Clinical Pharmacology Review

PRODUCT (Generic Name):	Eszopiclone
NDAs:	21-476/S0045
SUBMISSION DATE	4/10/2012
PRODUCT (Brand Name):	Lunesta
DOSAGE FORM:	Tablet
DOSAGE STRENGTHS:	1 mg, 2 mg, and 3 mg
INDICATION:	Treatment of insomnia
NDA TYPE:	Pediatric Supplement
SPONSOR:	Sunovian Pharmaceuticals Inc.
OCP REVIEWER:	Jagan Mohan Parepally, Ph.D.
PHARMACOMETRICS REVIEWER:	Joo-Yeon Lee, Ph.D.
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OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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I. EXECUTIVE SUMMARY

Eszopiclone (Lunesta®) is a non benzodiazepine hypnotic acting as $GABA_A$ agonist indicated for the treatment of insomnia. This submission is a pediatric supplemental NDA in response to pediatric written request (PWR). The PWR included juvenile animal toxicity studies, pharmacokinetic-pharmacodynamic, tolerability studies and efficacy and safety studies.

The sponsor submitted two clinical pharmacology studies investigating a single doses of 1 mg, 2mg and 3 mg eszopiclone in adolescents (12 to 17 years of age) and 0.6 mg, 1 mg, 2mg and 3 mg eszopiclone in children (6 to 11 years of age) with attention deficit hyperactivity disorder (ADHD) associated insomnia (Studies 190-201 and 190-202, respectively). Population PK report (Study 008037) based on data derived from Study 190-201 and 190-202 was also submitted.

Dose selection for phase 3 pivotal efficacy and safety study (190-246) was based on the PK-PD and tolerability studies. Efficacy of eszopiclone in adolescents and children with attention deficit hyperactivity disorder (ADHD)-associated insomnia was not demonstrated in this study.

Pediatric exclusivity was granted to the sponsor on June 29th, 2012.

II. RECOMMENDATION

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed sNDA #21-476. This submission is acceptable from Clinical Pharmacology perspective.

III. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Summary of PK in Pediatrics.

The exposure in adolescent population (12 to 17 years) was similar to that observed in the adult population when the same dose levels are administered. In younger children (6 to 11 years) exposure (i.e., AUC) was relatively higher (approximately 1.3 fold) in children

than adults when compared with study 190-002. Dose selection for pivotal phase 3 efficacy and safety study (190-246) was based on these findings:

- lower doses (1 mg and 2 mg) were selected in younger 6-11 years old children
- 2 and 3 mg selected for 12-17 years old.

Dose-response relationship for efficacy/safety of eszopiclone

A total of 483 subjects (308 males and 175 females) were randomized in a 1:1:1 ratio to either low-dose eszopiclone (1 mg for children ages 6 to 11 years, 2 mg for adolescents ages 12 to 17 years), high-dose eszopiclone (2 mg for children ages 6 to 11 years, 3 mg for adolescents ages 12 to 17 years), or placebo in pivotal Study 190-246. Dose selection in children was based on comparable exposure in adults (at the approved dose) and tolerability. In younger children, 1 mg and 2 mg doses were compared to placebo. The exposure based on 1 mg dose appears to be lower than comparable exposure at the approved dose in adults. However, there was no dose-response relationship for efficacy and safety of eszopiclone.

There was no statistically significant difference from placebo for either the high-dose (2 or 3 mg) eszopiclone ($P = 0.3749$) or the low-dose (1 or 2 mg) eszopiclone ($P > 0.9999$) groups in the primary efficacy endpoint of change from baseline to Week 12 in PSG-defined LPS. The overall incidences of TEAEs for Study 190-246 were 74 [46.0%], 97 [59.5%], and 97 [61.0%] subjects in the placebo, low-dose eszopiclone, and high-dose eszopiclone groups, respectively.

Effect of Covariates: Body weight (or age) was the only covariate that had a significant effect on apparent clearance and volume of distribution, and there were no other covariates which significantly influenced the PK of eszopiclone.

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Jagan Mohan Parepally, Ph.D. Date
Reviewer
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cc: HFD-120 sNDA# 21-476
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Mohan Parepally.

IV. QUESTION BASED REVIEW

What are the design features of the clinical pharmacology studies conducted per pediatric written request?

The pharmacokinetic (PK) and pharmacodynamic (PD) data to provide information pertinent to dosing of the study drug in the relevant pediatric population were obtained from Clinical Studies 190-201 and 190-202. Preliminary tolerability was also obtained in the range of doses, from 0.6 mg to 3 mg.

PK studies included patients in the following age groups:

- 6 to 11 years of age: Doses 0.6 mg, 1 mg, 2mg and 3 mg
- 12 to 17 years of age: Doses 1 mg, 2mg and 3 mg

These studies were single-dose PK studies that explored the range [equivalent to ≥ 12 to <18 years) of tolerated doses based on age group. Clinical Study 190-201 and 190-202 were multicenter, open-label, in-clinic studies in male and female children (190-202) or adolescents (190-201) with a prior diagnosis of ADHD and insomnia established by a medical interview and insomnia established by history and PSG screening.

What is the phase 3 dose selection rationale for different age groups?

Dose selection for pivotal phase 3 efficacy and safety study was based on two clinical pharmacology studies 190-201 and 190-202. Following table represents comparison of PK parameters in different pediatric age groups with mean PK parameters obtained from study 190-002 and 190-003 in adults.

		190-202 (6-11 yrs)			190-201 (12-17yrs)			Adults (190-002, 190-003)	
Eszopiclone Dose Group		N	Mean	SD	N	Mean	SD	N	Means from 2 studies (two sub groups in 003)
1 mg	Cmax (ng/mL)	13	11.8	3.62	11	6.62	2.18	9-11	10/12/14
	AUC(0-∞) (ng•hr/mL)	12	95.4	27.2	9	54.4	15.8	9-11	62/58/79
2 mg	Cmax (ng/mL)	11	20.2	7.97	12	13.6	4.99	9-11	22/25
	AUC(0-∞) (ng•hr/mL)	9	187	49.9	11	126	39.2	9-11	140/148
3 mg	Cmax (ng/mL)	12	29.0	11.2	12	22.9	6.18	9-11	25/36/37
	AUC(0-∞) (ng•hr/mL)	12	242	86.3	10	229	45.2	9-11	195/222/250

Note: 190-002: Caucasians; 190-003: Including two subgroups, Caucasians and Japanese
in blue: 190-002
in red: 003 – Caucasion subbroup
in green: 003 – Japanese subgroup

The overall exposure (AUC) in adolescent population (12 to 17 years) was similar to that observed in the adult population when the same dose levels were administered.

In younger children (6 to 11 years), the overall exposure (i.e., AUC) was relatively higher (1.3 to 1.5 fold) in children than adults when compared to study 190-002. Since body weight (or age) is highly correlated, a dose of 1 mg and 2 mg doses were selected in younger children. However, the overall exposure (AUC) of 1 and 2 mg dose appears to be lower than the exposures of the approved dose (2 to 3 mg) in adults.

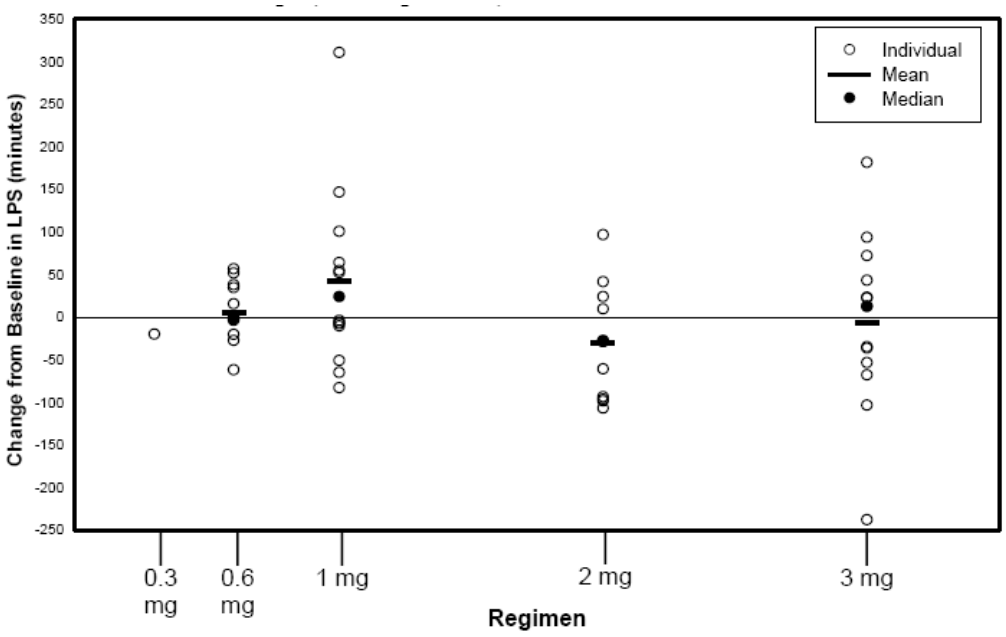
The sponsor used the above information, matching the adult exposure (AUC), to determine the doses for the efficacy/safety trials in the Pediatrics.

A total of 483 subjects (308 males and 175 females) were randomized in a 1:1:1 ratio to either low-dose eszopiclone (1 mg for children ages 6 to 11 years, 2 mg for adolescents ages 12 to 17 years), high-dose eszopiclone (2 mg for children ages 6 to 11 years, 3 mg for adolescents ages 12 to 17 years), or placebo.

Reviewer's Comment: The sponsor only compared the AUC and matched it to the adults for the dose selection for the efficacy/safety trial in the pediatrics. The dose selection did not take Cmax into consideration. Currently, the relationship between AUC/Cmax and clinical endpoint is unknown. In addition, the selected PD makers are not considered well validated in the indicated population, children with ADHD associated insomnia. Therefore, it is hard to comment on the optimization of the selected dosing regimen from a clinical pharmacology perspective.

Figure below illustrates lack of dose response relationship on the primary PD end point change from baseline in Latency to Persistent Sleep (LPS) over the dose range tested in children with ADHD.

Scatter Plot of Change from Baseline in Latency to Persistent Sleep (LPS, the primary PD end point) Based on PSG vs. Dose for Eszopiclone

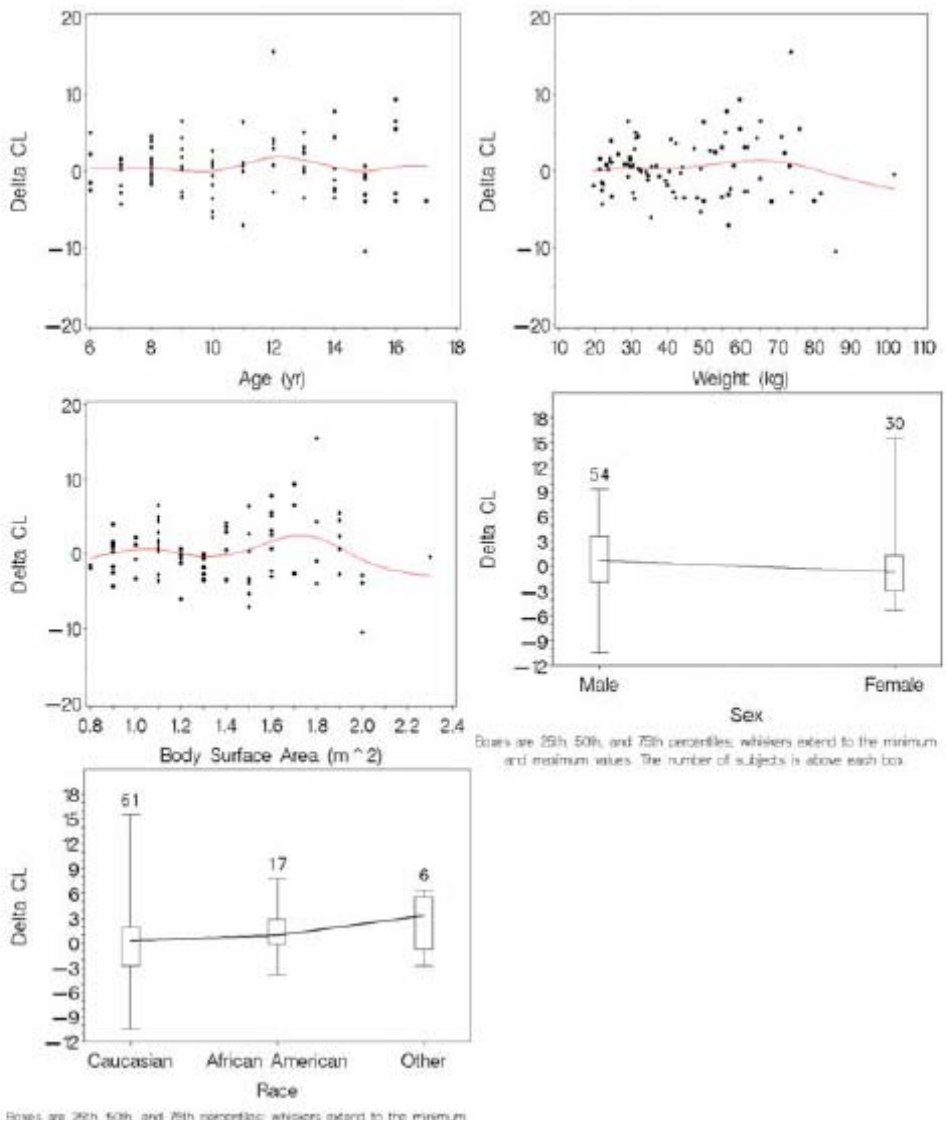


What is the effect of covariates on the PK of eszopiclone in adolescents and children with attention deficit hyperactivity disorder (ADHD)-associated insomnia?

The sponsor performed the population pharmacokinetic analyses using data from two Phase I studies (190-201, 190-202) to characterize the PK disposition of eszopiclone and to identify any covariate which influences the PK of eszopiclone in adolescents and children with attention deficit hyperactivity disorder (ADHD)-associated insomnia. The study of 190-201 included 36 male and female adolescents 12 to 17 years of age who received single oral eszopiclone doses of 1.0 mg, 2.0 mg, or 3.0 mg, and there were 49 male and female children 6 to 11 years of age who were assigned to single oral eszopiclone doses of 0.6 mg, 1.0 mg, 2.0 mg, or 3.0 mg in the study of 190-202.

Body weight (or age) was the only covariate that had a significant effect on apparent clearance and volume of distribution, and there were no other covariates which influenced the PK of eszopiclone as shown in the figure below. Simulations using the final PK model (see Pharmacometrics review) were performed to predict the eszopiclone concentration-time profiles after single oral doses of 1 mg and 2 mg in children 6 to 11 years of age and single oral doses of 2 mg and 3 mg in adolescents 12 to 17 years of age. A dose range of 1.0 to 2.0 mg was recommended for study in children 6 to 11 years of age and 2.0 to 3.0 mg in adolescents.

Figure: The relationship between covariates and CL/F. Delta CL on the Y-axis indicate individual parameter estimates subtracted by typical (population mean) value of parameter.



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V. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Lunesta. The proposed description related to clinical pharmacology studies (Section 8.4 Pediatric Use) should be deleted:

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

8.4 Pediatric Use


(b) (4)

VI. APPENDIX

VII. INDIVIDUAL STUDY REVIEWS

190-201: A Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Evaluation of Single Oral Doses of Eszopiclone in Adolescents 12 to 17 Years of Age with Attention Deficit Hyperactivity Disorder and Insomnia.

Objective: To determine the safety, tolerability, and pharmacokinetic (PK)/ pharmacodynamic (PD) profile of single doses of eszopiclone in adolescents aged 12 to 17 years (inclusive) with attention deficit hyperactivity disorder (ADHD) and insomnia.

Study Design	This was a multicenter, open-label, in-clinic study in male and female adolescents 12 to 17 years of age (inclusive), with a prior diagnosis of ADHD.
Study Population	Male and female adolescents with ADHD Age: 12 to 17 years **Planned:** A maximum of 72 subjects were to be enrolled in up to 4 PK/PD dose groups (n=12 per dose group; 48 total), 2 repeat doses to provide additional safety data (n=6 per dose group, 12 total) and a PD-only dose group (n=12 total). **Enrolled and Analyzed:** A total of 36 subjects were enrolled, treated, and analyzed in 3 PK/PD dose groups.
Treatment Groups	• Dose group 1 (PK/PD) - 1.0 mg: 1 x 1.0 mg eszopiclone tablet • Dose group 2 (PK/PD) - 2.0 mg: 1 x 2.0 mg eszopiclone tablet • Dose group 3 (PK/PD) - 3.0 mg: 1 x 3.0 mg eszopiclone tablet
Sampling: Blood	Plasma concentrations of eszopiclone and (S)-desmethylzopiclone [(S)- were assayed from blood samples collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 18 hours post-dose using a validated bioanalytical method with a limit of quantification of 1 ng/mL.
Analysis	Eszopiclone and Des-methylzopiclone concentrations were determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 1 ng/mL for both the analytes. **Eszopiclone**

Parameter	Quality Control Samples	Standard Curve Samples

Quality Control or Standard Curve Concentration (ng/mL)	3, 20, and 40 ng/mL	1, 2, 4, 8, 16, 32, 48 and 64 ng/mL
Between Batch Precision (%CV)	4.6 to 6.4	2.0 to 6.4
Accuracy (%RE)	1.5 to 1.7	-5.5 to 3.1
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.996	
Linear Range (ng/mL)	1 to 64 ng/mL	
Sensitivity (LLOQ, ng/mL)	1 ng/mL	

(S) Desmethyl Zopiclone

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	3, 20, and 40 ng/mL	1, 2, 4, 8, 16, 32, 48 and 64 ng/mL
Between Batch Precision (%CV)	5.5 to 7.1	5.1 to 11.3
Accuracy (%RE)	2.5 to 7.0	-3.3% to 3.1 %
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.998	
Linear Range (ng/mL)	1 to 64 ng/mL	
Sensitivity (LLOQ, ng/mL)	1 ng/mL	

Safety	Safety assessments included adverse events (AE), clinical laboratory assessments, vital sign measurements, 12-lead electrocardiogram (ECG), and physical/neurological examination findings.
PK Assessments	PK parameters Cmax tmax, $t_{1/2}$, AUC0-last were presented by dose group for each analyte. Graphical displays of individual, mean, and median PK parameters (apparent total body clearance [Cl/F] and apparent volume of distribution [Vd/F]) were presented by dose group for eszopiclone.
PD Assessments	Objective sleep parameters were measured via PSG including Latency to Persistent Sleep (LPS), Total Sleep Time (TST), Sleep Efficiency (SE), and Wake time After Sleep Onset (WASO). Subjective sleep and next-day effects parameters were assessed via questionnaires. All PD parameters (objective and subjective sleep parameters), and Coding Copy Subtest/ Digit Symbol Substitution Test (DSST) were summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) by dose group. Changes from baseline were also summarized for each of these parameters.

Statistical Methods	Plasma concentrations for eszopiclone and (S)-DMZ were summarized using the intent-to-treat (ITT) population. All PD and safety assessments were performed using the ITT population. All hypothesis tests were 2 sided with a 5% significance level, and 90% confidence intervals (CIs). For continuous outcomes, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum the coefficient of variation (CV) were presented by dose group.

Selection of Doses in the Study
The starting dose and escalation schedule used in this study were both based on toxicology studies performed in juvenile rats and dogs and the established clinical PK profile in adults. The NOAELs of 2 and 1 mg/kg/day (lowest dosages evaluated) from the toxicology studies in juvenile rats and dogs, respectively, were considered for calculating the Human Equivalent Dose (HED).

PHARMACOKINETIC RESULTS:

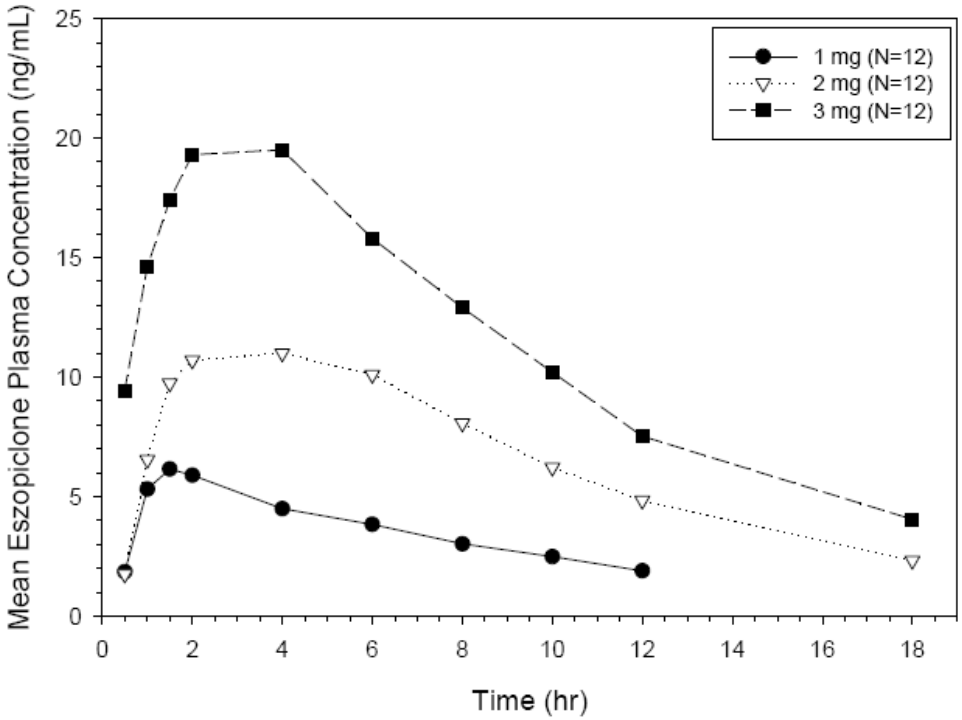
Following table represents the mean (SD) pharmacokinetic parameters of eszopiclone.

Mean (SD) Pharmacokinetic Parameters of Eszopiclone Following Single Dose of 1 mg, 2 mg, or 3 mg

Parameter	Eszopiclone Dose Group								
	1 mg (N = 11)			2 mg (N = 12)			3 mg (N = 12)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max} (ng/mL)	11	6.62	2.18	12	13.6	4.99	12	22.9	6.18
tmax (hrs)	11	1.50	1.00-6.00	12	3.00	1.00-6.00	12	2.00	1.00-8.00
$AUC_{(0\text{-last})}$ (ng*hr/mL)	11	44.1	13.4	12	119	42.2	12	193	50.9
$AUC_{(0\text{-}\infty)}$ (ng*hr/mL)	9	54.4	15.8	11	126	39.2	10	229	45.2
$t_{½}$ (hrs)	11	4.66	1.37	12	5.30	1.51	10	5.52	1.22
Cl/F (L/hr)	9	19.6	5.06	11	17.7	6.87	10	13.6	2.83
Vd/F (L)	9	115	31.6	11	123	42.0	10	107	27.0

Following figure represents the mean pharmacokinetic profile of eszopiclone following 1 mg, 2 mg, or 3 mg single dose.

Mean Eszopiclone Plasma Concentration-time Profiles Following a Single Oral Dose of 1 mg, 2 mg, or 3 mg Eszopiclone



Following table represents dose proportionality analysis using the power model with and without covariates (gender, body weight and BSA).

Dose Proportionality of Eszopiclone Following 1 mg, 2 mg, or 3 mg Doses

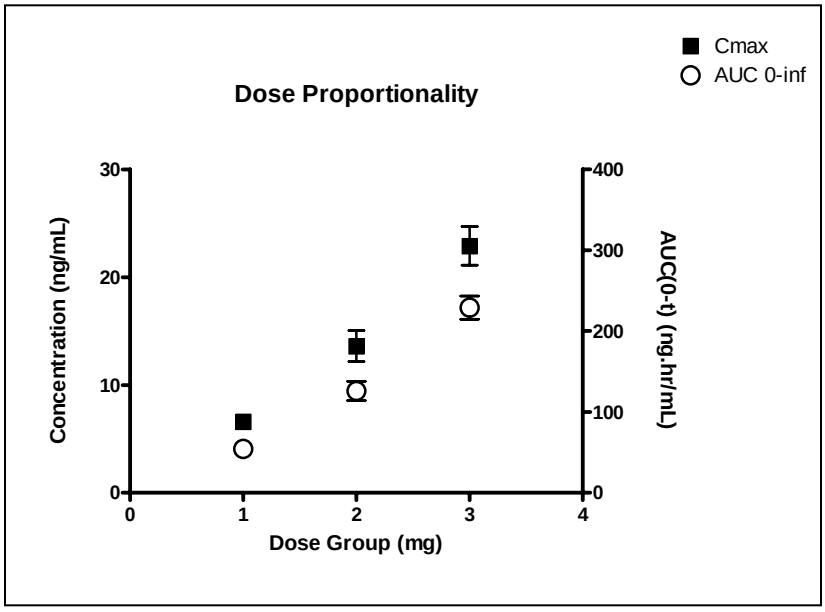
Parameter	Statistic	AUC(0-last)	AUC(0–∞)	Cmax
Dose Proportionality	Intercept Estimate	3.758	3.937	1.823
	Standard Error	0.094	0.089	0.091
	Slope Estimate	1.348	1.309	1.126
	Standard Error	0.123	0.117	0.120
	90% Confidence Interval	1.140, 1.557	1.109, 1.508	0.924, 1.329
Dose Proportionality with Gender as a Covariate	Intercept Estimate	3.798	3.949	1.849
	Standard Error	0.100	0.096	0.098
	Slope Estimate	1.358	1.313	1.132
	Standard Error	0.123	0.120	0.121
	90% Confidence Interval	1.150, 1.566	1.109, 1.517	0.928, 1.337
	Gender p-value	0.255	0.679	0.457
Dose Proportionality with Body Weight as a Covariate	Intercept Estimate	4.302	4.523	2.494
	Standard Error	0.206	0.195	0.183
	Slope Estimate	1.312	1.303	1.081
	Standard Error	0.112	0.101	0.100
	90% Confidence Interval	1.122, 1.502	1.131, 1.476	0.912, 1.250
	Body Weight p-value	0.007	0.003	<0.001
Dose Proportionality with Body Surface	Intercept Estimate	4.712	4.860	2.987
	Standard Error	0.319	0.309	0.282

Area as a Covariate	Slope Estimate	1.311	1.301	1.081
	Standard Error	0.110	0.103	0.098
	90% Confidence Interval	1.124, 1.498	1.126, 1.476	0.916, 1.247
	BSA p-value	0.004	0.005	<0.001

Dose proportionality was assessed based on the inclusion of 1.0 in the 90% confidence interval estimate.

The Cmax and AUC were dose proportional. Body weight and body surface area were found to be statistically significant covariates in the power model analysis of the change in exposure with dose. The gender was not a statistically significant covariate.

Following figure represents the mean and SD of Cmax and AUC at1 mg, 2 mg, or 3 mg Eszopiclone dose.



Following table represents the pharmacokinetic parameters of desmethyl zopiclone following 1 mg, 2 mg, or 3 mg eszopiclone.

Mean ± SD Pharmacokinetic Parameters (S)-DMZ Following Single Dose of 1 mg, 2 mg, or 3 mg (PK Population)

Parameter	**Eszopiclone Dose Group**								
	1 mg (N = 11)			**2 mg (N = 12)**			**3 mg (N = 12)**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max} (ng/mL)	0	NC	NC	5	1.56	0.15	11	2.72	0.46

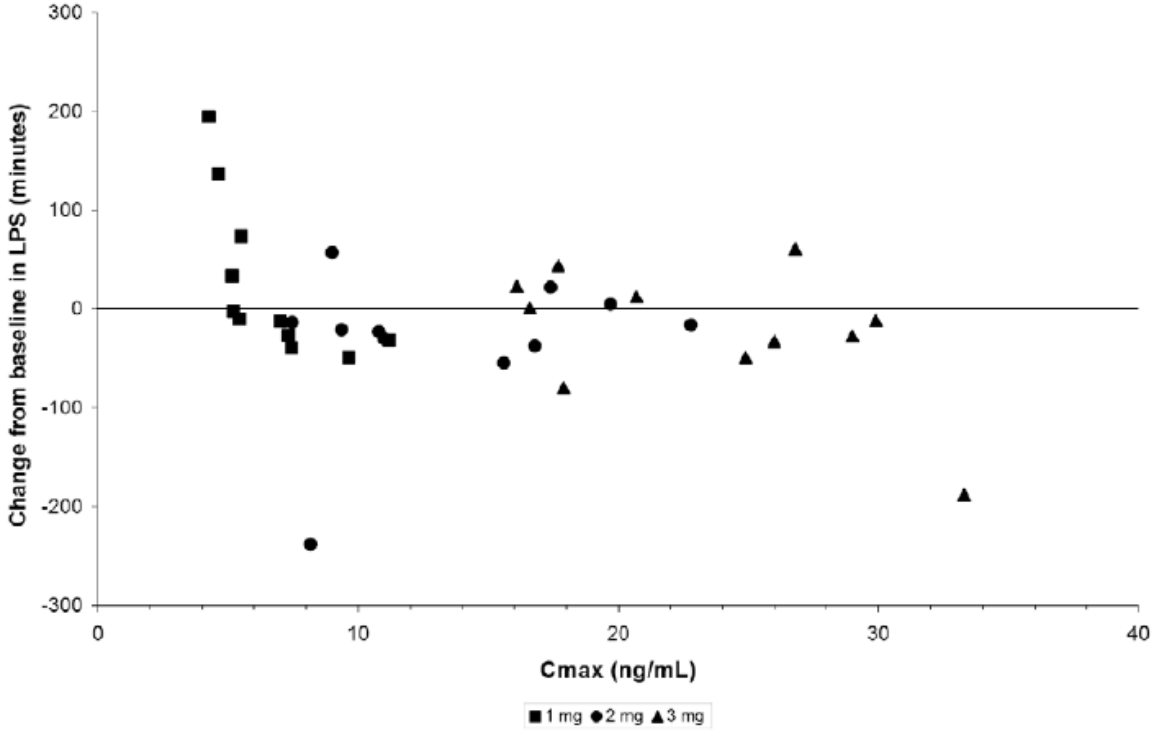
t_{max} (hrs)	0	NC	NC	5	5.92	4.00-10.0	11	6.00	1.50-12.0
$AUC_{(0\text{-last})}$ (ng*hr/mL)	0	NC	NC	5	11.4	1.86	11	27.1	7.31
$AUC_{(0\text{-}\infty)}$ (ng*hr/mL)	0	NC	NC	0	NC	NC	2	43.6	3.51
$t_{½}$ (hrs)	0	NC	NC	1	10.4	NC	6	7.63	1.71

(S)DMZ was not quantifiable in low dose groups. Plasma concentrations of (s)DMZ were approximately 8.5 fold lower than eszopiclone.

PHARMACODYNAMIC RESULTS:

- PSG and sleep architecture parameters were variable between individual subjects with no apparent dose response effect observed.
- There was no apparent relationships between PK (Cmax and AUC[0-last]) and PD (LPS, TST, WASO) parameters in this population (see figure below).

Scatter Plot of Change From Baseline in LPS Based on PSG vs Cmax for Eszopiclone in Adolescents



Note: 1 mg (N = 12); 2 mg (N = 11); 3 mg (N = 11)

Following tables represent individual, mean, and median change from baseline in LPS, TST, Sleep efficacy and WASO following single oral doses of 1 mg, 2 mg, or 3 mg.

Polysomnography - Latency to Persistent Sleep (minutes)

Visit/Timepoint	Statistic	Eszopiclone Dose Group		
		1 mg (N=12)	2 mg (N=12)	3 mg (N=12)
Visit 1 Baseline	n	12	12	12
	Mean	86.38	79.33	98.75
	SD	52.31	82.27	92.69
	Median	70.25	47.50	57.25
	Minimum	27.5	32.0	32.0
	Maximum	183.5	309.0	325.0
Visit 2 Change from Baseline Values	n	12	11	11
	Mean	19.33	-31.86	-22.36
	SD	77.31	74.80	68.43
	Median	-11.50	-21.00	-11.50
	Minimum	-49.0	-238.0	-188.0
	Maximum	194.5	57.0	61.0

Total Sleep Time (minutes)

Visit/Timepoint	Statistic	Eszopiclone Dose Group		
		1 mg (N=12)	2 mg (N=12)	3 mg (N=12)
Visit 1 Baseline	n	12	12	12
	Mean	375.54	393.04	386.79
	SD	60.36	107.17	85.52
	Median	376.00	426.00	420.50
	Minimum	278.5	168.0	213.5
	Maximum	474.0	479.0	495.5
Visit 2 Change from Baseline Values	n	12	12	11
	Mean	-21.54	-5.67	27.32
	SD	112.96	142.25	71.34
	Median	11.00	12.75	40.50
	Minimum	-313.5	-399.5	-66.5
	Maximum	96.0	200.0	175.0

Sleep Efficiency (minutes)

Visit/Timepoint	Statistic	Eszopiclone Dose Group		
		1 mg (N=12)	2 mg (N=12)	3 mg (N=12)
Visit 1 Baseline	n	12	12	12
	Mean	74.82	76.35	74.21
	SD	10.09	19.50	16.01
	Median	78.01	83.15	80.55
	Minimum	58.0	35.0	39.5
	Maximum	87.8	88.7	91.8
Visit 2 Change from Baseline Values	n	12	12	11
	Mean	-5.27	-0.99	4.01
	SD	20.46	29.50	13.50

	Median	-0.25	2.74	5.59
	Minimum	-57.1	-83.2	-12.6
	Maximum	20.0	41.7	32.4

Wake Time after Sleep Onset (minutes)

Visit/Timepoint	Statistic	Eszopiclone Dose Group		
		1 mg (N=12)	2 mg (N=12)	3 mg (N=12)
Visit 1 Baseline	n	12	12	12
	Mean	43.92	42.58	39.29
	SD	30.25	35.15	36.25
	Median	40.00	30.25	27.75
	Minimum	8.5	7.0	3.5
	Maximum	94.0	132.0	127.0
Visit 2 Change from Baseline Values	n	12	11	11
	Mean	11.63	1.91	3.32
	SD	53.55	27.25	33.13
	Median	-4.75	-2.50	6.50
	Minimum	-66.5	-46.5	-58.0
	Maximum	102.5	42.5	51.0

CONCLUSIONS:

- Pharmacokinetic parameters Cmax and AUC were dose proportional. Body weight and BSA were statistically significant covariates; their impact upon dose proportionality was relatively less. Gender was not statistically significant covariate.

- Plasma concentrations of (S)-DMZ were approximately 8.5-fold lower than for the parent drug.

- Sleep parameters were variable between individual subjects.

- There was no apparent relationship observed between PK and PD (LPS, TST, WASO) parameters.

190-202: A Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Evaluation of Single Oral Doses of Eszopiclone in Children 6 to 11 Years of Age with Attention Deficit Hyperactivity Disorder and Insomnia.

Objective: To determine the safety, tolerability, and pharmacokinetic (PK)/ pharmacodynamic (PD) profile of single doses of eszopiclone in children ages 6 to 11 years (inclusive) with attention deficit hyperactivity disorder (ADHD) and insomnia.

<table>
<tr><td>Study Design</td><td>This was a multicenter, open-label, in-clinic study in male and female children 6 to 11 years of age (inclusive), with a prior diagnosis of ADHD.</td></tr>
<tr><td>Study Population</td><td>Male and female children with ADHD
Age: 6 to 11 years
Planned:
A maximum of 84 subjects were to be enrolled in up to 5 PK/PD dose groups (n=12 per dose group; 60 total), 2 repeat doses to provide additional safety data (n=6 per dose group, 12 total) and a PD-only dose group (n=12 total).
Enrolled and Analyzed:
A total of 49 subjects were enrolled, treated, and analyzed in 4 PK/PD dose groups.</td></tr>
<tr><td>Treatment Groups</td><td>• Dose group 1 (PK/PD) – 0.3 mg: 2 x 0.3 mg eszopiclone tablet
• Dose group 2 (PK/PD) - 1.0 mg: 1 x 1.0 mg eszopiclone tablet
• Dose group 3 (PK/PD) - 2.0 mg: 1 x 2.0 mg eszopiclone tablet
• Dose group 4 (PK/PD) - 3.0 mg: 1 x 3.0 mg eszopiclone tablet</td></tr>
<tr><td>Sampling: Blood</td><td>Plasma concentrations of eszopiclone and (S)-desmethylzopiclone [(S)- were assayed from blood samples collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 18 hours post-dose using a validated bioanalytical method with a limit of quantification of 1 ng/mL.</td></tr>
<tr><td>Analysis</td><td>Eszopiclone and Des-methylzopiclone concentrations were determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 1 ng/mL for both the analytes.

Eszopiclone

<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3, 20, and 40 ng/mL</td><td>1, 2, 4, 8, 16, 32, 48 and 64 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.1 to 5.3</td><td>5.1 to 10.9</td></tr>
<tr><td>Accuracy (%RE)</td><td>-1.5 to 4.3</td><td>-5.2 to 2.5</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.997</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 64 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table>

(S) Desmethyl Zopiclone</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3, 20, and 40 ng/mL</td><td>1, 2, 4, 8, 16, 32, 48 and 64 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>4.3 to 9.4</td><td>6.0 to 13.4</td></tr>
<tr><td>Accuracy (%RE)</td><td>-0.5 to 2.0</td><td>-2.6 to 1.3</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.996</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 64 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Safety</td><td>Safety assessments included adverse events (AE), clinical laboratory assessments, vital sign measurements, 12-lead electrocardiogram (ECG), and physical/neurological examination findings.</td></tr>
<tr><td>PK Assessments</td><td>PK parameters Cmax tmax, $t_{1/2}$, AUC0-last were presented by dose group for each analyte. Graphical displays of individual, mean, and median PK parameters (apparent total body clearance [Cl/F] and apparent volume of distribution [Vd/F]) were presented by dose group for eszopiclone.</td></tr>
<tr><td>PD Assessments</td><td>Objective sleep parameters were measured via PSG including Latency to Persistent Sleep (LPS), Total Sleep Time (TST), Sleep Efficiency (SE), and Wake time After Sleep Onset (WASO). Subjective sleep and next-day effects parameters were assessed via questionnaires.
All PD parameters (objective and subjective sleep parameters), and Coding Copy Subtest/ Digit Symbol Substitution Test (DSST) were summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) by dose group. Changes from baseline were also summarized for each of these parameters.</td></tr>
<tr><td>Statistical Methods</td><td>Plasma concentrations for eszopiclone and (S)-DMZ were summarized using the intent-to-treat (ITT) population. All PD and safety assessments were performed using the ITT population. All hypothesis tests were 2 sided with a 5% significance level, and 90% confidence intervals (CIs).
For continuous outcomes, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum the coefficient of variation (CV) were presented by dose group.</td></tr>
</table>

Selection of Doses in the Study

The starting dose and escalation schedule used in this study were both based on toxicology studies performed in juvenile rats and dogs and the established clinical PK profile in adults. The NOAELs of 2 and 1 mg/kg/day (lowest dosages evaluated) from the toxicology studies in juvenile rats and dogs, respectively, were considered for calculating the Human Equivalent Dose (HED).

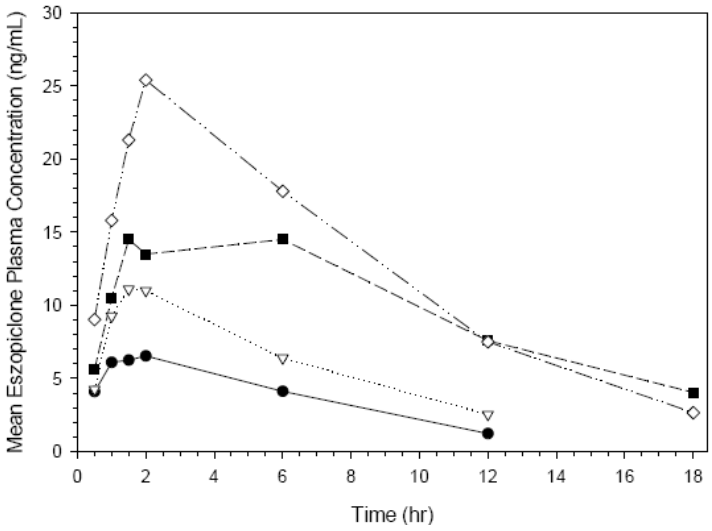
PHARMACOKINETIC RESULTS:

Table below represents the pharmacokinetic parameters of eszopiclone following 0.6 mg, 1 mg, 2 mg, or 3 mg.

Mean (SD) Pharmacokinetic Parameters of Eszopiclone Following Single Dose of 0.6 mg, 1 mg, 2 mg, or 3 mg

	Eszopiclone Actual Dose Group											
	0.6 mg			1 mg			2 mg			3 mg		
Parameter	(N=9)			(N = 13)			(N = 11)			(N = 12)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max} (ng/mL)	9	8.44	3.25	13	11.8	3.62	11	20.2	7.97	12	29.0	11.2
t_{max} (hrs)	9	2.00	1.00-6.00	13	1.53	1.00-6.00	11	1.52	1.50-6.00	12	2.00	0.50-6.00
$AUC_{(0\text{-last})}$ (ng•hr/mL)	9	47.4	19.6	13	80.4	24.2	11	182	57.8	12	222	82.4
$AUC_{(0\text{-}\infty)}$ (ng•hr/mL)	6	65.0	18.1	12	95.4	27.2	9	187	49.9	12	242	86.3
$t_{½}$ (hrs)	7	3.93	0.81	12	4.41	1.17	10	5.67	1.85	12	4.75	1.79
Cl/F (L/hr)	6	9.81	2.52	12	11.3	3.22	9	11.3	2.70	12	13.7	4.44
Vd/F (L)	6	57.0	20.5	12	70.1	19.3	9	85.3	27.4	12	92.7	37.1

Mean Eszopiclone Plasma Concentration-time Profiles Following a Single Oral Dose of 0.6, 1 mg, 2 mg, or 3 mg Eszopiclone



Dose Proportionality of Eszopiclone Following 0.6 mg, 1 mg, 2 mg, or 3 mg Doses

Parameter	Statistic	$AUC_{(0\text{-last})}$	$AUC_{(0-\infty)}$	C_{max}

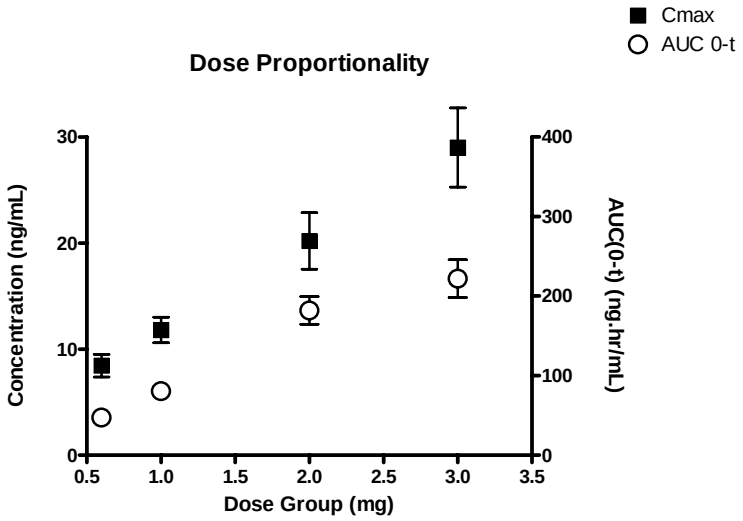
Dose Proportionality	Intercept Estimate	4.340	4.552	2.438
	Standard Error	0.059	0.057	0.061
	Slope Estimate	0.999	0.833	0.765
	Standard Error	0.084	0.079	0.086
	90% Confidence Interval	0.858, 1.140	0.701, 0.966	0.620, 0.910
Dose Proportionality with Body Surface Area as a Covariate	Intercept Estimate	4.900	5.018	3.201
	Standard Error	0.254	0.227	0.250
	Slope Estimate	1.033	0.869	0.812
	Standard Error	0.081	0.077	0.080
	90% Confidence Interval	0.896, 1.170	0.739, 0.999	0.677, 0.947
	BSA p-value	0.029	0.041	0.003
Dose Proportionality with Body Weight as a Covariate [c]	Intercept Estimate	4.618	4.792	2.827
	Standard Error	0.154	0.136	0.153
	Slope Estimate	1.031	0.865	0.810
	Standard Error	0.083	0.078	0.082
	90% Confidence Interval	0.892, 1.170	0.734, 0.996	0.672, 0.948
	Body Weight p-value	0.058	0.062	0.009
Dose Proportionality with Gender as a Covariate	Intercept Estimate	4.282	4.491	2.394
	Standard Error	0.069	0.065	0.072
	Slope Estimate	1.000	0.838	0.766
	Standard Error	0.082	0.076	0.086
	90% Confidence Interval	0.862, 1.139	0.709, 0.967	0.622, 0.911
	Gender p-value	0.125	0.088	0.263

Dose proportionality was assessed based on the inclusion of 1.0 in the 90% confidence interval estimate.

The $AUC_{0\text{-inf}}$ was dose proportional. And the observed C_{max} and $AUC_{0\text{-t}}$ were approximately dose proportional for the doses tested as shown in the figure below.

Body weight and body surface area were found to be statistically significant covariates in the power model analysis of the change in exposure with dose. The gender was not a statistically significant covariate.

Following figure represents the mean and SD of Cmax and AUC at 0.6 mg,1 mg, 2 mg, or 3 mg Eszopiclone dose.



Following table represents the pharmacokinetic parameters of desmethyl zopiclone following 1 mg, 2 mg, or 3 mg eszopiclone.

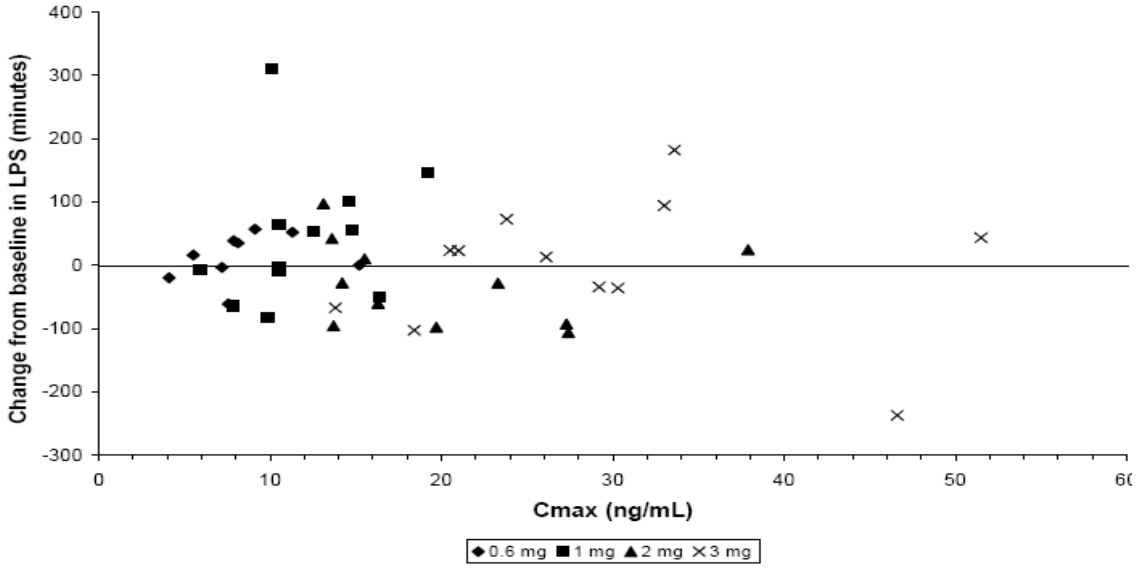
Mean ± SD Pharmacokinetic Parameters (S)-DMZ Following Single Dose of 0.6 mg, 1 mg, 2 mg, or 3 mg.

Parameter	Eszopiclone Dose Group											
	0.6 mg (N=9)			1 mg (N = 13)			2 mg (N = 11)			3 mg (N = 12)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max} (ng/mL)	1	2.24	NC	1	2.31	NC	5	2.69	(0.81)	10	4.46	(2.21)
t_{max} (hrs)	1	2.00	(2.00-2.00)	1	6.00	(6.00-6.00)	5	6.00	(1.50-6.00)	10	6.00	(2.00-12.0)
$AUC_{(0\text{-last})}$ (ng•hr/mL)	1	8.83	NC	1	19.0	NC	5	29.1	(10.9)	10	47.0	(21.1)
$AUC_{(0\text{-}\infty)}$ (ng•hr/mL)	0	NC	NC	0	NC	NC	1	56.6	NC	6	65.7	(19.0)
$t_{½}$ (hrs)	0	NC	NC	0	NC	NC	3	21.8	(17.7)	7	6.61	(2.02)

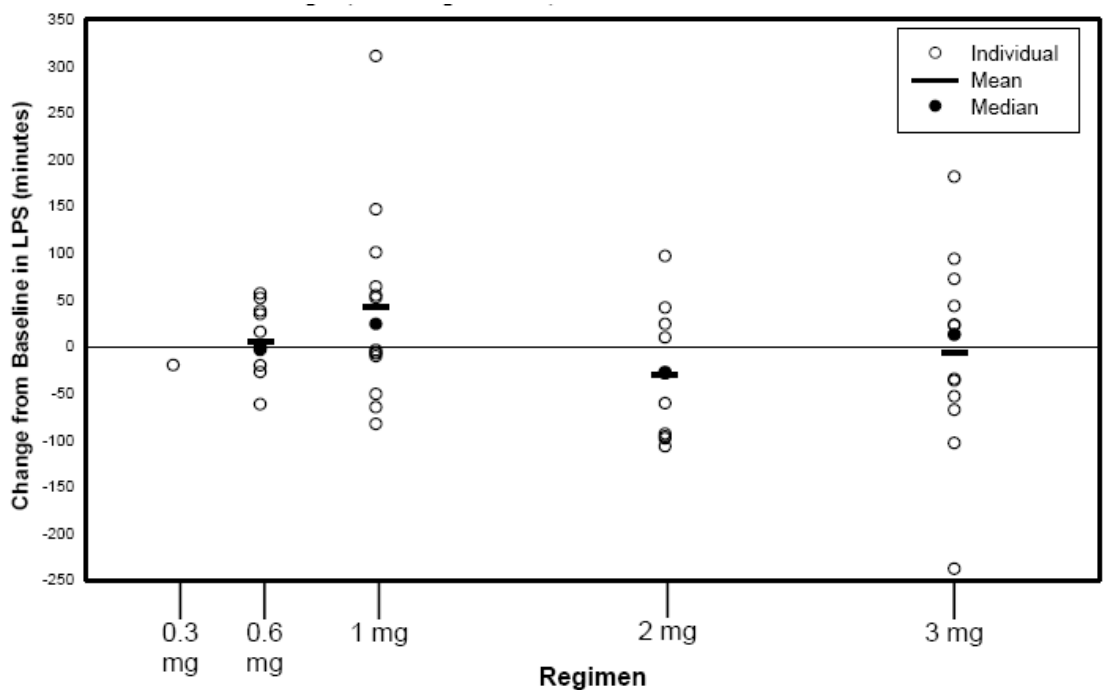
PHARMACODYNAMIC RESULTS:

- PSG and sleep architecture parameters were variable between individual subjects.
- There were no apparent relationships between PK (Cmax and AUC[0-last]) and PD (latency to persistent sleep [LPS], total sleep time [TST] and wake time after sleep onset [WASO]) parameters in this population (figure below).

Scatter Plot of Change from Baseline in Latency to Persistent Sleep (LPS, the primary PD end point) Based on PSG vs. Cmax for Eszopiclone



Scatter Plot of Change from Baseline in Latency to Persistent Sleep (LPS, the primary PD end point) Based on PSG vs. Dose for Eszopiclone



Tables below show individual, mean, and median change in LPS, TST, Sleep Efficiency, WASO following single oral doses of 0.6 mg, 1 mg, 2 mg, or 3 mg

Polysomnography - Latency to Persistent Sleep (minutes)

		Eszopiclone Dose Group (Actual)				
Visit/Timepoint	**Statistic**	**0.3 mg (N=1)**	**0.6 mg (N=10)**	**1 mg (N=13)**	**2 mg (N=12)**	**3 mg (N=13)**
Visit 1/Screening	n	1	10	13	12	13

	Mean	28.00	60.65	69.54	110.71	152.65
	SD	NA	28.98	51.00	64.13	134.82
	Median	28.00	54.50	44.00	106.00	79.50
	Minimum	28.0	29.5	33.5	33.5	46.5
	Maximum	28.0	124.0	206.5	229.5	527.0
Visit 2/ Change from Baseline Values	n	1	10	13	12	13
	Mean	-19.50	8.65	38.96	-30.33	-6.15
	SD	NA	38.14	105.06	64.41	102.77
	Median	-19.50	8.00	-3.50	-28.25	13.00
	Minimum	-19.5	-61.5	-82.5	-106.5	-237.5
	Maximum	-19.5	57.0	311.0	97.0	182.0

Total Sleep Time (minutes)

		Eszopiclone Dose Group			
Visit/Timepoint	**Statistic**	**0.6 mg (N=12)**	**1 mg (N=12)**	**2 mg (N=12)**	**3 mg (N=13)**
Visit 1/Screening	n	12	12	12	13
	Mean	439.25	422.17	377.13	369.58
	SD	58.87	76.40	66.98	113.30
	Median	430.00	430.50	383.50	398.00
	Minimum	353.5	274.0	265.0	80.5
	Maximum	548.0	526.0	530.5	512.0
Visit 2/ Change from Baseline Values	n	12	12	12	13
	Mean	43.08	-10.63	80.50	16.27
	SD	61.89	109.89	82.28	116.66
	Median	26.25	6.75	70.75	43.50
	Minimum	-31.5	-279.5	-32.5	-188.5
	Maximum	193.0	162.0	254.5	219.0

Sleep Efficiency (minutes)

		Eszopiclone Dose Group			
Visit/Timepoint	**Statistic**	**0.6 mg (N=12)**	**1 mg (N=12)**	**2 mg (N=12)**	**3 mg (N=13)**
Visit 1/Screening	n	12	12	12	13
	Mean	83.15	80.86	69.20	67.64
	SD	7.28	12.12	10.39	19.95
	Median	86.32	85.31	70.58	76.67
	Minimum	68.1	51.6	55.0	14.9
	Maximum	91.4	92.0	88.4	88.4
Visit 2/ Change from Baseline Values	n	12	12	12	13
	Mean	1.64	-3.78	12.66	0.28
	SD	8.23	19.09	13.99	19.97
	Median	3.68	-1.71	13.87	5.27

	Minimum	-9.1	-51.6	-4.7	-34.9
	Maximum	19.3	22.6	42.4	37.6

Wake Time After Sleep Onset (minutes)

Visit/Timepoint	Statistic	Eszopiclone Dose Group			
		0.6 mg (N=12)	1 mg (N=12)	2 mg (N=12)	3 mg (N=13)
Visit 1/Screening	n	12	12	12	13
	Mean	33.63	36.50	70.83	33.77
	SD	25.93	31.30	75.65	26.82
	Median	22.25	29.50	36.25	33.00
	Minimum	7.5	2.5	2.5	0.0
	Maximum	95.5	111.0	236.5	85.5
Visit 2/ Change from Baseline Values	n	12	12	12	13
	Mean	-4.50	-21.67	-45.71	6.12
	SD	31.18	34.56	79.92	59.23
	Median	-2.25	-15.00	-19.50	3.50
	Minimum	-78.0	-109.5	-230.5	-55.0
	Maximum	60.0	17.5	49.0	183.0

CONCLUSIONS:

- Pharmacokinetic parameter $AUC_{0\text{-}inf}$ was dose proportional. However, C_{max} and $AUC_{0\text{-}t}$ were approximately dose proportional. Body weight and BSA were statistically significant covariates; their impact upon dose proportionality was relatively small. Gender was not a statistically significant covariate.

- Plasma concentrations of (S)-DMZ were approximately 6.5-fold lower than for the parent drug.

- Sleep parameters were variable between individual subjects.

- There was no apparent relationship observed between PK and PD parameters.

VIII. PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRICS REVIEW

SUMMARY OF FINDINGS

The sponsor performed the population pharmacokinetic analyses using data from two Phase I studies (190-201, 190-202) to characterize the PK disposition of eszopiclone and to identify any covariate which influences the PK of eszopiclone in adolescents and children with attention deficit hyperactivity disorder (ADHD)-associated insomnia. The study of 190-201 included 36 male and female adolescents 12 to 17 years of age who received single oral eszopiclone doses of 1.0 mg, 2.0 mg, or 3.0 mg, and there were 49 male and female children 6 to 11 years of age who were assigned to single oral eszopiclone doses of 0.6 mg, 1.0 mg, 2.0 mg, or 3.0 mg in the study of 190-202.

Blood samples were drawn at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 18 hours post-dose in the study of 190-201, and they were measured at pre-dose and 0.5, 1, 1.5, 2, 6, 12, and 18 hours post-dose in the study of 190-202.

The summary of patients' characteristics in two studies is presented in Table 1.

Here is the summary of findings from the sponsor's analyses:

1. The final population PK model was a 1-compartment model with first-order absorption, absorption lag time and first-order elimination, parameterized in terms of absorption rate constant (ka), absorption lag time (Tlag), apparent oral clearance (CL/F), and apparent volume of distribution (V/F), with interindividual variability (IIV) estimated for ka, Tlag, CL/F, and V/F using exponential error models (**Table 2**, Figure 1)

2. Body weight (or age) was the only covariate that had a significant effect on apparent clearance and volume of distribution, and there was no other covariates which influenced the PK of eszopiclone (**Figure 2**).

3. Simulations using the final PK model were performed to predict the eszopiclone concentration-time profiles after single oral doses of 1 mg and 2 mg in children 6 to 11 years of age and single oral doses of 2 mg and 3 mg in adolescents 12 to 17 years of age. The simulation results showed that

- Systemic exposure as determined by CL/F (or AUC) was similar between adolescent subjects (12 to 17 years of age) and healthy adults.

    - The mean (SD) AUC for a 3.0-mg dose in adolescents 12 to 17 years of age and the mean (SD) AUC for a 2.0-mg dose in children 6 to 11 years of age are 198.48 (65.60) ng•h/mL and 175.73 (58.77) ng•h/mL, respectively.
    - These predicted exposure values are similar to the mean (SD) AUC (dose-normalized to 3 mg) in non-elderly healthy adults after multiple doses of eszopiclone (197.9 (51.5) ng•h/mL (Table 3, Figure 3).
- There was an inverse relationship between body weight and exposure (AUC). since body weight and age are highly correlated, a dose range of 1.0 to 2.0 mg was recommended for study in children 6 to 11 years of age and 2.0 to 3.0 mg in adolescents.

Reviewer's comment: The sponsor's population PK analyses are acceptable.

Table 1. The summary of covariates included in the population PK model by the study.

Covariates		Study 190-201	Study 190-202
Age (y)	Mean (SD)	14.06 (1.43)	8.69 (1.47)
	Median	14.00	9.00
	Minimum, Maximum	12.0, 17.0	6.0, 11.0
	N	36	49
Weight (kg)	Mean (SD)	58.29 (16.57)	33.46 (10.94)
	Median	56.95	30.80
	Minimum, Maximum	30.4, 101.8	19.5, 61.2
	N	36	49
Body surface area (m^2)	Mean (SD)	1.63 (0.27)	1.13 (0.21)
	Median	1.60	1.10
	Minimum, Maximum	1.1, 2.3	0.8, 1.6
	N	36	49
Creatinine clearance (mL/min/1.73 m^2)	Mean (SD)	147.15 (28.94)	140.14 (32.55)
	Median	143.70	136.20
	Minimum, Maximum	91.1, 203.3	83.3, 298.2
	n	36	49
Creatinine clearance capped at 160 mL/min (mL/min/1.73 m^2)	Mean (SD)	139.97 (19.50)	135.23 (19.24)
	Median	143.70	136.20
	Minimum, Maximum	91.1, 160.0	83.3, 160.0
	N	36	49
Total bilirubin (mg/dL)	Mean (SD)	0.49 (0.28)	0.31 (0.17)
	Median	0.40	0.30
	Minimum, Maximum	0.2, 1.3	0.1, 0.8
	N	36	49
Alanine aminotransferase (U/L)	Mean (SD)	13.83 (6.46)	14.24 (4.16)
	Median	12.50	13.00
	Minimum, Maximum	6.0, 42.0	8.0, 24.0
	N	36	49
Race, n (%)	White	26 (72.2)	36 (73.5)
	Black or African American	8 (22.2)	9 (18.4)
	Native Hawaiian or Other Pacific Islander	1 (2.8)	0 (0.0)
	Multiple	0 (0.0)	4 (8.2)
	Other	1 (2.8)	0 (0.0)
Sex, n (%)	Male	23 (63.9)	31 (63.3)
	Female	13 (36.1)	18 (36.7)

Covariates		Study 190-201	Study 190-202
Concomitant use of methylphenidate-like agents, n (%)	No	20 (55.6)	29 (59.2)
	Yes	16 (44.4)	20 (40.8)
Concomitant use of amphetamine-like agents, n (%)	No	30 (83.3)	30 (61.2)
	Yes	6 (16.7)	19 (38.8)

Abbreviations: SD, standard deviation.

Table 2. The parameter estimates from the sponsor's final PK model.

	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
Parameter	Typical Value	%SEM	Final Estimate	%SEM
Absorption rate constant - k_a (1/h)	1.33	13.8	105.4	15.3
Absorption lag time - T_{lag} (h)	0.295	12.6	72.5	44.0
Apparent clearance - CL/F (L/h)	13.1	3.3	28.7	20.4
Effect of weight on CL/F as a power function	0.425	13.7		
Apparent volume of distribution - V/F (L)	89.8	3.4	22.0	38.6
Effect of weight on V/F as a power function	0.720	11.7		
IIV covariance term (CL/F and V/F)	0.0475	25.7	NE	NA
IIV covariance term (k_a and T_{lag})	-0.196	63.3	NE	NA
Residual variability*	0.21	20.1	NA	NA
Minimum value of the objective function = -616.60				

Abbreviations: %CV, percent coefficient of variation; NA, not applicable; NE, not estimated; %SEM, percent standard error of the mean.

*Residual variability was reported as standard deviation in log concentration units.

Table 3. Summary statistics of the individual parameter estimates from the simulation.

Subject Characteristic		6 - 11 Years		12 - 17 Years	
		1 mg	2 mg	2 mg	3 mg
AUC (ng × h/mL)	Mean (SD)	88.08 (26.20)	175.73 (58.77)	133.83 (45.10)	198.48 (65.60)
	Median	85.88	164.73	126.60	188.42
	Minimum, Maximum	29.2, 188.4	60.2, 447.9	47.0, 363.9	77.4, 473.4
	n	500	500	500	500
C_{max} (ng/mL)	Mean (SD)	10.06 (3.74)	19.97 (7.11)	12.95 (4.62)	19.16 (7.06)
	Median	9.75	18.95	12.49	18.38
	Minimum, Maximum	1.5, 25.5	4.4, 47.5	2.5, 32.3	4.8, 49.7
	n	500	500	500	500
T_{max} (h)	Mean (SD)	2.52 (1.57)	2.47 (1.48)	2.72 (1.83)	2.79 (1.79)
	Median	2.16	2.18	2.27	2.30
	Minimum, Maximum	0.2, 10.6	0.3, 9.5	0.3, 15.7	0.4, 11.3
	n	500	500	500	500
Elimination $t_{1/2}$ (h)	Mean (SD)	4.56 (1.00)	4.54 (1.02)	5.45 (1.16)	5.47 (1.15)
	Median	4.46	4.46	5.34	5.30
	Minimum, Maximum	2.4, 8.6	2.4, 8.5	2.6, 9.7	3.0, 10.5
	n	500	500	500	500
Absorption $t_{1/2}$ (h)	Mean (SD)	0.86 (1.17)	0.82 (1.03)	0.91 (1.39)	0.90 (1.10)
	Median	0.51	0.51	0.51	0.49
	Minimum, Maximum	0.0, 13.6	0.0, 8.8	0.0, 16.1	0.0, 10.2
	n	500	500	500	500

Figure 1. Dose- normalized eszopiclone concentrations versus time after dose for each dose level.

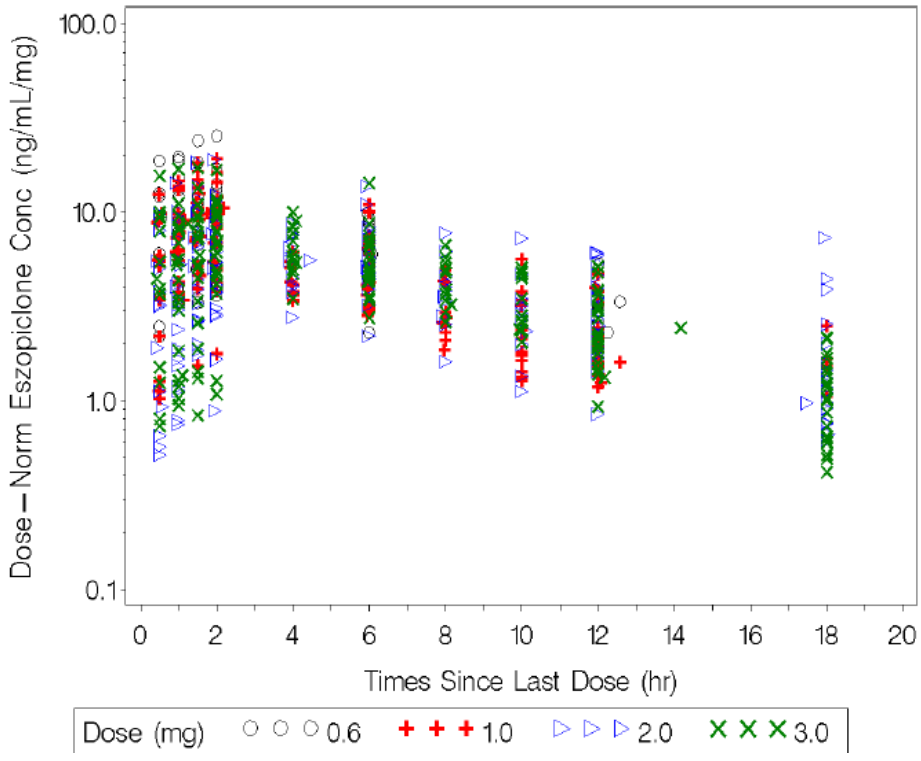


Figure 2. The relationship between covariates and CL/F. Delta CL on the Y-axis indicate individual parameter estimates subtracted by typical (population mean) value of parameter.

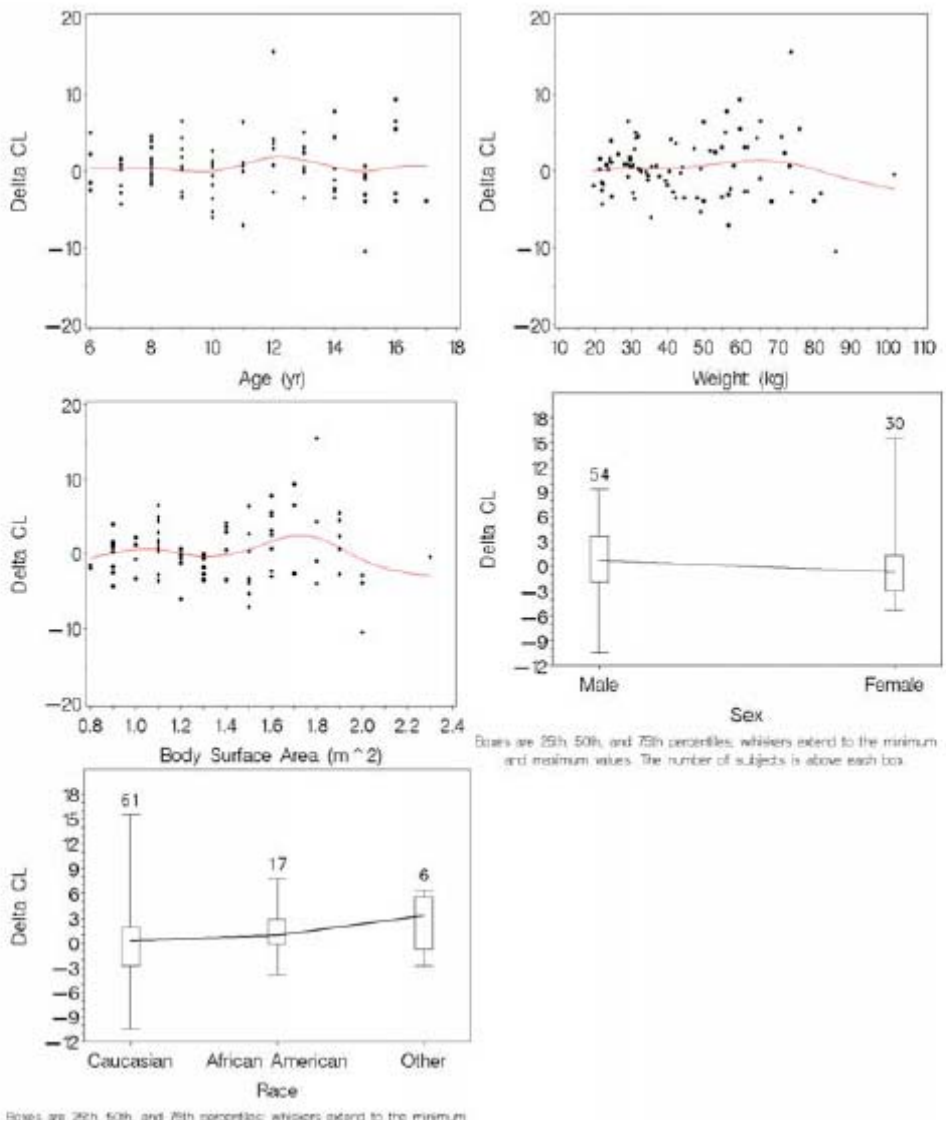


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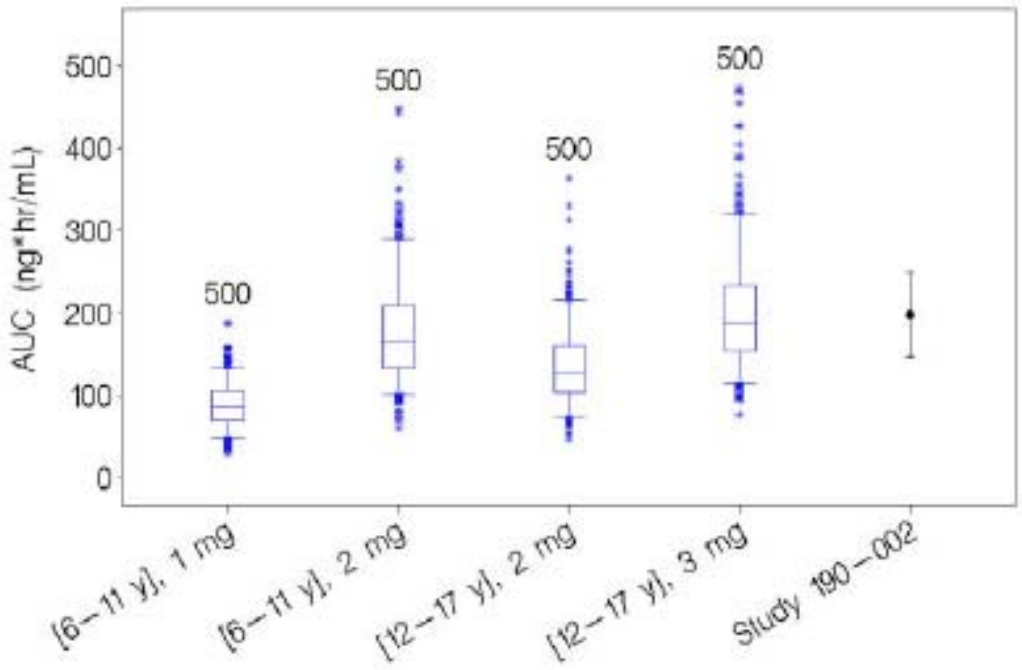
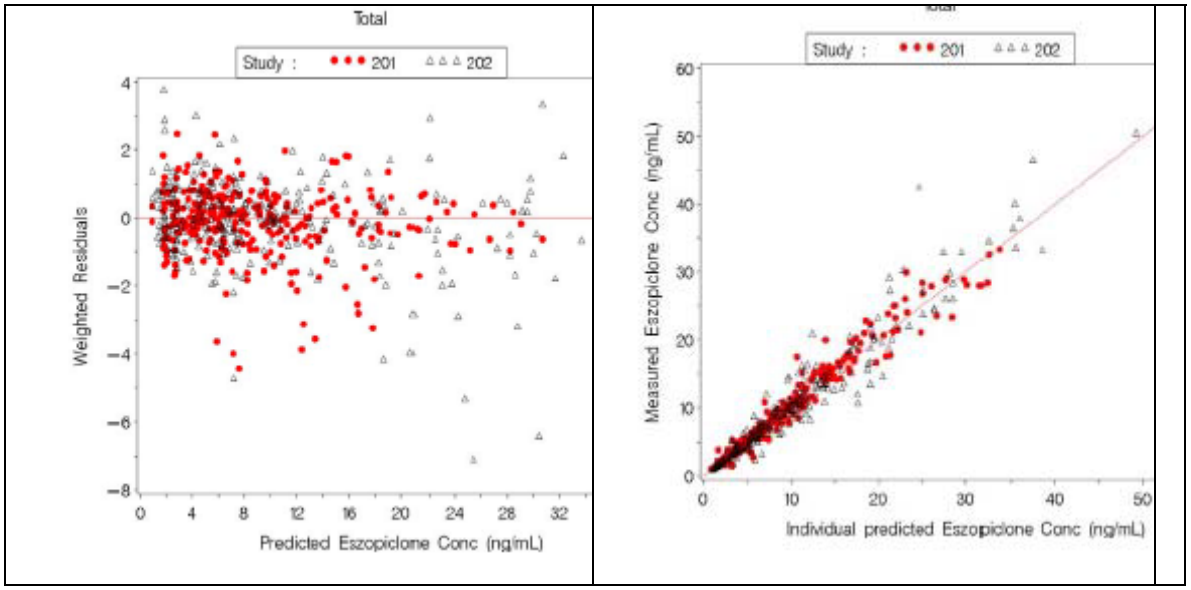
Figure 3. Comparisons between simulated eszopiclone pediatric exposures and exposures in non-elderly adults (dose-normalized to 3 mg) after multiple doses in the study of 190-002.

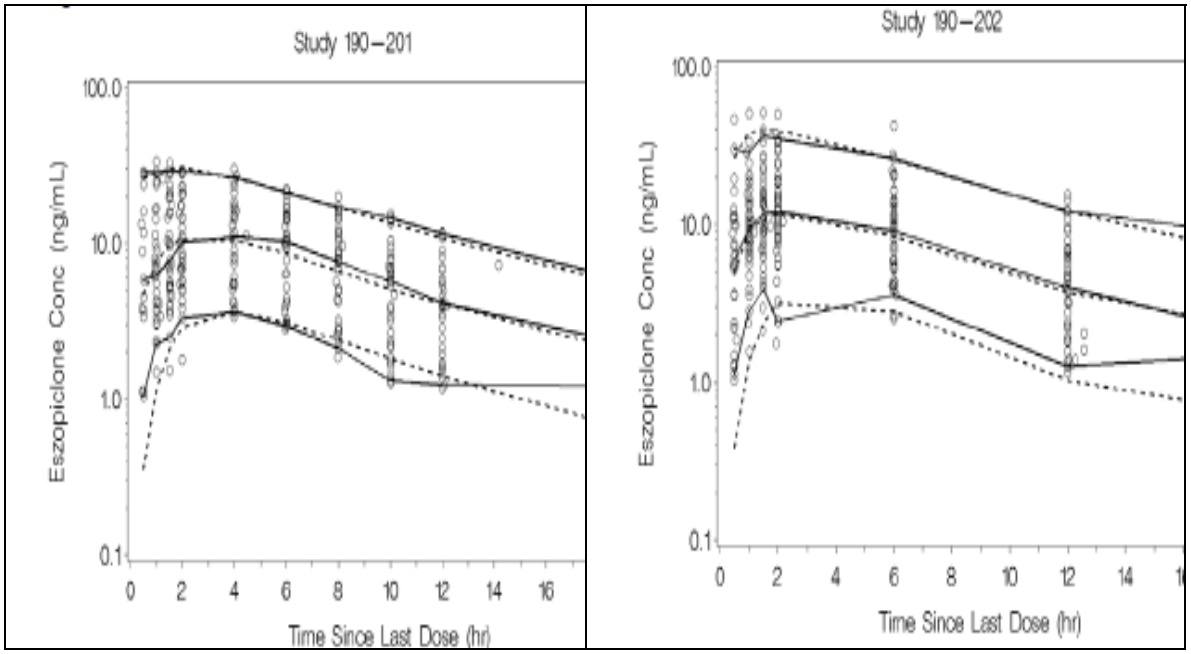


Appendix

1. Model diagnostics: The left panel shows weighted residual vs. predicted concentration, and the right panel shows the relationship between observed and predicted concentration.



2. Visual Predictive Check of the Pharmacokinetic Model Stratified by Study : the solid lines are the percentiles (5^{th}, 50^{th}, 95^{th}) of observed data, and the dotted lines indicate the percentiles (5^{th}, 50^{th}, 95^{th}) from predicted values.



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