A Pharmacokinetic and Safety Evaluation of Single Oral Doses of Eszopiclone in Pediatric Subjects from 6 to 17 Years of Age with Attention Deficit Hyperactivity Disorder and Insomnia

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Introduction

- Eszopiclone is a single-isomer, nonbenzodiazepine, cyclopyrrolone agent that has demonstrated efficacy with both polysomnography (PSG) and patient-reported measures in non-elderly adults with chronic primary insomnia in long-term and short-term studies.[1-6]
- Following oral administration in healthy adults, maximum eszopiclone plasma drug concentration (T_{max}) occurs at 1 hour post-dose.[7] Eszopiclone is primarily metabolized by CYP3A4 and CYP2E1 to (S)-N-desmethylzopiclone and (S)-zopiclone-N-oxide.
- The pharmacokinetics (PK) for eszopiclone are linear over the range of 1.0 to 6.0 mg daily in adults.[8]
- Two Phase I studies were conducted in pediatric subjects with attention deficit hyperactivity disorder (ADHD) associated insomnia to characterize the safety and PK profile following single dose administration at bedtime.
- Pharmacokinetic modeling and simulation were used in the clinical development program for eszopiclone in pediatric insomnia, in part, as a basis for dose selection.

Objective

- To determine the safety and PK profile of single oral doses of eszopiclone administered at bedtime in pediatric subjects 6 - 17 years of age with ADHD-associated insomnia.
- Utilize modeling and simulation approaches to support dose selection for Phase III.

Methods

Study Design and Data

- Phase 1, single-dose, multicenter, randomized, open-label, dose-escalation, in-clinic studies of the PK, tolerability, and safety of eszopiclone in male and female subjects (children aged 12 - 17 years in Study 190-201 and adolescents aged 6 - 11 years in Study 190-202).
- Eszopiclone was administered in both studies as an immediate-release tablet taken with water, approximately 30 minutes prior to bedtime.
- Doses administered were: 0.6 mg (Study 190-202 only), 1.0 mg, 2.0 mg, or 3.0 mg.

Data Analysis

- Noncompartmental PK analysis was performed using standard methods with WinNonlin® Professional (Version 5.2).[9]
- The relationships between latency to persistent sleep (LPS) based on PSG, total sleep time (TST), and wake time after sleep onset (WASO) versus eszopiclone exposure were explored for Studies 190-201 and 190-202.
- Population PK analysis was performed using NONMEM, Version V, Level 1.1.[10] and included estimation of between-patient (interindividual) variability (IIV) in PK parameters and within-patient (residual) variability (RV) in drug concentrations.
- Covariates assessed were age, body weight, race, and sex.

Simulations

- Simulations of 4 dosing regimens were performed: single oral eszopiclone doses of 1 mg and 2 mg for children 6 to 11 years of age, and doses of 2 mg and 3 mg in adolescents 12 to 17 years of age.
- Populations of 500 children and 500 adolescents in the corresponding age ranges were randomly generated using pediatric demographic information (age, weight, and gender) from the National Health and Nutrition Examination Survey (NHANES) database.[11]
- Predicted eszopiclone exposures were: area under the concentration-time curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), and half-life of the terminal elimination phase ($t_{1/2}$).

Results

Data Description

- 594 eszopiclone concentrations from 85 subjects were available for analysis.
- Demographic characteristics are shown in **Table 1**.
- There were no deaths, SAEs, or discontinuations due to AEs. Additionally there were no clinically significant laboratory tests, vital signs, ECG findings or dose dependent findings; headache was the only AE reported more than once in cohort. All AEs were mild or moderate in intensity.

Table 1. Demographic Characteristics

Covariates		Study 190-201	Study 190-202
Age (y)	Mean (SD)	14.56 (1.56)	9.19 (1.50)
	Minimum, Maximum	12.1, 17.3	6.3, 11.9
	N	36	49
Weight (kg)	Mean (SD)	58.29 (16.57)	33.46 (10.94)
	Minimum, Maximum	30.4, 101.8	19.5, 61.2
	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)

Abbreviations: SD, standard deviation.

Noncompartmental PK Analysis and Graphical PKPD Assessment

- Mean eszopiclone plasma concentrations increased with dose as shown in **Figure 1A-B**.
- The mean PK parameters of eszopiclone for adolescents (Study 190-201) and children (Study 190-202) are shown in **Table 2** and **Table 3**, respectively.
- The relationship between C_{max} and LPS is presented in **Figure 2A-B.**[12,13] Similar outcomes were seen with TST and WASO (data not shown).

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

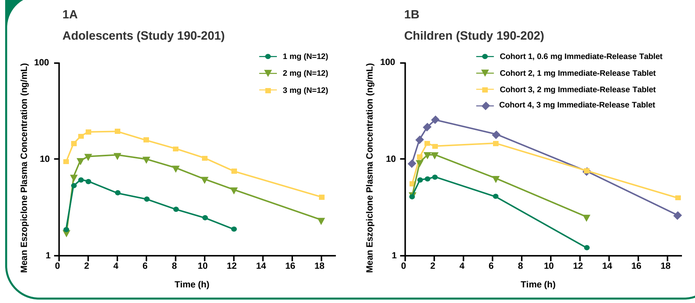


Table 2. Mean (SD) Pharmacokinetic Parameters of Eszopiclone in Adolescents Following Single Dose of 1 mg, 2 mg, or 3 mg (Study 190-201)

	Eszopiclone Dose Group								
	1 mg (N=11)			2 mg (N=12)			3 mg (N=12)		
Parameter	**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
t_{max} (hrs)[a]	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
$t_{1/2}$ (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

Abbreviations: C_{max}=Maximum observed concentrations; $AUC_{(0\text{-}last)}$=Area under the drug concentration-time curve from time 0 to the time fo the last postdose quantifiable concentration; $t_{1/2}$=Terminal half-life; t_{max}=Time of occurrence of C_{max}; $AUC_{(0\text{-}\infty)}$=Area under the drug concentration-time curve from time 0 to infinity; SD=Standard deviation; Cl/F=Apparent oral clearance; Vd.F=Apparent volume of distribution.

Note: The last measured timepoint was 18 hours. Note: All values are rounded to 3 significant figures.

[a]The median (minimum-maximum) are reported for t_{max}.

Table 3. Mean (SD) Pharmacokinetic Parameters of Eszopiclone in Children Following Single Dose of 1 mg, 2 mg, or 3 mg (Study 190-202)

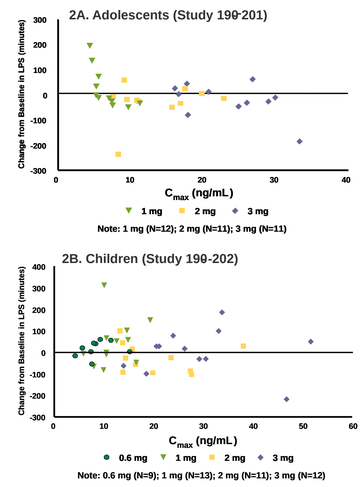
	0.6 mg (N=9)			1 mg (N=13)			2 mg (N=11)			3 mg (N=12)		
Parameter	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max} (ng/mL)	9	8.44	3.25	13	11.8	3.62	11	20.2	7.97	12	29.0	11.2
t_{max} (hrs)[a]	9	2.00	1.00-6.00	13	1.53	1.00-6.00	11	1.52	1.50-6.00	12	2.00	0.50-6.00
$AUC_{(0\text{-}last)}$ (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
$t_{1/2}$ (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

Abbreviations: C_{max}=Maximum observed concentrations; $AUC_{(0\text{-}last)}$=Area under the drug concentration-time curve from time 0 to the time fo the last postdose quantifiable concentration; $t_{1/2}$=Terminal half-life; t_{max}=Time of occurrence of C_{max}; $AUC_{(0\text{-}\infty)}$=Area under the drug concentration-time curve from time 0 to infinity; SD=Standard deviation; Cl/F=Apparent oral clearance; Vd.F=Apparent volume of distribution.

Note: The last measured timepoint was 18 hours. Note: All values are rounded to 3 significant figures.

[a]The median (minimum-maximum) are reported for t_{max}.

Figure 2. Scatter Plot of Change From Baseline in LPS Based on PSG Versus C_{max} for Eszopiclone in Adolescents (Study 190-201) and Children (Study 190-202) BECOMES 2AB



Population PK Model Development

- A 1-compartment model with first-order absorption, absorption lag time, and first-order elimination was found to be an appropriate model to fit these data (**Table 4**).
- Body weight was included in the base structural model as an allometric function to describe the variability in CL/F and V/F related to body size.
- Eszopiclone CL/F is increased with increasing body weight (typical eszopiclone CL/F is13.1 L/h).
- Eszopiclone V/F is increased with increasing body weight (typical V/F is 89.8 L).
- **Figure 3** displays a goodness-of-fit plot for the final population PK model.

Simulations

- Simulated eszopiclone pediatric exposures and the mean (SD) eszopiclone exposures obtained in non-elderly healthy adults following multiple-dose administration in Study 190-002[8] are compared in **Figure 4**.
- 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 x h/mL and 175.73 (58.77) ng x h/mL, respectively.
- The predicted exposure values in adolescents and children 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 x h/mL).

Table 4. Parameter Estimates and Standard Errors for the Pharmacokinetic Model

	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
Parameter	**Typical Value**	**%SEM**	**Final Estimate**	**%SEM**
Absorption rate constant - ka (1/h)	1.33	13.8	105.4	15.3
Absorption lag time - Tlag (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 (ka and Tlag)	-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.

Note: After selection of the final PK model, a dose record error was identified for 2 subjects. Subject 190202-0114-S002 in the 0.6-mg dose group received a dose of 0.3 mg by mistake; Subject 190202-0105-S001 in the 0.6-mg dose group received a dose of 1 mg by mistake. Therefore, the analysis dataset was updated as follows: Subject 190202-0114-S002 was excluded from the analysis; the dose for Subject 190202-0105-S001 was changed to 1 mg. The values in this table reflect the modeling results from the updated dataset.

Figure 3. Goodness-of-Fit Plots for the Pharmacokinetic Model

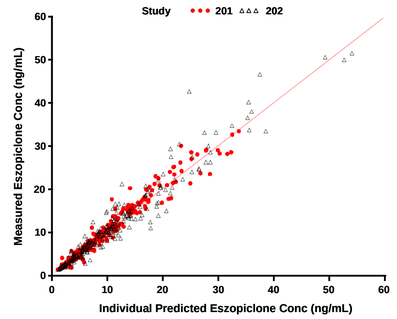
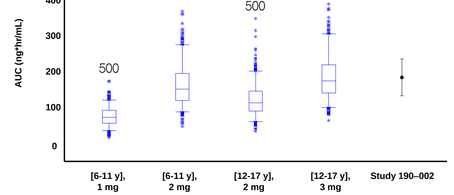


Figure 4. Comparisons of Simulated Eszopiclone Pediatric Exposures and Exposures in Non-Elderly Adults (Dose-Normalized to 3 mg) After Multiple Doses in Study 190-002



Boxes are 25th, 50th, and 75th; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of subjects is above each box. For Study 190–002, the dot represents the mean and the horizontal lines are one standard deviation.

Conclusions

- The population PK analysis indicated that apparent oral clearance and volume of distribution of eszopiclone increased with body weight.
- Based upon the population PK analysis in children and adolescent subjects, and the non-compartmental PK data from Studies 190-201 and 190-202, administration of 2 mg in children and 3 mg in adolescents resulted in similar drug exposures.
- Assessment of the 4 simulated dosing regimens in children and adolescents demonstrated that the distribution of modeled AUC's in children given 2 mg and adolescents administered 3 mg QD respectively compared favorably to the systemic exposure observed in adult subjects given 3 mg QD. These simulations provided further evidence supporting the doses selected for Phase III.
- Based on visual data inspection, there were no apparent relationships between eszopiclone exposure and LPS.
- In these studies, single doses of eszopiclone were well tolerated in pediatric subjects.

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