1521). In order to assess the S-ketamine and racemic ketamine MS response, standard spiking solutions at equivalent concentrations of the chiral S-ketamine and racemic ketamine were added to ketamine-d4 internal standard and analyzed according to this method. The results showed that there was no significant difference (difference%: 0.6% - 1.0%) between the MS response (peak area ratio of ketamine / Internal Standard) of chiral S-ketamine and racemic solutions.
 - In non-chiral LC-MS/MS method (BTM-2246) for quantitation of ketamine and norketamine in heparin human plasma (Study BA12075), the MS response of norketamine and racemic norketamine was compared. The results showed that there was no significant difference (difference%: -1.6% - 2.1%) between the MS response (peak area ratio of norketamine / internal standard) of chiral norketamine and racemic solutions.
2. There was no inversion from S(+)-ketamine to R(-)-ketamine in human PK studies following IV administration S(+)-ketamine based on multiple literature reports using chiral method (Geisslinger, G. 1993 and Ihmsen, H. 2001). In addition, no inversion from S(+)-ketamine to R(-)-ketamine could be demonstrated across different species in non-clinical studies using chiral methods.

- Geisslinger, G. studied the stereoselective disposition and pharmacodynamic characteristics of ketamine in surgical patients after i.v. administration of S(+)-ketamine (1 mg/kg) or racemic ketamine (2 mg/kg, N = 25) using a chiral HPLC method. Separation was achieved using a chiral alpha1-acid glycoprotein column without any derivatization procedure. The retention times of the internal standard, S(+)-norketamine, S(+)-ketamine, R(-)-ketamine and R(-)-norketamine were about 14.5 min, 17.5 min, 25 min and 28 min, respectively. The LLOQ was 40 ng/mL of plasma ketamine and norketamine enantiomers. The results show that the plasma concentration profiles of the enantiomers of ketamine and norketamine were similar after administration of racemate ketamine. S(+)-ketamine was not inverted to its R(-)-ketamine.
 - Ihmsen, H. studied the stereoselective PK of racemic ketamine ($0.2 \mu\text{g}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$) and S(+)-ketamine ($0.2 \mu\text{g}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$) following IV infusion using a computer-controlled device in healthy young male volunteers. The plasma concentrations of the enantiomers of ketamine and norketamine were analyzed with stereoselective HPLC. The LLOQ was 40 ng/mL. S(+) -ketamine showed a significantly higher clearance ($26.3 \pm 3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) compared with racemic ketamine and R(-)-ketamine in the PK profile. No inversion R(-)-ketamine was detected after administration of S(+)-ketamine.
 - In addition, no inversion from S(+)-ketamine to R(-)-ketamine could be demonstrated in mouse, rat, dog, and rabbit in non-clinical PK studies using chiral LC-MS/MS methods (Studies BTM-1518, BTM-1524, BTM-1528 and BTM-1526).
3. Long term storage stability of the separate enantiomer esketamine was demonstrated in human heparin plasma for 707 days at -20°C .

Measurement of Esketamine and Noresketamine in Plasma

The methods for quantification of esketamine and noresketamine in human plasma were developed and validated at Contract Research Organization (b) (4). The methods consist of a solid phase extraction sample preparation after addition of stable isotope labelled internal standards (ketamine-D4 and norketamine-D4). The resulting extracts were evaporated to dryness, reconstituted and then injected on a reversed phase HPLC column using a gradient method. Detection was done by tandem mass spectrometry in the multiple reaction monitoring (MRM) mode with TurboIonSpray™ ionization in the positive ion mode. Initially, in 2012 a manual solid phase extraction (SPE) method using individual SPE cartridges was developed and validated (method BTM-1487). Later, in 2016, a more automated SPE method was developed and validated using equivalent 96 well SPE plates (method BTM-2246). Both methods produce equivalent results as demonstrated by a cross validation with quality control samples. The summary of bioanalytical method and validation metrics is shown below.

Table 1. Summary Review of Bioanalytical Method Measuring Plasma Esketamine and Noresketamine.

Bioanalytical Method Review Summary	Method was adequately validated to support clinical studies				
Method BTM-1487					
Material for calibration curve & concentration	Ketamine Hydrochloride (b) (4) Lot No. 120M1210V, BRS12-095, Purity 100%)		Norketamine Hydrochloride (b) (4) Batch No. 1,BRS12-188/BRS12-094, Purity 100%)		
Internal Standard	Ketamine-d ₄		Norketamine-d ₄		
Validated Assay Range	0.500 (LLOQ) – 500 ng/mL		0.500 (LLOQ) – 500 ng/mL		
Recovery	92.5%		91.9%		
Regression Model & Weighting	Linear Regression, 1/x ²				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		ketamine	Acceptability	Norketamine	Acceptability
	Linearity	R ² ≥ 0.9886	Acceptable	R ² ≥ 0.9923	Acceptable
QC concentrations	Ketamine: 1.50 ng/mL, 80.0 ng/mL and 375 ng/mL Norketamine: 1.50 ng/mL, 80.0 ng/mL and 375 ng/mL				
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	91.5 -109.3	Acceptable	91.5 – 102.1	Acceptable
	Intra-run precision (%CV)	0.7 – 10.9	Acceptable	1.9 – 9.2	Acceptable
	Inter-run accuracy (%CV)	92.3 -106.0	Acceptable	92.5 – 100.5	Acceptable
	Inter-run Precision (%CV)	1.8 -8.2	Acceptable	2.0 – 7.8	Acceptable
Inter-conversion from ketamine to norketamine	There was no inter-conversion from ketamine to norketamine (below the quantitation limit)				

S-Ketamine QC sample bench-top stability	18 hours at room temperature				
S-Ketamine QC sample freeze/thaw stability	3 freeze (-20°C) thaw (room temperature) cycles				
Method BTM-2246					
Material for calibration curve & concentration	Ketamine Hydrochloride ^{(b) (4)} Lot No. I0J272, BRS13-165, Purity 99.9)		Norketamine Hydrochloride ^{(b) (4)} Batch No. 2, BRS16-300, Purity 100%)		
Internal Standard	Ketamine-d ₄		Norketamine-d ₄		
Validated Assay Range	0.500 – 500 ng/mL		0.500 – 500 ng/mL		
Recovery	88.6%		88.5%		
Regression Model & Weighting	Linear Regression, 1/x ²				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		ketamine	Acceptability	Norketamine	Acceptability
	Linearity	R ² ≥ 0.9986	Acceptable	R ² ≥ 0.9979	Acceptable
QC concentrations	Ketamine: 0.500 ng/mL, 1.50 ng/mL, 80.0 ng/mL and 375 ng/mL Norketamine: 0.500 ng/mL, 1.50 ng/mL, 80.0 ng/mL and 375 ng/mL				
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-2.7% - 7.8%	Acceptable	-4.0 – 2.0%	Acceptable
	Intra-run precision (%CV)	1.0% -7.1%	Acceptable	1.3% – 7.4%	Acceptable
	Inter-run accuracy (%CV)	-2.0% - 2.2%	Acceptable	-1.3% - 5.7%	Acceptable
	Inter-run Precision (%CV)	1.8%– 7.1%	Acceptable	2.2% - 5.7%	Acceptable

Cross validation with Method BTM-1487	Intra-run accuracy (%)	Within Criteria		Within Criteria	
	Intra-run precision (%CV)	≤ 6.9	Acceptable	≤ 7.7	Acceptable

Measurement of Esketamine and Noresketamine in Human Urine

A non-chiral LC-MS/MS assay to enable quantification of esketamine and norketamine in human urine was developed and validated at (b) (4) (method BTM-2059). The method consists of a direct dilution of the sample after addition of stable isotope labelled internal standards (ketamine-D4 and norketamine-D4), followed by reverse phase HPLC using a gradient method and detection by tandem mass spectrometry in the MRM mode with TurboIonSpray™ ionization in the positive ion mode.

Table 2. Summary Review of Bioanalytical Method Measuring Esketamine and Noresketamine in Urine.

Bioanalytical Method Review Summary	Method was adequately validated to support clinical studies				
Method BTM-2059					
Material for calibration curve & concentration	Ketamine Hydrochloride (b) (4) Lot No. I0J272, BRS13-165, Purity 99.9)		Norketamine Hydrochloride (b) (4) Batch No. 1, BRS15-111, Purity 100%)		
Internal Standard	Ketamine-d ₄		Norketamine-d ₄		
Validated Assay Range	1.00 (LLOQ) – 1000 ng/mL		1.00 (LLOQ) – 1000 ng/mL		
Regression Model & Weighting	Linear Regression, 1/x ²				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		ketamine	Acceptability	Norketamine	Acceptability
	Linearity	R ² ≥ 0.9974	Acceptable	R ² ≥ 0.9951	Acceptable
QC concentrations	Ketamine: 1.00 (LLOQ), 3.00, 160, 750, and 37500 ng/mL (Dilution QC)				

	Norketamine: 1.00 (LLOQ), 3.00, 160, 750, and 37500 ng/mL (Dilution QC)				
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-2.3% to 2.5%	Acceptable	-1.2% to 3.1%	Acceptable
	Intra-run precision (%CV)	1.3% to 2.6%	Acceptable	1.5% to 2.6%	Acceptable
Cross validation with Method BTM-1487	Intra-run accuracy (%)	Within Criteria		Within Criteria	

4.1.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve used for clinical sample analysis was from 0.500 to 500 ng/mL for plasma samples and 1.00 to 1000 ng/mL for urine samples. The assay range combined with the validated dilution methods are acceptable based on serum esketamine and norketamine concentrations observed in the studies.

Appendix 4.2 Population PK Analyses

Objective

The objective of the population pharmacokinetic (POP PK) analysis was to simultaneously characterize the PK of esketamine and metabolite noresketamine after administration as a nasal spray, intravenous infusion (IV), and oral solution (PO), more specifically:

1. To obtain estimates of typical PK parameters for esketamine and noresketamine after nasal administration in healthy and TRD subjects and quantify their inter-individual variability (IIV);
2. Provide a quantitative assessment of the potential effect of the intrinsic and extrinsic factors including subject demographics and other covariates on esketamine and noresketamine PK and evaluate the need for esketamine exposure-based dose adjustments in special populations.

Data

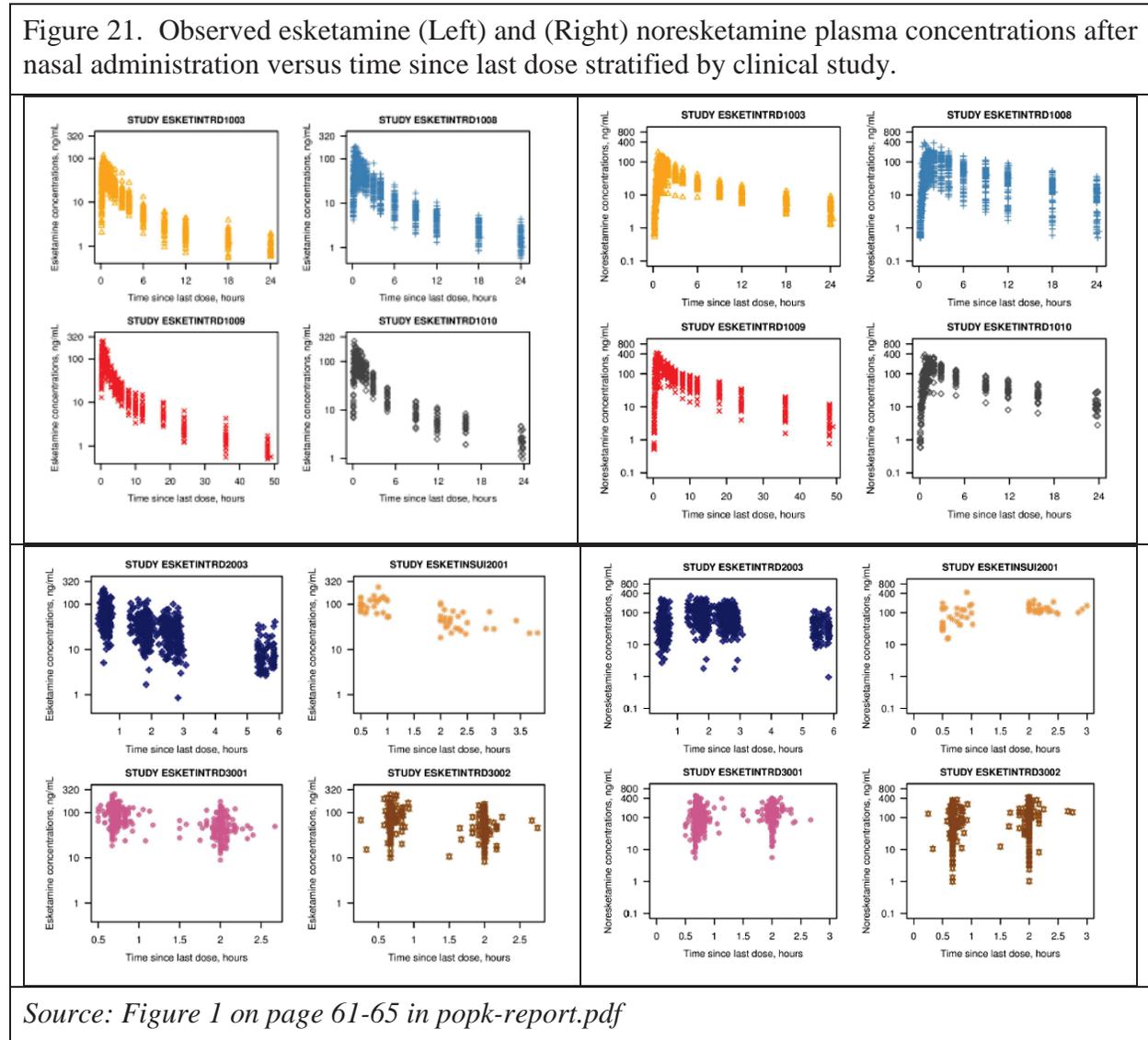
Rich and sparse plasma concentration data of esketamine and noresketamine obtained from 13 clinical studies [ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1003, ESKETINTRD1008, ESKETINTRD1009, ESKETINTRD1010, ESKETINTRD1012, ESKETINTRD1015, ESKETINTRD2003, ESKETINSUI2001, ESKETINTRD3001 (TRANSFORM-1), ESKETINTRD3002 (TRANSFORM-2), and ESKETINTRD3005 (TRANSFORM-3)] were pooled for the POP PK analysis using non-linear mixed effect modelling approach (NONMEM®).

In total, 9784 and 9397 plasma concentrations of esketamine and noresketamine, respectively, were collected from 820 subjects, including 256 (31.4%) healthy subjects from Phase 1 studies and 564 (68.8%) subjects with treatment-resistant depression (TRD) enrolled in Phase 2 and Phase 3 studies, receiving twice weekly nasal administration of esketamine. Subjects received esketamine as a single 28 mg IV dose (N=18), 84 mg PO dose (N=14), or single (N=111) and multiple (N=677) nasal administration with a dose ranging from 28 to 112 mg.

From the 820 subjects included in the POP PK analysis, 41.6% were male (N=341; 138 healthy males and 203 males with TRD) and the remainder were female (N=479; 118 healthy females and 361 females with TRD). The median age was 45 years and ranged from 18 to 86 years. The median subject weight was 74 kg, ranging from 39 to 170 kg. Most subjects were White (72.4%, N=594), with approximately 89.1% (N=529) not Hispanic nor Latino and 10.9% (N=65) Hispanic or Latino. In addition, 10.9% (N=65) were Black, of African heritage or African American, 13.7% (N=112) were Asian, of which 64.3% Japanese (N=72) and 35.7% non-Japanese (N=40), and the remaining 7.07% (N=58) were another race, including Native Hawaiian or Other Pacific Islander, American Indian or Alaskan Native. The median (range) of alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin (TB), baseline albumin (ALB), total protein (TP), and the estimated glomerular filtration rate (eGFR) were 20 U/L (6-157 U/L), 20 U/L (6-103 U/L), 65 U/L (21-244 U/L), 19 U/L (5-289 U/L), 198 U/L (90-546 U/L), 9 µmol/L (3-38 µmol/L),

44 g/L (31-57 g/L), 71 g/L (52-86 g/L), and 93 mL/min (43-150 mL/min) respectively. A total of 716 subjects (87.3%) included in the analysis had missing values for LDH.

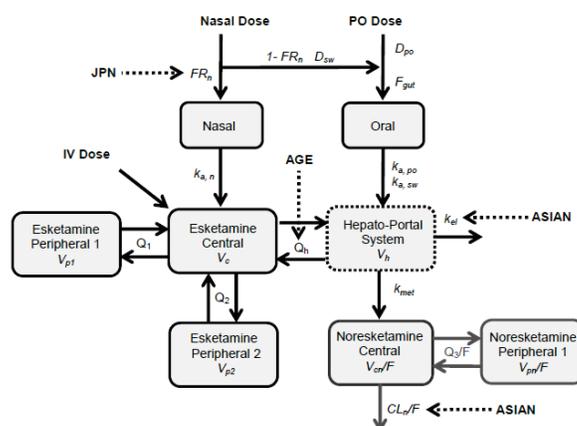
Figure 21 shows the observed plasma concentrations of esketamine and noresketamine from representative studies included in the analysis.



PK Model

The applicant used the model, as shown in Figure 22, to fit the data and evaluate the impact of various extrinsic/intrinsic factors on esketamine pharmacokinetic parameters.

Figure 22. Schematic of the final pop pk model for esketamine and noresketamine.

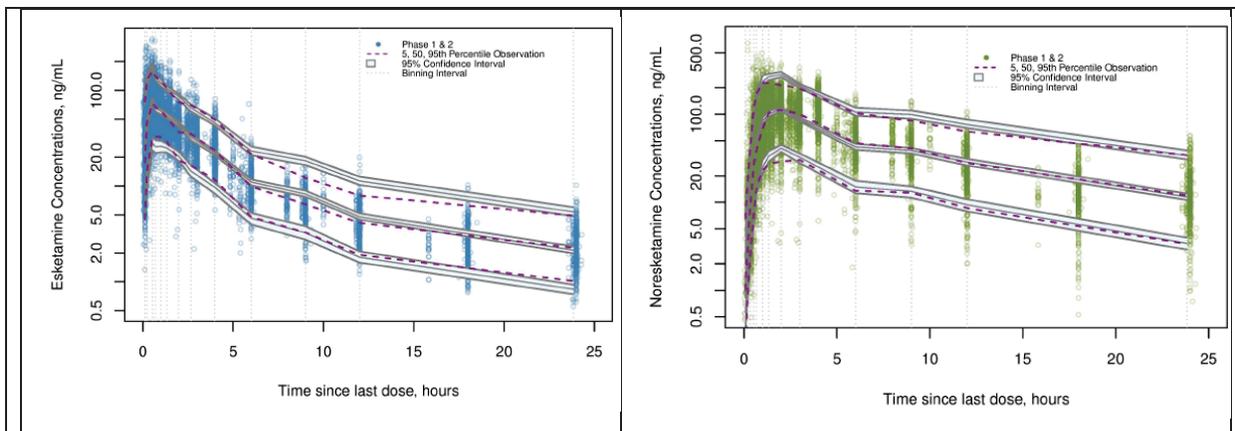


FR_n is the fraction of the nasal dose absorbed in the nasal cavity; D_{sw} (h) is the zero-order absorption duration of the nasal dose which is swallowed; D_{po} (h) is the zero-order absorption duration of the PO solution dose; $k_{a,n}$ (1/h) is the esketamine first-order nasal absorption rate constant; $k_{a,po}$ (1/h) is the esketamine first-order PO solution absorption rate constant; Dose effect is the dose-dependent effect in FR_n ; F_{gut} is percentage of the PO dose of esketamine which reaches the hepato-portal system after pre-systemic elimination; V_c, V_{p1}, V_{p2} (L) are esketamine central, shallow and deep peripheral volumes of distribution, respectively; Q_1 (L/h) is the esketamine inter-compartmental clearance between the central and the shallow peripheral compartment; Q_2 (L/h) is the esketamine inter-compartmental clearance between the central and the deep peripheral compartment; Q_3 (L/h) is the hepatic flow and V_h (L) is the hepatic volume of distribution; k_{el} (1/h) is esketamine elimination rate-constant; k_{met} is esketamine rate-constant of metabolism to noresketamine; $V_{c/F}, V_{p1/F}$ (L) are noresketamine apparent central and apparent peripheral volumes of distribution respectively; Q_3/F (L/h) is the noresketamine apparent inter-compartmental clearance between the central and the peripheral compartment; CL_w/F (L/h) is the apparent clearance of noresketamine.

Source: Figure A1 on page 17 in popk-report.pdf

The model was able to adequately fit the data, as shown in Figure 23.

Figure 23. Prediction-Corrected Visual predictive check of the final POP PK model for (Left) esketamine and (Right) noresketamine after nasal dosing for 24 hours post dose



Source: Figure 20 and 21 on page 119 in *poppk-report.pdf*

The estimates of various pharmacokinetic parameters are shown in Table 3.

Table 3. Parameter estimates with the relative standard error (rse, %) for the reference pop pk model for esketamine and noreскетamine.

		Structural model parameters		Inter-individual variability (CV %)	
		Parameter	Estimate (RSE%)	Parameter	Estimate (RSE%)
Esketamine					
Absorption	Nasal Dose	FR_n Dose on FR_n	0.64 (1.66) 0.61 (1.38)	ωFR_n	84.0 (11.1)
		$k_{a,n}$ (1/h)	2.73 (3.07)	$\omega k_{a,n}$	67.5 (13.0)
		D_{sw} (h) $k_{a,sw}$ (1/h)	0.59 (3.07) 1.12 (3.75)	$\omega k_{a,sw}$	132.7 (12.2)
	PO Dose	D_{po} (1/h) $k_{a,po}$ (1/h)	0.33 (9.80) 0.85 (15.3)	$\omega k_{a,po}$	132.7 (12.2)
		F_{gut}	0.67 (1.55)		
		Disposition	V_c (L)	196 (2.66)	ωV_c
Q_1 (L/h)	93.8 (2.28)				
V_{p1} (L)	169 (2.98)		ωV_{p1}	50.0 (16.8)	
Q_2 (L/h)	39.2 (1.96)				
V_{p2} (L)	432 (1.57)				
Q_h (L/h)	158 (2.38)		ωQ_h	24.8 (17.2)	
V_h (L)	116 (3.49)		ωV_h	38.6 (20.7)	
k_{el} (1/h)	1.63 (4.26)		ωk_{el}	76.6 (11.8)	
k_{met} (1/h)	2.06 (2.60)		ωk_{met}		
Noresketamine					
Disposition	V_{cr}/F (L)	53.8 (2.96)	$\omega V_{cr}/F$	30.5 (19.4)	
	CL_r/F (L/h)	28.1 (2.14)	$\omega CL_r/F$	26.0 (17.5)	
	V_{pr}/F (L)	87.4 (2.27)			
	Q_3/F (L/h)	19.6 (3.45)			
		Objective function value		Residual variability (CV %)	
		-14036.115		σ_1 (esketamine)	27.5 (0.45)
				σ_2 (noresketamine)	42.0 (0.39)

RSE, relative standard error; CV, coefficient of variation; FR_n is the fraction of the nasal dose absorbed in the nasal cavity; D_{sw} (h) is the zero-order absorption duration of the nasal dose which is swallowed; D_{po} (h) is the zero-order absorption duration of the PO solution dose; $k_{a,n}$ (1/h) is the esketamine first-order nasal absorption rate constant; $k_{a,sw}$ (1/h) is the esketamine first-order nasal-swallowed absorption rate constant; $k_{a,po}$ (1/h) is the esketamine first-order PO solution absorption rate constant. Dose effect is the dose-dependent effect in FR_n (i.e., the fraction of dose absorbed through the nasal cavity is reduced to 61% for the subsequent 28-mg doses); F_{gut} is percentage of the PO dose of esketamine which reaches the hepato-portal system after pre-systemic elimination; V_c, V_{p1}, V_{p2} (L) are esketamine central, shallow and deep peripheral volumes of distribution, respectively; Q_1 (L/h) is the esketamine inter-compartmental clearance between the central and the shallow peripheral compartment; Q_2 (L/h) is the esketamine inter-compartmental clearance between the central and the deep peripheral compartment; Q_h (L/h) is the hepatic flow and V_h (L) is the hepatic volume of distribution; k_{el} (1/h) is esketamine elimination rate-constant; k_{met} is esketamine rate-constant of metabolism to noresketamine; $V_{cr}/F, V_{pr}/F$ (L) are noresketamine apparent central and apparent peripheral volumes of distribution respectively, Q_3/F (L/h) is the noresketamine apparent inter-compartmental clearance between the central and the peripheral compartment; CL_r/F (L/h) is the apparent clearance of noresketamine.

Source: Table 5 on page 57 in poppk-report.pdf

The findings from population pharmacokinetic analyses are shown below:

- The volume of distribution at steady-state is large (752 L), reflecting distribution into tissues.
- Esketamine clearance is 114 L/h.
- Noresketamine is also widely distributed (apparent volume of distribution 185 L) and rapidly cleared with an apparent clearance of 38.0 L/h. The IIV of V_c for parent drug and V_{cn}/F and CL/F for metabolite was low (<32%), and moderate to large for other PK parameters.
- The terminal half life, $t_{1/2}$, of esketamine and noresketamine is 11.1 hours and 7.5 hours, respectively. Following a twice weekly administration as a nasal spray, no accumulation of esketamine and noresketamine in plasma is expected, since the inter-dose interval is greater than the wash-out period (four half-lives).
- Sex, body weight, ALT, AST, ALP, GGT, TP, ALB, TB, eGFR, and disease state (ie., subjects with TRD versus healthy subjects) had no discernable impact on the PK parameters of esketamine and noresketamine.
- Relative to non-Asians, the Asian population showed a 64.0% and 19.4% decrease in k_{el} and CL_n/F , respectively, Japanese subjects exhibited a 34% increase in FR_n relative to other races (non-Asians and Asian non-Japanese), Q_h , decreased at a rate 21.9 L/h \times 10 years from 60 years of age onwards. These relationship between the covariates and PK parameters was not clinically relevant and, consequently, esketamine dose adjustment based on these covariates is not warranted.

Reviewer's Comments: The reviewer agrees with the findings as reported by the applicant. The labeling statements regarding the influence of gender and body weight on pharmacokinetics of esketamine and noresketamine are acceptable.

Appendix 4.3 Exposure-Response Analyses

4.3.1 Exposure-Efficacy Analyses

The relationship between exposure and efficacy was not explored by the reviewer. Clinical studies suggested a flat dose-response relationship between 56 and 84 mg dose groups.

4.3.2 Exposure-Safety Analyses

The reviewer analyzed the time-course of safety events in relation to time course of esketamine and noresketamine concentrations. These findings are provided in Sections 3.3.2 in the review.

Appendix 4.4 Physiological-based Pharmacokinetic Modeling Review

NDA/BLA Number	NDA 211243
Generic Name	Esketamine
Trade Name	SPRAVATO
Submission Type	New NDA (Priority Review)
Sponsor	Janssen Pharmaceuticals, Inc.
Dosage Form and Strengths	28 mg single-use nasal spray device
Proposed Indication	Treatment Resistant Depression (TRD)
Dose Regimen	Induction Phase (weeks 1-4): Two treatment sessions/week: Starting day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg Maintenance Phase: Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly
Primary PBPK Reviewer	Jianghong Fan, Ph.D.
Secondary PBPK Reviewer	Yuching Yang, Ph.D.

Executive Summary

PBPK (physiologically-based pharmacokinetic) analysis was used to evaluate the potential DDI of esketamine as perpetrator with midazolam. FDA's analyses showed that,

- 1) The midazolam AUC ratios are predicted to be within a range of 0.93-1.01 after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine.
- 2) When the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 16 a single oral dose of midazolam (6 mg) was administered, the midazolam AUC ratios are predicted to be within a range of 0.90-1.00.

The worst-case scenario analysis by using noresketamine CYP3A K_i towards testosterone (0.96 μ M) showed that,

- 1) The midazolam AUC ratios are predicted to be within a range of 1.24-1.43 after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine.
- 2) When the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 16 a single oral dose of midazolam (6 mg) was administered, the midazolam AUC ratios are predicted to be within a range of 1.23-1.41.

1. Objectives

To evaluate the adequacy of the Applicant's PBPK model analyses and evaluate the potential drug-drug interaction (DDI) between esketamine (CYP3A inducer and inhibitor) and its metabolite, noresketamine (CYP3A inhibitor) and midazolam (sensitive CYP3A substrate) in various exposure scenarios.

2. Background

Esketamine is a non-competitive, subtype non-selective, activity-dependent, glutamate receptor modulator. The intranasal administration of esketamine is being developed for use as a rapidly acting antidepressant in adults with treatment-resistant depression (TRD).

Dosage forms and strengths

The nasal spray formulation of esketamine is a clear and colorless solution of esketamine hydrochloride (HCl) in water for injection. The nasal spray device is a single-use device that delivers 28 mg of esketamine in 2 sprays. The product is intended for administration by a patient under the observation of a healthcare professional, using 1 device (for 28 mg), 2 devices (for 56 mg), or 3 devices (for 84 mg), with a 5-minute interval between each device.

Pharmacokinetics

Esketamine is rapidly absorbed through the nasal mucosa following administration as a nasal spray and can be measured in plasma within 7 minutes. The mean absolute bioavailability of 84 mg esketamine administered as a nasal spray is approximately 48% (TRD1009).

The volume of distribution at steady state is 709 L (TRD1009) following intravenous administration of Esketamine. The unbound plasma fraction is 57-55% and blood to plasma ratio ranges from 0.74-0.94. Esketamine is not a substrate of P-glycoprotein (P-gp, multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3.

Esketamine is extensively metabolized in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to form the major metabolite noresketamine. The main CYP enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A. Other enzymes, including CYP2C19 and CYP2C9, contribute to a much smaller extent. Noresketamine is subsequently metabolized via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation.

Drug Interaction

○ *In vitro study*

The in vitro inhibition study using human liver microsomes showed that the IC₅₀ values of CYP3A inhibition by esketamine and noresketamine are 61.5 μ M and 1.92 μ M respectively using testosterone as a substrate. On the other hand, esketamine showed no inhibition and noresketamine showed minimal inhibition (IC₅₀ = 62.4 μ M) towards the CYP3A substrate midazolam. No or minimal inhibitory effect of noresketamine or esketamine on the CYP2B6, CYP1A2 or CYP2C pathways was observed. No potential for time dependent inhibition was observed for esketamine and noresketamine up to 30 μ M towards CYP3A and the other important

CYPs (FK13008). Esketamine and noresketamine do not inhibit the efflux membrane transporters and the uptake membrane transporters (FK10795&FK10796). Esketamine was found to induce CYP2B6 and CYP3A in human hepatocytes. However, positive induction criteria were reached only at the highest concentration tested (10 µM) (FK10376).

o *Clinical studies*

The following table (Table 1) lists the results of clinical DDI studies conducted by the Applicant.

Table 1. Results of clinical DDI studies between esketamine and CYP enzyme substrates or CYP enzyme modulators

		Dosing regimen	Observed Parent AUCR	Sources
Esketamine as a perpetrator with CYP enzyme substrates				
Bupropion	CYP2B6 substrate	Esketamine: NS, 84 mg, biw for 2 weeks Bupropion: oral, 150 mg	~1	TRD1010, Table 2 #6
Midazolam	CYP3A substrate	Esketamine: NS, 84 mg, biw for 2 weeks Midazolam: oral, 6 mg, dosed 24 hr after the last dose of esketamine	0.84	TRD1010, Table 2 #6
Esketamine as a victim with CYP enzyme modulators				
Ticlopidine	CYP2B6 inhibitor	Ticlopidine: Oral, 250 mg, bid for 9 days Esketamine: NS, 56 mg, dosed on day 9	1.29	TRD1020, Table 2 #10
Clarithromycin	CYP3A inhibitor	Clarithromycin: Oral, 500 mg, bid for 4 days Esketamine: NS, 84 mg, dosed on day 4	1.04	TRD1009, Table 2 #5
Rifampicin	CYP3A and CYP2B6 inducer	Rifampicin: Oral, 600 mg, qd, for 6 days Esketamine: NS, 56 mg, dosed 24 hr after the last dose of rifampicin	0.72	TRD1008, Table 2 #4

On Oct. 3, 2018, the information request (IR) was issued, requesting the submission of model workspace files, observed data and concentration-time profiles which were not included in the original submitted PBPK report and dataset (Appendix).

1. Applicant’s PBPK Model Effort

Physiologically Based PK (PBPK) software

Simcyp v14.1 (Simcyp Ltd, UK) was used to develop the PBPK model and predict the potential DDI between esketamine and noresketamine, and midazolam (a sensitive CYP3A substrate) following multiple intranasal administrations of esketamine and a single oral dose of midazolam administered together with the last dose of esketamine. The changes of midazolam plasma AUC after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine was also simulated.

Model development

Applicant developed the PBPK models for esketamine to describe the esketamine and noresketamine PK profiles following IV and PO routes. The model was built and verified based on physicochemical properties, in vitro data and route-specific clinical PK data. Table 2 summarizes the clinical studies used for model development and model verification. The contribution of CYP2B6 (63.7%), CYP3A (23.3%), CYP2C9 (small) and CYP2C19 (small) in the overall clearance of esketamine was verified with the available literature DDI data (Table 2, #11, 12 and 13). The contribution of CYP2B6 in the metabolism of noresketamine was verified based on the clinical data (Table 2, #10). The in vitro study results were used to calibrate the CYP2A6 contribution to the noresketamine clearance (Table 2, # 14).

Table 2. Summary of clinical studies used in Esketamine and Noresketamine model development and verification

	Study	Relevant Study Features
1	ESKETINTRD1001	A Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine in Healthy Subjects
2	ESKETINTRD1002	An Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine in Healthy Japanese and Caucasian Subjects
3	ESKETINTRD1004	An Open-Label Phase 1 Study to Evaluate the Pharmacokinetics of Intranasal Esketamine Administered With and Without a Nasal Guide on the Intranasal Device
4	ESKETINTRD1008	An Open-Label, Single-Dose Study to assess the Pharmacokinetics, Safety and Tolerability of Intranasally Administered Esketamine in Healthy Han Chinese, Korean, Japanese and Caucasian Subjects and the Effects of Rifampin on the Pharmacokinetics of Intranasally Administered Esketamine.
5	ESKETINTRD1009	An Open-Label Study to Evaluate the Pharmacokinetics of Intravenous, Intranasal, and Oral Esketamine and Effects of Clarithromycin on the Pharmacokinetics of Intranasal Esketamine in Healthy Subjects.
6	ESKETINTRD1010	An open-label study to evaluate the pharmacokinetics of intranasal esketamine and its effects on the pharmacokinetics of orally administered midazolam and bupropion in healthy subjects.
7	ESKETINTRD1012	An Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Intranasally Administered Esketamine in Elderly (≥ 75 years of Age) and Healthy Younger Adult Subjects (18 to 55 Years of Age, Inclusive).
8	ESKETINTRD1013	A Randomized, Double-Blind (Periods 1 to 3), Placebo- and Positive-Controlled, Single-Dose, 4-Period, Crossover Study to Evaluate the Effects of Esketamine on Cardiac Repolarization in Healthy Subjects
9	ESKETINTRD1016	An Open-label, Single-dose Mass Balance Study with a Microtracer Dose of ¹⁴ C-esketamine in Healthy Male Subjects. Dose normalization of the data was performed to lead to the dose of 28 mg IV of Esketamine and 84 mg PO of Esketamine.
10	54135419TRD1020	A fixed-sequence, open-label study to assess the effect of ticlopidine on the pharmacokinetics, safety and tolerability of intranasally administered esketamine in healthy subjects.
11	Literature Study	Hagelberg, N.M. et al. Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral Sketamine. Eur. J. Pain 14:625-629, 2010
12	Literature Study	Peltoniemi, M.A. et al. Exposure to oral S-ketamine is unaffected by itraconazole but greatly increased by ticlopidine. Clin Pharmacol Ther. 90:296-302, 2011.
13	Literature Study	Peltoniemi, M.A. et al. Rifampicin has a profound effect on the pharmacokinetics of oral S-ketamine and less on intravenous S-ketamine. Basic Clin. Pharmacol. 111:325-332, 2012.
14	FK 13007	An in-vitro study on the microsomal cytochrome P-450 form(s) and other enzymes involved in the metabolism of ¹⁴ C- JNJ-64609337 (noresketamine, metabolite M10 of JNJ-54135419)

To obtain the esketamine PK profile following the intranasal administration, the applicant assumed that the esketamine PK profile following the intranasal route can be computed by combining the simulated PK profiles via IV and PO routes. The applicant stated that the observed absolute bioavailability (50.4%) following intranasal dosing implied a combination of 57.5% PO

administration and 42.5% IV administrations, given the mean absolute bioavailability following PO administration is 14.1 % (TRD1009, Table 2 #5). Applicant verified their modeling approach for intranasal administration by comparing the simulated and intranasal clinical PK data (Table 2, # 1, 2, 3, 6,7 and 8) and clinical DDI data (Table 2, #4 and 5). The input parameters for esketamine and noresketamine used for PK prediction and DDI assessment are shown in Appendix Table 1 and 2. The model verification results are shown in Appendix Figure 1.

Reviewer's comments

1. Available in-vitro data, clinical and literature DDI data are sufficient to support dosing recommendation when esketamine is coadminstrated with a CYP3A or CYP2B6 inhibitor.
2. The Applicant's PBPK model described the overall rate of esketamine absorption in nasal mucosa as a zero-order input process. However, the zero-order absorption model is not capable of adequately describing the observed esketamine plasma concentration-time profile, as evidenced by a long plateau plasma esketamine level in the predicted concentration-time profile, which was not observed in the clinical study (Appendix Fig.1, #3).
3. The Applicant's esketamine PBPK model did not adequately capture the clinical observed esketamine data. The predicted esketamine Cmax and AUC were 0.5- and 0.6-fold of the observed values, respectively, following a single oral administration of 84 mg esketamine (Fig.2 and Appendix Fig.1, #2).
4. The Applicant used the default midazolam PBPK model in SimCYP V14 for DDI prediction. The reviewer noticed the version difference between SimCYP V14 vs SimCYP V17 with respect to the midazolam PBPK model. There is minor difference in the predicted Cmax and AUC values of midazolam between V14 and V17. The predicted midazolam Cmax and AUC values using V17 are in better agreement with the observed clinical data compared to those predicted using V14. However, the predicted midazolam AUC ratio in the presence and absence of esketamine is the same between V 14 and V17.
5. In the FDA analyses, the reviewer refined and conducted the PBPK analyses using SimCYP V17. The default midazolam PBPK model was used to assess the DDI between esketamine and midazolam.

DDI Assessment Strategy

Applicant's Modeling approach

The effects of esketamine and noresketamine on midazolam PK after intranasal administration of esketamine was investigated by assessing the inhibitory potential of both the PO and IV part, and the induction potential of the PO part. A deconvolution approach was used to get the net gut interaction and the net systemic interaction of esketamine and noresketamine on midazolam PK following the intranasal administrations of esketamine.

- **Net gut interaction:**

The gut interaction is estimated by simulating the interaction between midazolam and 48.5 mg oral esketamine with the DDI parameters on esketamine and noresketamine. The ratio of the midazolam fraction escaping gut metabolism (F_g) with and without esketamine was obtained from the PBPK model output file. The ratio of F_g is applied to the AUC of midazolam without esketamine to obtain the net gut effect of esketamine and noresketamine on the plasma AUC of midazolam after an oral administration of esketamine.

○ **System interaction:**

Applicant's simulations indicated that esketamine does not have an effect on the midazolam plasma exposure after a single or repeated intravenous administrations of 35.5 mg esketamine. Therefore, only the effect of noresketamine on the midazolam plasma AUC was evaluated following the intravenous administration of esketamine. Applicant stated that simulated liver noresketamine AUC following intravenous administration of 90 mg esketamine would be similar to those simulated following the intranasal administration of 84 mg esketamine. This IV scenario was used to determine the systemic effect of esketamine and noresketamine on midazolam following the intranasal administration of esketamine.

○ **Overall interaction:**

The overall effect of esketamine on midazolam plasma PK following an intranasal administration of 84 mg esketamine can be calculated by adding the difference of midazolam AUC values obtained with and without esketamine from the oral simulations and the midazolam AUC with esketamine from the IV simulations.

Noresketamine CYP3A K_i values

Noresketamine CYP3A K_i towards midazolam (31.2 μM) from the in vitro CYP inhibition study results was used in the DDI assessment. In addition, noresketamine CYP3A K_i towards testosterone (0.96 μM , 30-fold lower than those reported for midazolam in vitro CYP inhibition study) was used for the worst-case scenario analysis.

Reviewer's comments

- 1. In the Applicant's analysis, the contributions of PO and IV routes to the PK of esketamine following the intranasal administration was derived by adjusting the ratio of PO and IV routes to match the bioavailability (50.4%) reported in the clinical study following a single intranasal administration of esketamine, given the mean absolute bioavailability following a single PO administration is 14.1 %. The Applicant concluded that the intranasal dose was divided into a PO and IV dose per ratio 57.5/42.5 and no drug loss was assumed. However, the calculated plasma metabolite/parent drug AUC ratio was slightly higher than that observed. (3.33-vs-3.08). Thus, there might be some discrepancy with respect to the estimated percentage of the administered drug absorbed through the nasal mucosa and the estimated percentage of the administered drug absorbed through the gut following the nasal administration.*

2. Reviewer’s analysis indicated that, to match both the bioavailability and metabolite/parent drug AUC ratio following the intranasal administration of esketamine, 12% of the dosed drug loss, 46.5% of the dosed drug absorbed through the gut wall, and 41.5% of the dosed drug absorbed through the nasal mucosa must be attained (Table 3&4).

Table 3 Information extracted from Applicant’s model and FDA reviewer’s analysis results with respect to the drug loss, percent of drug absorbed through the gut, percent of drug absorbed through the nasal mucosa, bioavailability and metabolite over parent drug AUC ratios following a single intranasal administration of 84 mg esketamine

Intranasal Esketamine	Applicant’s analysis	Reviewer’s analysis
Loss	0 %	12%
Percent of drug absorbed through the gut	57.5% (48.3 mg)	46.5% (39.06 mg)
Percent of drug absorbed through the nasal mucosa	42.5% (35.7 mg)	41.5% (34.86 mg)
Bioavailability	50.6% ^a	48.0% ^b
AUC _M /AUC _P (GMR)	3.33 ^c	3.08 ^d

a: obtained from Applicant’s PBPK modeling report (FK12081)

b: obtained from Summary of Clinical Pharmacology Studies

c: computed by reviewer based on the PO and IV dose ratios and the esketamine and noresketamine AUC values following a single oral and intravenous administration

d: calculated based on the observed AUC values of parent drug and metabolite in report FK13248

Table 4 The observed metabolite over parent drug AUC ratios and bioavailability following a single intravenous administration of 24 mg esketamine, a single oral administration of 84 mg esketamine and a single intranasal administration of 84 mg esketamine.

Esketamine	AUC _M /AUC _P (GMR)	BA
28 mg IV	1.71 ^b	100%
84 mg Oral	12.46 ^b	14.1% ^a
84 mg Intranasal	3.08 ^b	48.0% ^c

a: obtained from PBPK report FK12081

b: calculated based on the observed AUC values of parent drug and metabolite in report FK13248

c: obtained from Summary of Clinical Pharmacology Studies

3. The Applicant proposed that the DDI effect of esketamine on midazolam PK following intranasal administrations of esketamine can be predicted by adding the net gut interaction and net systemic interaction of esketamine and noresketamine with midazolam (see “DDI Assessment Strategy” in “Applicant’s PBPK Model Effort” section). The Applicant assumed that the net systemic interaction with midazolam following IV dose of 90 mg esketamine was the same as that following intranasal administration of 84 mg esketamine. As shown in the Fig

.1, although the liver exposure (AUC) following the intravenous administration of 90 mg esketamine is close to that following intranasal administration of 84 mg esketamine, the liver concentration-time profiles are different. Different liver PK profiles may influence the DDI prediction of noresketamine as a perpetrator with midazolam.

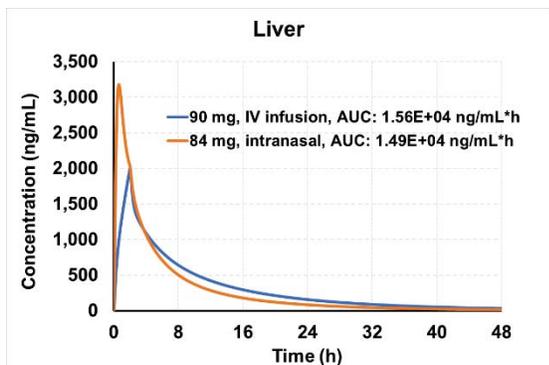


Figure 1. Simulated liver noresketamine concentration-time profiles following intravenous infusion (2 hr) of 90 mg esketamine and intranasal administration of 84 mg esketamine using Applicant’s PBPK model

4. The Applicant conducted two sets of DDI simulations using two *in-vitro* CYP3A K_i of noresketamine towards testosterone ($0.96 \mu\text{M}$) or midazolam ($31.2 \mu\text{M}$). However, the model parameter values were optimized by setting the noresketamine CYP3A K_i as $0.96 \mu\text{M}$. Thus, the predicted esketamine and noresketamin plasma concentration did not match the observed PK profiles when the noresketamine CYP3A K_i was set as $31.2 \mu\text{M}$.

Model Based DDI Assessment Results

Table 5 shows the predicted DDI effect of esketamine on PKs of midazolam following a single or repeat intranasal administrations of esketamine using Applicant’s PBPK models.

Table 5. Simulated midazolam plasma AUC ratios after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine or after a single oral dose of 6 mg midazolam with and without multiple intranasal administrations of 84 mg esketamine with noresketamine CYP3A $K_i = 31.2 \mu\text{M}$ or $0.96 \mu\text{M}$ (midazolam was dosed together with the last dose of esketamine).

	Ki= 31.2 μM	Ki= 0.96 μM Worst-case scenario
MDZ AUC ratio (Geometric mean) after a single intranasal administration of esketamine (84 mg)	NA	1.46
MDZ AUC ratio (Geometric mean) after multiple intranasal administrations of esketamine (84 mg)	0.99	1.31

(Table 12, 13 and 14 in PBPK report FK13248).

Reviewer's comments

1. The reviewer agrees that, due to the very low plasma level of noresketamine 24 hours after the last dose of esketamine, the DDI effects observed in ESKETINTRD1010 (Table 3 #6) reflects the induction potential of esketamine.
2. The reviewer agrees that a K_i value of 0.96 μM (30X lower than that reported for midazolam) is sufficient to quantify the uncertainty related to the in-vitro to in-vivo extrapolation. Reviewer also noted that it has been suggested that the inhibition potency of a drug on CYP3A pathway should be evaluated using multiple sensitive CYP3A substrates in-vitro^{1,2,3}.

4. Reviewer's analysis

Given the limitations identified in Applicant's PBPK modeling approach, the FDA's reviewer conducted an additional analysis to reassess the DDI effects of esketamine and noresketamine as the perpetrators on PKs of midazolam. First, the reviewer refined the Applicant's PBPK model by re-optimizing the model parameters to improve the fit between the simulated and observed PK data, and then conducted a worst-case scenario simulation by assuming the nasal administered esketamine was absorbed completely through the gut.

Model refinement and verification

Simcyp V17 (Simcyp Ltd, UK) was used for PBPK simulation. The reviewer refined the Applicant's esketamine and noresketamine PBPK models to improve the agreement between the observed versus predicted results. Then the refined models were used to predict the concentration-time profiles of esketamine and noresketamine following a single oral (84 mg) or intravenous (28 mg, infusion 0.67hr) administration of esketamine. **Table 6** lists the parameters for esketamine and noresketamine which values were different from those used in the Applicant's models. As shown in [Fig. 2](#), the refined esketamine and noresketamine PBPK models adequately capture the observed PK profiles following a single oral administration of esketamine. Additional model verifications are in [Appendix Fig 2](#).

Table 6 Esketamine and noresketamine parameter values comparison between the Applicant's submitted model and the FDA reviewer's refined model

A. Esketamine

¹ K. E. Kenworthy, J. C. Bloomer, S. E. Clarke & J. B. Houston. CYP3A4 drug interactions: correlation of 10 in vitro probe substrates. *Br J Clin Pharmacol.* 1999 Nov; 48(5): 716–727.

² Foti RS1, Rock DA, Wienkers LC, Wahlstrom JL. Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. *Drug Metab Dispos.* 2010 Jun;38(6):981-7.

³Obach RS, Walsky RL, Venkatakrishnan K, Houston JB, Tremaine LM. In vitro cytochrome P450 inhibition data and the prediction of drug-drug interactions: qualitative relationships, quantitative predictions, and the rank-order approach. *Clin Pharmacol Ther.* 2005 Dec;78(6):582-92.

Esketamine parameters	Applicant's model^a	Reviewer's model^a (Noresketamine CYP3A Ki= 31.2µM)	Reviewer's model^a (Noresketamine CYP3A Ki= 0.96 µM)
Elimination	Enzyme kinetics		
Recombinant Cl _{int} CYP3A (µl/min/ pmol CYP)	0.6	0.3	0.39
Recombinant Cl _{int} CYP2B6 (µl/min/ pmol CYP)	9	4.5	5.85
Recombinant Cl _{int} CYP2C19 (µl/min/ pmol CYP)	7.6	3.8	4.94
Recombinant Cl _{int} CYP2C9 (µl/min/ pmol CYP)	0.114	0.057	0.0741
Additional HLM liver clearance (µl/min/ mg)	60	0	0
Interaction			
CYP3A Induction			
Ind slope	1.8	2.6	2.6

B. Noresketamine

Noresketamine parameter values	Applicant's model	Reviewer's model^b
Distribution	Minimal PBPK	
V_{ss} (L/kg)	1.5	1.7
kin (1/h)	0	0.1
kout(1/h)	0	0.08
V_{sac} (L/kg)	0	0.2
Elimination	Enzyme kinetics	
HLM Cl _{int} CYP2B6 (µl/min/mg)	7	5.25
HLM Cl _{int} CYP2A6 (µl/min/mg)	31	23.25

a: optimized based on the clinical data

b: for both Noresketamine CYP3A Ki= 31.2µM and Noresketamine CYP3A Ki= 0.96 µM

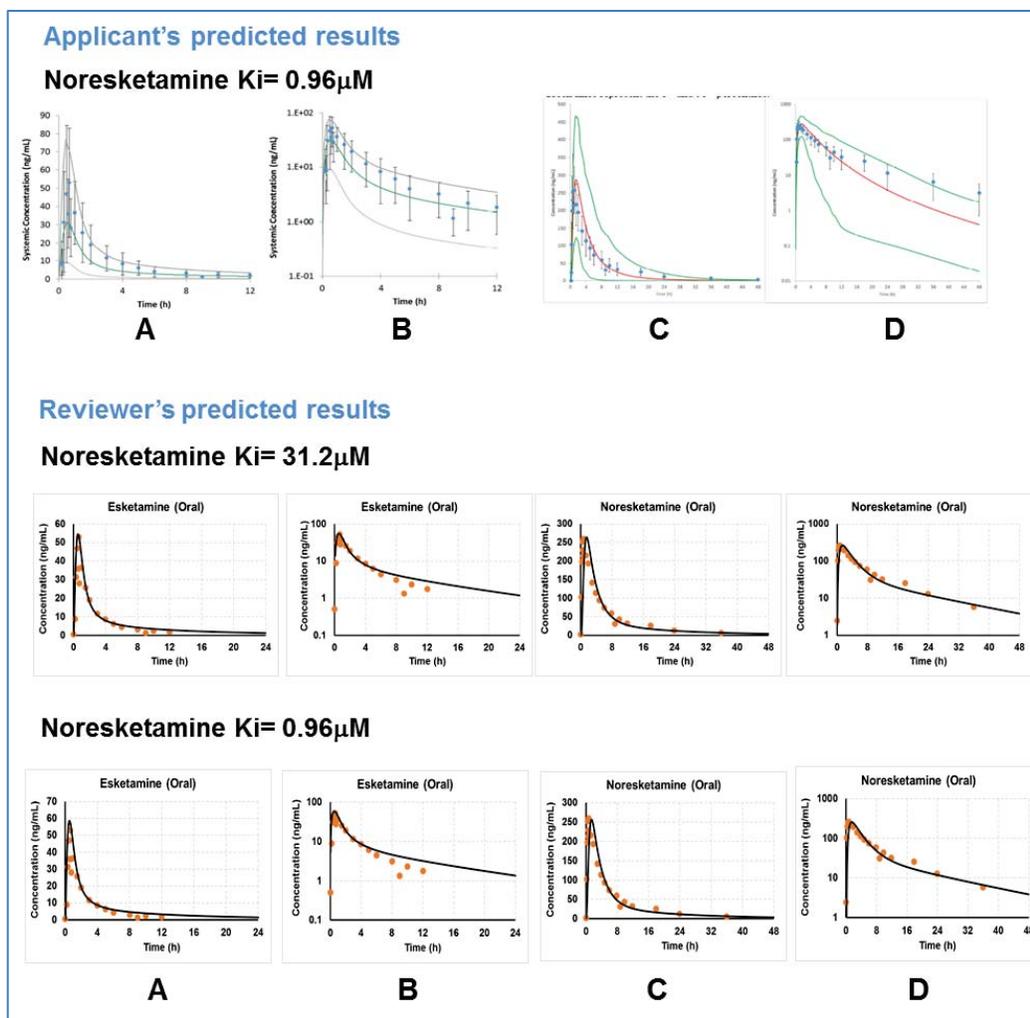


Figure 2 The simulated and observed plasma concentration-time profiles of esketamine and noresketamine following a single oral administration of 84 mg esketamine. Reviewer's results were simulated using the reviewer's refined PBPK models. The Applicant's results were taken from the Applicant's Response to FDA Request for Information. **Simulated PK profiles:** black, green and red lines. **Observed PK profiles:** yellow and blue dots. The observed data were from report FK13248 and Response to FDA Request for Information (Oct. 23, 2018). **A and C:** linear scale; **B and D:** logarithmic scale. **A and B:** esketamine concentration-time profiles; **C and D:** noresketamine concentration-time profiles.

DDI assessment strategy

As aforementioned in reviewer's comments to the Applicant's "***DDI Assessment Strategy***", the clinical study ESKETINTRD1010 can be used to evaluate the CYP3A induction potential of esketamine on midazolam PK. The study result indicated that esketamine, as a weak CYP3A inducer, reduced C_{max} and AUC_{∞} of midazolam by approximately 11% and 16%, respectively, after repeated administrations of esketamine. Based on this information, the reviewer applied the modeling and simulation approach to evaluate the CYP3A inhibitory potential of noresketamine when midazolam was dosed together with the last dose of esketamine.

A worst-case scenario was considered in which the nasal administered esketamine was absorbed completely through the gut to the systemic circulation. The metabolite-to-parent drug ratio after oral administration (about 12.46) was approximately 7.2 and 4-fold of that reported after IV (1.7) and intranasal (3.08) administration of esketamine (Table 4). Therefore, assuming 100% of intranasally administered esketamine absorbed through the gut allows to predict the maximum CYP3A inhibitory potential of noresketamine, although it is unlikely to occur.

Following Applicant’s DDI simulation scenario, noresketamine CYP3A Ki towards midazolam (31.2 µM) was used in the DDI assessment. In addition, noresketamine CYP3A Ki towards testosterone (0.96 µM) was used for the worst-case scenario analysis.

Model Based DDI Assessment Results

1. Simulation of DDI between a single oral administration of 6 mg midazolam and a single intravenous or oral administration of 84 mg esketamine in healthy subjects

Table 7 shows the predicted midazolam AUC ratios in 10 trials of 10 healthy subjects with either intravenous or oral administration of 84 mg esketamine. The simulated midazolam geometric mean AUC ratio was 1.01 and 0.93 following a single dose of 84 mg esketamine via intravenous and oral route, respectively when CYP3A Ki of noresketamine was 31.2 µM. The worst case DDI simulations were performed by setting the CYP3A Ki of noresketamine as 0.96 µM. The simulated midazolam geometric mean AUC ratio was 1.24 or 1.43 following a single oral or intravenous dose of 84 mg esketamine when CYP3A Ki of noresketamine was 0.96 µM.

Table 7 Simulated midazolam plasma AUC ratios after a single oral dose of 6 mg midazolam with and without co-administration of a single intravenous or oral administration of 84 mg esketamine. (with Noresketamine CYP3A Ki = 31.2 µM or 0.96 µM)

	Ki = 31.2 µM	Ki = 0.96 µM Worst-case scenario
MDZ AUC ratio (Geometric mean) after a single intravenous administration of esketamine (84 mg)	1.01	1.24
MDZ AUC ratio (Geometric mean) after a single oral administration of esketamine (84 mg)	0.93	1.43

2. Deconvoluted DDI of esketamine and noresketamine as the perpetrators with midazolam following multiple intranasal administrations of esketamine and a single oral dose of midazolam administered together with the last dose of esketamine

In this analysis, the potential DDI of esketamine as a CYP3A perpetrator with midazolam was evaluated using a deconvoluted approach following multiple administrations of intranasal administration of 84 mg esketamine. This deconvoluted approach was based on the observed CYP3A induction effect of esketamine on midazolam PK, the predicted pure CYP3A induction

effect of esketamine and pure CYP3A inhibition effect of noresketamine. The detailed analysis is as follows.

a. Pure CYP3A induction effect of esketamine and pure CYP3A inhibitory effect of noresketamine on midazolam PK during Phase I following multiple oral administrations of 84 mg esketamine

As aforementioned, assuming that 100% of intranasally administered esketamine was absorbed through the gut allows a prediction of the maximum CYP3A inhibitory potential of noresketamine and the maximum CYP3A induction potential of esketamine. In this section, a phase I simulation protocol was defined as multiple oral administrations of 84 mg esketamine over a 15-day period on day 2, 5, 9, 12 and 16, and a single oral dose of midazolam (6 mg) administered on day 16 together with the last dose of esketamine as illustrated in Fig 3. The simulations were performed in 100 virtual healthy subjects (10 trials of 10 subject each).

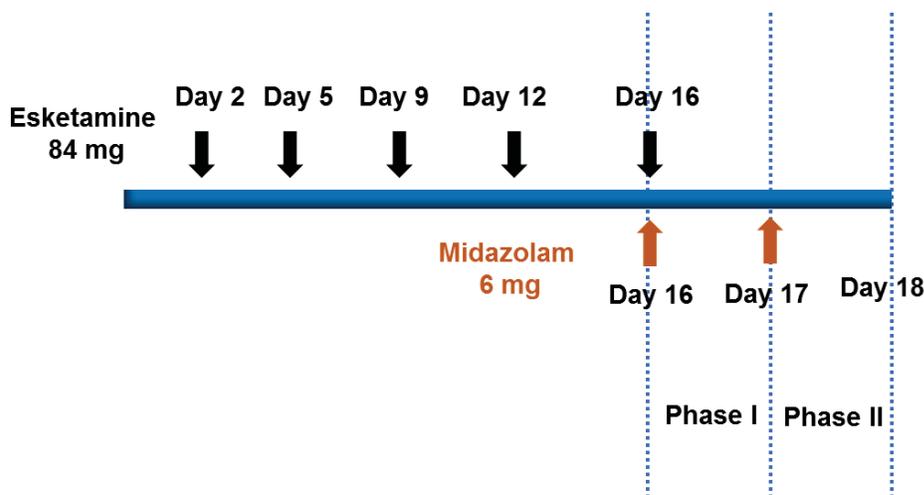


Figure 3 Esketamine and midazolam dosing regimen. Esketamine (84 mg, intravenous, oral or intranasal administration) was administered on day 2, 5, 9, 12 and 16. Midazolam (6 mg, p.o.) was administered together with the last dose of esketamine on day 16 or 24 hours after the last dose of esketamine on day 17

As shown in Table 8, the simulated midazolam AUC ratio decreased from 0.9 to 0.89 by turn-off the CYP3A inhibitory effect of noresketamine in the model. It suggested that noresketamine (CYP3A $K_i = 31.2 \mu\text{M}$) had no inhibitory effect on midazolam PK. When the induction effect of esketamine was turn-off in the model, the model predicted a 13 percent increase in midazolam AUC when midazolam was co-administrated with repeat oral doses of 84 mg esketamine. These simulation results suggest that the CYP3A inhibitory effect of noresketamine (CYP3A $K_i = 31.2 \mu\text{M}$) on midazolam PK was masked by the CYP3A induction effect of esketamine since the effect of esketamine on midazolam PK (AUC ratio: 0.9) is similar to that after the inhibition effect was turn-off in the model (AUC ratio: 0.89).

When the noresketamine CYP3A K_i was set as 0.96 μM , the CYP3A inhibitory effect of noresketamine would affect midazolam PK. The predicted midazolam AUC ratio with and without repeat oral doses of 84 mg esketamine was 1.41 and 1.71, respectively, with and without including the induction effect of esketamine in the model (Table 8).

b. Pure induction effect of esketamine on midazolam PK during Phase I and phase II following multiple intranasal administration of 84 mg esketamine

In clinical DDI study (ESKETINTRD1010), the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 17 a single oral dose of midazolam (6 mg) was administered. Due to the very low plasma level of noresketamine observed 24 h after the last dose of esketamine (Phase II), the CYP3A inhibitory potential of noresketamine was expected to have no influence on midazolam PK. The reviewer further conducted simulations to verify this speculation.

A phase II simulation protocol was used in this section where midazolam was dosed 24 h after the last dose of esketamine (84 mg, p.o, on Day 2, 5, 9, 12 and 16 as illustrated in Fig. 3). The simulation results showed that noresketamine did not show any inhibitory effect on midazolam PK when the induction effect was turn-off and even a lowest CYP3A K_i (0.96 μM) was used in the model (result not shown). Therefore, the observed 11% and 16% reduction in midazolam C_{max} and AUC during phase II in study ESKETINTRD1010 were attributable to the pure CYP3A induction effect of esketamine. Assuming the CYP3A induction has reached steady state following a 15-day treatment with intranasal esketamine, the pure CYP3A induction effect of esketamine in Phase I would also be expected to be the same as that in phase II.

c. Deconvoluted pure CYP3A inhibitory effect of noresketamine on midazolam PK during Phase I following multiple intranasal administrations of 84 mg esketamine

Noresketamine (CYP3A $K_i = 31.2 \mu\text{M}$)

As shown in Table 8, if esketamine was administered intravenously, no induction and inhibitory effect on midazolam PK (AUC ratio=1) was simulated when the noresketamine CYP3A K_i was 31.2 μM . This result indicated that orally administered esketamine would cause a stronger inhibition on CYP3A activity compared to that when esketamine was dosed intranasally, since only portion of the drug is absorbed through the gut for the intranasally administered esketamine. Correspondingly, less than 13% increase in midazolam AUC would be expected if esketamine was dosed intranasally. The weak inhibitory effect of noresketamine (CYP3A $K_i = 31.2 \mu\text{M}$) on midazolam PK was also completely masked by the induction effect of esketamine following multiple intranasal administrations during phase I. The 16% reduction in midazolam AUC (AUC ratio: 0.84) would be expected during phase I following the intranasal administration of 84 mg esketamine.

Noresketamine (CYP3A $K_i = 0.96 \mu\text{M}$)

Parameter sensitivity analysis (PSA) indicates that the pure CYP3A inhibitory effect on midazolam PK is sensitive to the administered oral dose of esketamine. As shown in Fig. 4, midazolam AUC ratio increased from 1.38 to 1.61 over a dose range of 48.5 to 84 mg if noresketamine CYP3A K_i was 0.96 μM . Thus, it was speculated that the pure CYP3A inhibitory effect of intranasally administered esketamine (84 mg) would be less than that of orally

administered esketamine (84 mg). Hence, the total effect of esketamine and noresketamine on midazolam AUC during Phase I following intranasally administered esketamine would be less than that following orally administered esketamine. Correspondingly a less than 1.41 of midazolam AUC ratio would be expected to be obtained during Phase I following the intranasal administration of esketamine.

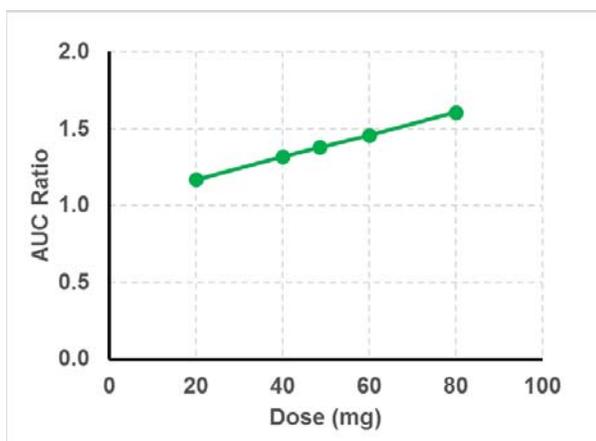


Figure 4 Sensitivity analysis of esketamine dose on the simulated midazolam AUC ratios following oral administration of esketamine under the condition that the CYP3A induction effect of esketamine was turn-off (pure CYP3A inhibition) in the model.

5. Conclusion

Several limitations were identified in Applicant's esketamine and noresketamine PBPK models. The Applicant's models were refined by FDA reviewer to better describe the observed clinical PK profiles of esketamine and noresketamine and then used to simulate the effects of esketamine on midazolam PK. By simulating the DDI effects following either IV- and oral- dosing of esketamine, the low and upper bound of DDI effects of esketamine on a sensitive substrate such as midazolam following a single or repeat nasal administration can be predicted.

- 1) The midazolam AUC ratios are predicted to be within a range of 0.93-1.01 after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine.
- 2) When the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 16 a single oral dose of midazolam (6 mg) was administered, the midazolam AUC ratios are predicted to be within a range of 0.90-1.00.

The worst-case scenario analysis by using noresketamine CYP3A K_i towards testosterone (0.96 μM) showed that,

- 1) The midazolam AUC ratios are predicted to be within a range of 1.24-1.43 after a single oral dose of 6 mg midazolam with and without co-administration of a single intranasal administration of 84 mg esketamine.

- 2) When the intranasal esketamine (84 mg) was administered over a 15-day period on day 2, 5, 9, 12 and 16, and on day 16 a single oral dose of midazolam (6 mg) was administered, the midazolam AUC ratios are predicted to be within a range of 1.23-1.41.

Table 8 Simulated midazolam AUC ratios after a single oral dose of 6 mg midazolam with and without co-administration of oral or intravenous administration of 84 mg esketamine or deconvoluted midazolam AUC ratios after a single oral dose of 6 mg midazolam with and without co-administration of intranasal administration of 84 mg esketamine with both CYP3A induction and CYP3A inhibition, with only CYP3A induction or with only CYP3A inhibition. A phase I simulation protocol was used where midazolam was dosed together with the last dose of esketamine (84 mg, p.o, on Day 2, 5, 9,12 and 16 as illustrated in Fig. 3).

	Simulated MDZ PK	Simulated MDZ PK (without CYP3A induction)	Simulated MDZ PK (without CYP3A inhibition)
	AUC Ratio	AUC Ratio	AUC Ratio
Noresketamine CYP3A Ki = 0.96 µM			
DDI of 84 mg oral esketamine with midazolam	1.41	1.72	0.89
DDI of 84 mg IV infusion esketamine with midazolam	1.23	1.24	0.99
DDI of 84 mg IN esketamine with midazolam	<1.41^b	<1.72^b	0.84^a
Noresketamine CYP3A Ki = 31.2 µM			
DDI of 84 mg oral esketamine with midazolam	0.90	1.13	0.89
DDI of 84 mg IV infusion esketamine with midazolam	1.00	1.01	0.99
DDI of 84 mg IN esketamine with midazolam	≈ 0.84^b	< 1.13^b	0.84^a

a: observed data from study TRD1010

b: deconvoluted based on simulation and clinical DDI data with midazolam

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