Eszopiclone for Insomnia Associated With Attention-Deficit/Hyperactivity Disorder

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KEY WORDS

eszopiclone, ADHD, pediatric insomnia, benzodiazepine agonist

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
AE—adverse event
ANCOVA—analysis of covariance
CGI-I—Clinical Global Impression of Improvement
CGI-S—Clinical Global Impression of Severity
C-SSRS—Columbia Suicide Severity Rating Scale
GABA—γ-aminobutyric acid
ITT—intent-to-treat
LPS—latency to persistent sleep
PDSS—Pediatric Daytime Sleepiness Scale
PSG—polysomnography
QTcF—QT interval corrected using Fridericia's formula
WASO—wake time after sleep onset

Drs Sangal and Lankford coordinated and supervised data collection at 1 site, contributed to the conceptualization and initial draft of the manuscript, and critically reviewed and revised the manuscript; Dr Blumer assisted in the initial conceptualization and design of the trial and then participated in its oversight and contributed to the initial conceptualization of the manuscript and then participated in its reviews and revision; Dr Huang carried out the initial analyses and reviewed and revised the manuscript; Mr Grinnell contributed to the conceptualization and initial draft of the manuscript and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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This trial has been registered at www.clinicaltrials.gov (identifiers NCT00856973 and NCT00857220).

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WHAT'S KNOWN ON THIS SUBJECT: Sleep disorders are common in children and adolescents and have a substantial negative impact on daily life and school performance. Long-term evaluations of the efficacy and safety of pharmacologic treatment options for sleep disorders are lacking in pediatric patients.

WHAT THIS STUDY ADDS: These 2 studies provide the first evaluation of the effectiveness and safety of eszopiclone in children and adolescents with insomnia associated with ADHD. Data presented here encompass longer-term (up to 1 year) pediatric exposure to eszopiclone.

abstract

OBJECTIVE: To evaluate efficacy and safety of eszopiclone compared with placebo in children and adolescents with insomnia associated with attention-deficit/hyperactivity disorder (ADHD).

METHODS: A 12-week, randomized, double-blind, placebo-controlled trial evaluated efficacy and safety of high- or low-dose eszopiclone (1 or 2 mg in children aged 6–11 years, 2 or 3 mg in children ages 12–17 years), given every evening, in 486 patients with ADHD-related insomnia. The primary efficacy variable was change in latency to persistent sleep from baseline to week 12, based on polysomnography. Key secondary measures were polysomnography-measured wake time after sleep onset, Clinical Global Impression Parent/Caregiver and Child scales, and the Conners' ADHD rating scales. The safety of eszopiclone was further studied over 1 year of open-label treatment in 55 patients who completed the double-blind study, and 249 patients with no previous eszopiclone exposure.

RESULTS: Neither low-dose nor high-dose eszopiclone significantly reduced latency to persistent sleep compared with placebo after 12 weeks of treatment. Secondary outcomes were considered nonsignificant based on the hierarchical statistical analysis plan. The most frequent treatment-emergent adverse events over 12 weeks with eszopiclone were headache, dysgeusia, and dizziness. The study results demonstrated that eszopiclone was well tolerated over 1 year of treatment, with 11.2% of patients discontinuing open-label treatment because of an adverse event.

CONCLUSIONS: Eszopiclone (up to 3 mg) failed to reduce latency to persistent sleep on polysomnography after 12 weeks in children aged 6 to 17 years with ADHD-related insomnia. Eszopiclone was well tolerated in the 1-year study. *Pediatrics* 2014;134:e1095–e1103

Insomnia and other sleep difficulties are common in children and adolescents, particularly those with attention-deficit/hyperactivity disorder (ADHD).[1–7] The prevalence of pediatric insomnia in the general population ranges from 1% to 6% when considering symptoms beyond bedtime refusal and night wakings.[4] In community-based studies of adolescents aged 11 to 17 years, the prevalence of insomnia, based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria, was 5.1% to 9.4%.[2,7] Sleep difficulties affect as many as 50% to 60% of children and adolescents with ADHD.[4] Moreover, the effects of stimulant medications do not fully account for the sleep disturbances observed in ADHD patients.[3] Chronic pediatric sleep disturbance has a negative impact on the health and well-being of affected children and adolescents and their families.[7,8]

There is a dearth of research evaluating the efficacy and safety of pharmacologic agents to treat these sleep difficulties in pediatric populations,[4,9] and none of the products currently approved to treat insomnia in adults are indicated for use in pediatric populations. Thus, a wide range of over-the-counter and prescription products are used to treat insomnia and other sleep difficulties in children and adolescents, with little evidence of efficacy.[4,8–12]

A randomized, double-blind, placebo-controlled study of zolpidem in the treatment of ADHD-related insomnia in children (aged 6–11 years) and adolescents (aged 12–17 years) found no significant difference between zolpidem and placebo in reduction of sleep latency after 4 weeks of treatment, although zolpidem provided better Clinical Global Impression of Improvement (CGI-I) scores for adolescents.[13] Overall, 62.5% of zolpidem-treated patients and 47.7% of patients receiving placebo experienced at least 1 treatment-emergent adverse event (AE). The most common AEs in patients receiving zolpidem were dizziness (24%), headache (13%), and hallucinations (7%). The failure of this zolpidem study underscores a persistent need to identify effective therapies for this patient population. The studies reported here evaluated the efficacy and safety of eszopiclone in the treatment of ADHD-related insomnia using polysomnography (PSG) and actigraphy[14] to measure objective sleep parameters and standardized, validated instruments to assess daytime functioning and behavior. The safety of eszopiclone was evaluated by monitoring the incidence of AEs, vital signs, clinical laboratory parameters, and suicidal ideation/behavior (using the Columbia Suicide Severity Rating Scale [C-SSRS][15]).

METHODS

Protocols for both studies were approved by institutional review boards. Written informed consent from parents or legal guardians and informed assent from each patient were obtained before study participation. Investigators and other study personnel received training in the administration of outcome measures to enhance the consistency of assessments. Patients received nominal compensation for study visits and overnight PSG visits, as approved by the institutional review boards.

Randomized Controlled Trial (Study 190-246)

This randomized, double-blind, placebo-controlled, multicenter study was conducted at 63 sites in the United States from April 2009 through July 2011. The objective was to evaluate the efficacy and safety of eszopiclone in the treatment of children and adolescents with ADHD-associated insomnia.

Patients

The study enrolled children (aged 6–11 years) and adolescents (aged 12–17 years) with a diagnosis of ADHD (defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria and confirmed by the M.I.N.I. International Neuropsychiatric Interview for Children and Adolescents)[16,17] and complaints of insomnia. Insomnia was defined as difficulty with sleep initiation or consolidation, as described by the patient or parent/legal guardian, despite adequate age-appropriate time and opportunity for sleep. Enrolled patients were required to have latency to persistent sleep (LPS) >30 minutes or wake time after sleep onset (WASO) >45 minutes as determined by baseline PSG, insomnia not attributable to the direct effects of a drug of abuse or misuse of prescription medication, and daytime functional impairment as a result of sleep problems (reported by patient or parent). Eligible patients were in general good health, without significant previous or current medical conditions or clinically relevant abnormalities on physical examination, clinical laboratory assessments, or electroencephalogram. Exclusion criteria included another primary sleep disorder, other major psychiatric disorders (ie, bipolar I or II disorder, major depression, conduct disorder, generalized anxiety disorder [other than obsessive-compulsive disorder], or any history of psychosis), current alcohol or substance abuse or history of abuse within 3 months of study participation, tobacco/nicotine use within the past 30 days, or a history of an adverse experience with zopiclone or eszopiclone. Patients were stabilized on all long-term therapies, including ADHD treatment, for a least 1 month before study participation. Energy drinks, herbal products, over-the-counter sleep aids, and medications with sympathomimetic activity were prohibited. Female patients of childbearing age agreed to use birth control.

Procedures

A 12-week double-blind treatment period to assess efficacy and safety was followed by a 2-week, single-blind washout period to assess rebound

effects. Eligible patients were randomized to receive low-dose eszopiclone (1 mg for children aged 6–11, 2 mg for adolescents aged 12–17), high-dose eszopiclone (2 mg for children aged 6–11 years, 3 mg for adolescents aged 12–17), or placebo in a 1:1:1 ratio. Randomization was stratified by age (6–11 years, 12–17 years) and gender. The randomization schedule was administered via an interactive voice response system.[18] Study medication was taken orally at bedtime. Patients were instructed to return all unused study medication and empty packaging, and treatment compliance was assessed at each study visit by counting the number of returned tablets. At every study visit, the investigator completed the CGI-Severity (CGI-S) and the CGI-I for insomnia. Assessments of subjective sleep measures (patient/parent reports of sleep-onset latency, total sleep time, WASO, number of awakenings after sleep onset, and sleep quality), daytime sleepiness (using the Pediatric Daytime Sleepiness Scale [PDSS][19]), and daytime functioning and behavior were administered at randomization and all subsequent study visits. The Conners' ADHD Rating Scale was administered at randomization, week 6, and week 12. Wrist actigraphy monitors were provided to a subgroup of patients at a subset of investigative sites. Data recordings were collected automatically and scored for sleep parameters at a central facility.

Safety evaluations included reports of AEs, physical and neurologic examination findings, vital signs, 12-lead electrocardiography with QT interval corrected using Fridericia's formula [QTcF]), and clinical laboratory tests (standard blood chemistry, hematology, and urinalysis panels). AEs of special interest (eg, dizziness, skin reactions, hallucinations, or suicidality) were recorded. Additionally, the C-SSRS[15] was administered to assess suicidal ideation and behavior at randomization and at all subsequent study visits.

The 2-week single-blind placebo follow-up period was to evaluate treatment discontinuation effects. The single-blind follow-up population consisted of all subjects in the intent-to-treat (ITT) population who received at least 1 dose of single-blind (placebo) study drug during this period. AE reports were collected during this period, and morning residual effects were also assessed using the PDSS. Rebound and discontinuation effects were assessed using wrist actigraphy in the subset of actigraphy patients who completed double-blind treatment and entered the 14-day single-blind follow-up period.

Statistical Analysis

Sample size was based on ability to detect a minimum difference of 20 minutes (SD = 45 minutes) in mean

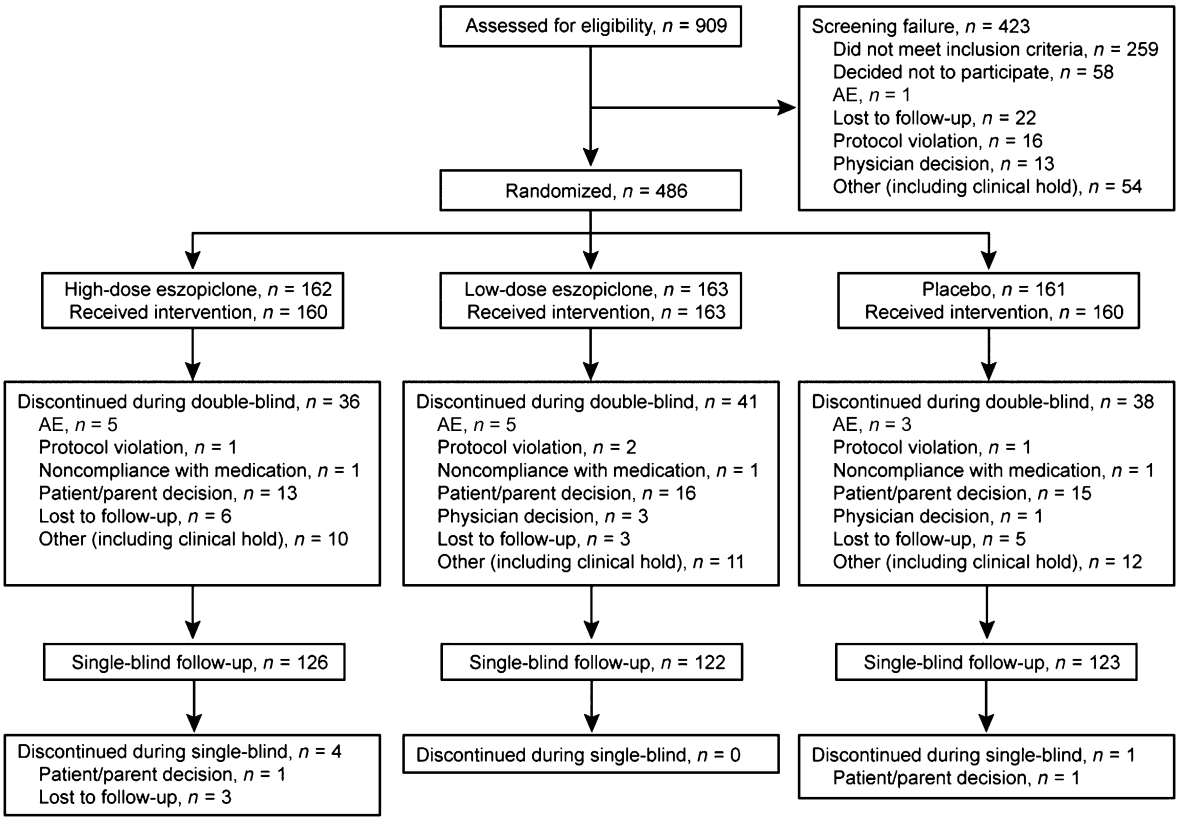

FIGURE 1
Patient disposition, randomized controlled trial.

TABLE 1 Patient Demographics and Baseline Clinical Characteristics for the Randomized Controlled Trial and Open-Label Study

	Randomized Controlled Trial			Open-Label Study
	High-Dose Eszopiclone[a] *n* = 160	Low-Dose Eszopiclone[b] *n* = 163	Placebo *n* = 160	Eszopiclone[a] *n* = 303
Age, mean (SD), y	11.3 (3.0)	11.4 (3.0)	11.6 (3.0)	11.2 (3.2)
Age range, *n* (%)				
6–11 y	86 (53.8)	86 (52.8)	85 (53.1)	171 (56.4)
12–17 y	74 (46.3)	77 (47.2)	75 (46.9)	132 (43.6)
Male, *n* (%)	104 (65.0)	103 (63.2)	101 (63.1)	184 (60.7)
Race, *n* (%)				
White	119 (74.4)	125 (76.7)	116 (72.5)	241 (79.5)
Black or African American	30 (18.8)	30 (18.4)	33 (20.6)	33 (10.9)
Other	11 (6.9)	8 (4.9)	11 (6.9)	29 (9.6)
Hispanic or Latino ethnicity, *n* (%)	27 (16.9)	26 (16.0)	22 (13.8)	50 (16.5)
Wt, mean (SD), kg	47.2 (20.3)	46.7 (19.0)	47.1 (18.5)	44.9 (19.8)
BMI, mean (SD) cm^2/kg	20.4 (5.4)	20.1 (4.7)	20.1 (4.8)	19.8 (5.4)
Latency to persistent sleep, min				
Mean (SD)	57.2 (42.6)	74.3 (72.7)	69.9 (50.4)	75.3 (58.1)[c]
Median	43.5	53.0	54.8	60.0
Range	0.0–205.0	0.0–482.5	0.0–237.0	0.0–366.0
Total sleep time, min				
Mean (SD)	401.3 (64.5)	387.2 (76.6)	392.6 (63.5)	368.1 (82.5)[d]
Median	412.0	399.5	401.5	382.5
Range	187.0–497.5	60.0–493.5	150.0–502.5	13.0–503.0
Wake time after sleep onset, min				
Mean (SD)	52.0 (48.4)	49.8 (47.5)	48.2 (45.5)	50.2 (50.6)[c]
Median	39.0	33.5	34.8	32.0
Range	5.0–285.5	0.0–248.0	3.5–243.0	3.5–334.5
Number of awakenings after sleep onset				
Mean (SD)	8.5 (5.2)	8.4 (5.3)	8.9 (5.7)	7.7 (4.6)[c]
Median	7.5	7.0	8.0	7.0
Range	0–25	0–26	0–33	0–27
Conners' ADHD rating scale (inattention)[e]	78.8 (12.2)	76.0 (12.2)	78.2 (11.3)[f]	—[g]
ADHD medication, n (%)				
Amphetamine	0 (0)	3 (1.8)	1 (0.6)	1 (0.3)
Atomoxetine	4 (2.5)	3 (1.8)	1 (0.6)	6 (2.0)
Dexamphetamine	1 (0.6)	1 (0.6)	0 (0)	1 (0.3)
Dexmethylphenidate	9 (5.7)	12 (7.4)	18 (11.2)	29 (9.6)
Lisdexamfetamine	28 (17.6)	32 (19.6)	24 (14.9)	58 (19.1)
Methylphenidate	34 (21.2)	50 (30.7)	40 (25.0)	89 (29.4)
Dextroamphetamine/amphetamine	25 (15.7)	26 (16.0)	27 (16.8)	54 (17.8)

[a] 2 mg for children aged 6–11 y, 3 mg for adolescents aged 12–17 y.
[b] 1 mg for children aged 6–11 y, 2 mg for adolescents aged 12–17 y.
[c] *n* = 301.
[d] *n* = 302.
[e] *T* scores standardized for age and gender, mean = 50, SD = 10.
[f] *n* = 159.
[g] not assessed.

change from baseline to week 12 in PSG-measured LPS for eszopiclone versus placebo, with a type 1 error of 5% after Bonferroni adjustment for 2 comparisons, and a 2-sided test. A sample size of 150 patients per group, assuming an ~30% dropout rate, yielded 84.3% power for each pairwise comparison (high-dose eszopiclone vs placebo, low-dose eszopiclone vs placebo).

The ITT population and the safety population were identical and included all randomized patients who received at least 1 dose of study medication during the double-blind period. The primary outcome measure, change from baseline to week 12 in PSG-measured LPS (defined as the time from lights-out to the beginning of the first sleep period of at least 10 minutes' duration), was analyzed using analysis of covariance (ANCOVA), with treatment group as a fixed effect and baseline value as a covariate. Key secondary outcomes (PSG-measured WASO, CGI-Parent/Caregiver, CGI-Child, and the Conners' ADHD rating scale) were analyzed similarly, except for CGI-I, which does not have a baseline value and was analyzed using analysis of variance with treatment as a fixed effect. Bonferroni adjustment for multiple comparisons was used for the primary and key secondary outcomes. All other secondary analyses were conducted without adjustment for multiplicity and used only

TABLE 2 Change From Baseline to Week 12 for Primary and Key Secondary Efficacy Measures

Outcome Measure	LS Mean Change (SE) Baseline to Week 12, High-Dose Eszopiclone,[a] $n = 160$	LS Mean Change (SE) Baseline to Week 12, Low-Dose Eszopiclone,[b] $n = 162$	LS Mean Change (SE) Baseline to Week 12, Placebo, $n = 160$	LS Mean Difference High-Dose Eszopiclone vs Placebo	*P* Value High-Dose Eszopiclone vs Placebo	LS Mean Difference Low-Dose Eszopiclone vs Placebo	*P* Value Low-Dose Eszopiclone vs Placebo
Primary outcome							
PSG LPS, min	−18.3 (3.9)	−23.4 (3.9)	−25.7 (3.9)	7.33	0.3749[c]	2.21	>0.9999
Key secondary outcomes							
PSG WASO, min	−23.4 (3.4)	−16.8 (3.4)	−17.3 (3.4)	−6.04	0.2118	0.55	0.9092
CGI-I-Parent/Caregiver[d]	2.3 (0.1)	2.6 (0.1)	2.7 (0.1)	−0.4	0.0090	−0.2	0.2386
CGI-I-Child[d]	2.3 (0.1)	2.5 (0.1)	2.7 (0.1)	−0.4	0.0026	−0.2	0.1285
Conners' ADHD (inattention)	−8.8 (1.0)	−5.8 (1.0)	−7.1 (1.0)	−1.7	0.2382	1.3	0.3518

[a] 2 mg for children aged 6–11 y, 3 mg for adolescents aged 12–17 y.
[b] 1 mg for children aged 6–11 y, 2 mg for adolescents aged 12–17 y.
[c] *P* value adjusted for 2 comparisons.
[d] The CGI-I involves an evaluation with respect to baseline, and the value is therefore presented as an absolute value rather than as the least squares mean change from the baseline value.

for descriptive purposes. A hierarchical analytic approach was used[20]; if the test for the primary endpoint was not statistically significant at $P \leq .05$, the tests for the key secondary outcomes were considered not statistically significant, regardless of *P* value.

Exploratory analysis of the effect of age group on the primary outcome (PSG-measured LPS) used an ANCOVA with treatment group, age, and interaction between treatment group and age as fixed effects and baseline value as a covariate. A nonparametric ranked ANCOVA model was performed to support the primary efficacy ANCOVA analysis; additional sensitivity analysis using ANCOVA with baseline observation carried forward (in all ITT subjects) was also performed for the primary endpoint. Safety data were summarized by treatment group and age using descriptive statistics.

Long-Term Open-Label Study (Study 190-247)

A 12-month open-label safety study was conducted at 60 sites in the United States from April 2009 through October 2011. The objective was to evaluate the long-term safety of treatment with eszopiclone in the children (aged 6–11 years) and adolescents (aged 12–17 years) with ADHD–associated insomnia.

Patients

Patients who completed the double-blind study and met the open-label study inclusion criteria were included in this study, as well as de novo patients with no previous eszopiclone treatment. Inclusion and exclusion criteria were the same as for the double-blind study.

Procedures

PSG was used only to confirm de novo patient eligibility. During the open-label study, children aged 6 to 11 years received 2 mg of eszopiclone, and adolescents aged 12 to 17 years received 3 mg (taken once daily at bedtime for both groups). Agents that could affect sleep or ADHD symptoms (eg, over-the-counter or prescription medications, herbal products, melatonin, and caffeine) were prohibited. Assessments were conducted at monthly study visits. Treatment compliance was assessed as described for the double-blind study.

Safety assessments included AEs, concomitant medication use, vital sign measurements, orthostatic effects, height and weight, physical examination findings, neurologic examination findings (including Romberg's test), 12-lead electroencephalogram findings (including 10-second rhythm strip), C-SSRS item responses, and clinical laboratory assessments (hematology, serum chemistry, urinalysis, and serum and urine pregnancy tests for female subjects ≥8 years of age).

Statistical Analysis of Safety End Points

Allowing for a dropout rate of >50% and the expected ADHD prevalence ratio of 2:1 boys to girls, the planned sample size was 300 enrolled patients to reach at least 50 female patients completing 12 months of treatment.

Safety outcomes were summarized by treatment group using descriptive statistics. The primary outcome measure was the incidence of AEs. Secondary outcome measures included physical and neurologic examinations, electrocardiography, clinical laboratory parameters, and vital sign measurements including orthostatic effects. AEs of special interest were skin reactions, dizziness, hallucinations, and suicidality (including C-SSRS responses).

RESULTS

Randomized Controlled Trial (Study 190-246)

Patients

Of 486 patients randomized, 371 patients (76.3%) completed the double-blind period

TABLE 3 AEs Reported by ≥2% of Patients in Either Eszopiclone Group During the Double-Blind Period (Safety Population)

AE, *n* (%)	High-Dose Eszopiclone[a] *n* = 159	Low-Dose Eszopiclone[b] *n* = 163	Placebo *n* = 161
Any AE	97 (61.0)	97 (59.5)	74 (46.0)
Headache[c]	22 (13.8)	19 (11.7)	19 (11.8)
Dysgeusia[c]	22 (13.8)	8 (4.9)	2 (1.2)
Dizziness[c]	13 (8.2)	6 (3.7)	3 (1.9)
Abdominal pain, upper[c]	8 (5.0)	6 (3.7)	5 (3.1)
Abdominal discomfort[c]	8 (5.0)	4 (2.5)	0 (0)
Pyrexia[c]	8 (5.0)	4 (2.5)	5 (3.1)
Nausea	7 (4.4)	4 (2.5)	6 (3.7)
Somnolence[c]	6 (3.8)	4 (2.5)	3 (1.9)
Nasopharyngitis[c]	6 (3.8)	9 (5.5)	7 (4.3)
Upper respiratory tract infection[c]	5 (3.1)	13 (8.0)	7 (4.3)
Vomiting[c]	5 (3.1)	10 (6.1)	3 (1.9)
Urinary tract infection[c]	4 (2.5)	1 (0.6)	1 (0.6)
Cough	4 (2.5)	3 (1.8)	4 (2.5)
Nasal congestion[c]	4 (2.5)	1 (0.6)	0 (0)
Diarrhea	3 (1.9)	4 (2.5)	6 (3.7)
Oropharyngeal pain[c]	3 (1.9)	6 (3.7)	4 (2.5)
Rash	3 (1.9)	4 (2.5)	5 (3.1)
Toothache[c]	2 (1.3)	4 (2.5)	0 (0)
Irritability[c]	0 (0)	4 (2.5)	0 (0)
AEs of special interest			
Dizziness[c]	14 (8.8)	6 (3.7)	4 (2.5)
Skin reactions	7 (4.4)	6 (3.7)	9 (5.6)
Hallucinations[c]	2 (1.3)	4 (2.5)	0 (0.0)
Suicidality	0 (0.0)	1 (0.6)	0 (0.0)

[a] 2 mg for children aged 6–11 y, 3 mg for adolescents aged 12–17 y.
[b] 1 mg for children aged 6–11 y, 2 mg for adolescents aged 12–17 y.
[c] AEs that were more frequent in the eszopiclone group than in the placebo group by at least 1%.

and 366 (75.3%) completed the subsequent single-blind follow-up period (Fig 1). The rate of discontinuation was similar across treatment groups. Median time of exposure to study medication was 85 days overall. The mean compliance rate, based on pill count (calculated as 100 × [number of doses taken/duration of exposure]), was 95.7%. Demographics and ADHD medications were similar across treatment groups (Table 1). Overall, 65.8% of patients were taking a stimulant medication approved for ADHD treatment.

Efficacy

There were no significant differences between eszopiclone (low-dose or high-dose) groups and the placebo group in change from baseline to week 12 on the primary efficacy outcome (PSG-measured LPS; Table 2). Sensitivity analyses were consistent with the results of the primary analysis.

An exploratory analysis that included age as a categorical variable (6–11 years, 12–17 years) detected no effect of treatment group or treatment by age interaction.

Per the hierarchical statistical analysis plan, because the primary outcome analysis was not statistically significant, all key secondary outcomes were considered nonsignificant. Key secondary outcomes are shown in Table 2 with unadjusted *P* values for descriptive purposes only. There were no clinically meaningful differences between groups observed on the other exploratory secondary endpoints (data not shown).

Safety

Treatment-emergent AEs were reported by 61.0%, 59.5%, and 46.0% of patients receiving high-dose eszopiclone, low-dose eszopiclone, and placebo, respectively (Table 3). The most commonly reported AEs with eszopiclone were headache, dysgeusia, and dizziness; all occurred in more patients in the high-dose group than the low-dose group.

A dose-response relationship (rate of AEs in the high-dose eszopiclone group > the low-dose eszopiclone group ≥ the placebo group) was observed for dysgeusia, abdominal discomfort, dizziness, and nasal congestion. AEs were generally similar across age groups, with the exception of dysgeusia, which was reported by 20 (8.8%) patients aged 12 to 17 years versus 12 (4.7%) of patients aged 6 to 11 years. Almost all AEs were mild to moderate in severity.

Treatment-emergent AEs led to study discontinuation for 5 patients (3.1%) receiving high-dose eszopiclone, 4 patients (2.5%) receiving low-dose eszopiclone, and 3 patients (1.9%) receiving placebo. AEs of special interest are shown in Table 3. Dizziness was more common among eszopiclone-treated patients than patients in the placebo group. The incidence of hallucinations was 1.3% to 2.5% of eszopiclone-treated patients. One patient (a 16-year-old boy in the low-dose eszopiclone group) reported suicidal ideation consisting of nonspecific thoughts without a plan or intent to act.

Patient interviews using the C-SSRS identified suicidal ideation in other patients as well: 1.3%, 1.8%, and 2.5% of patients in the high-dose eszopiclone, low-dose eszopiclone, and placebo groups, respectively. No suicidal behavior was reported.

Two patients in the 6- to 11-year-old range in the high-dose eszopiclone group had serious AEs, which were deemed unrelated to study medication; 1 patient experienced sedation on study day 2, and 1 patient experienced respiratory distress during the single-blind follow-up period. There were no deaths.

No safety concerns emerged during the single-blind follow-up period. On the PDSS, changes from week 12 to week 14 were small with no significant differences between groups. Wrist actigraphy

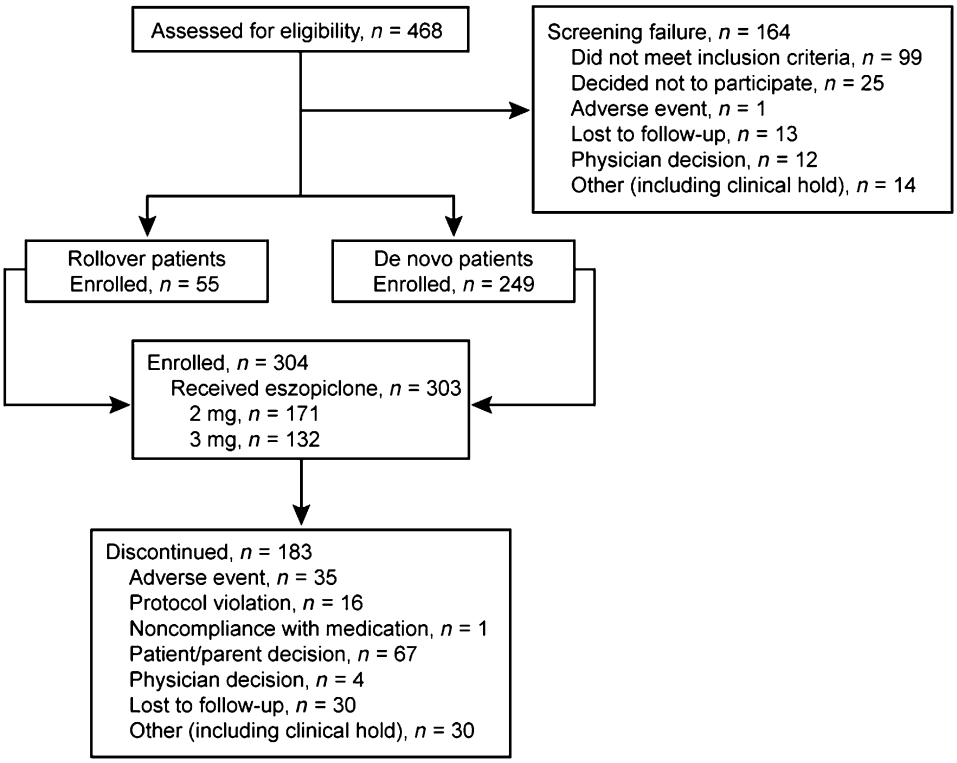

FIGURE 2
Patient disposition, open-label study.

showed no significant differences between eszopiclone and placebo in rebound effects or discontinuation effects.

Open-Label Study (Study 190-247)

Patients

Fifty-five (18.1%) patients enrolled in the open-label study had completed the earlier double-blind study, and 249 (81.9%) had no previous exposure to eszopiclone (Fig 2). One hundred twenty-one patients (39.8%; 69 boys and 52 girls) completed 12 months of treatment. The median duration of exposure to eszopiclone was 184 days; mean compliance rate (calculated as described earlier) was 93.6%.

Safety

Seventy percent of patients experienced at least 1 treatment-emergent AE (Table 4); AE rates were similar across age groups, with the exception of higher adolescent rates for headache (children: 17.0% vs adolescents: 27.3%), dysgeusia (9.4% vs 19.7%), and nasopharyngitis (2.9% vs 11.4%). Treatment-emergent AEs led to study discontinuation for 34 patients (11.2%). The incidence of AEs of special interest (dizziness, skin reactions, hallucinations, suicidality) is shown in Table 4. Skin reactions were mild or moderate in severity and did not result in study discontinuation. Four patients discontinued because of dizziness, and 5 patients discontinued because of hallucinations. Suicidality as an AE of special interest was noted in 3 patients: 1 patient with nonspecific suicidal thoughts, 1 patient who reported active suicidal ideation with a plan but did not harm himself, and 1 patient who reported self-injurious ideation without intent of suicide.

C-SSRS interviews identified 4 patients with suicidal ideation: 2 of the patients described earlier and 2 others with nonspecific suicidal thoughts. Two patients were discontinued from study participation as a result of suicidal ideation.

There was 1 death by accidental drowning, which was judged by the investigator as not related to study medication (eszopiclone 2 mg). Other serious AEs were 1 case each of arm fracture, viral infection, and delirium.

Orthostatic hypotension at any study visit occurred in 21.0% of patients, and orthostatic tachycardia was reported in 26.1% of patients. There were no reports of QTcF interval >450 milliseconds or increases in QTcF >60 milliseconds; 16 patients (5.3%) had a QTcF increase >30 milliseconds for at least 1 study visit.

DISCUSSION

In the 12-week, double-blind study, there was no significant difference between eszopiclone (high- or low-dose) and placebo on change from baseline at week 12 in PSG-measured LPS or WASO, CGI scores, or Conner's ADHD scale score. Eszopiclone was generally well tolerated in both the double-blind and open-label studies. The most common AEs were headache,

TABLE 4 AEs Reported by ≥2% of Patients During the Open-Label Study

AE, *n* (%)	Eszopiclone[a]
	N = 303
Any AE	212 (70.0)
Headache	65 (21.5)
Dysgeusia	42 (13.9)
Dizziness	30 (9.9)
Nasopharyngitis	20 (6.6)
Abdominal pain, upper	19 (6.3)
Pyrexia	16 (5.3)
Cough	16 (5.3)
Somnolence	15 (5.0)
Vomiting	15 (5.0)
Diarrhea	13 (4.3)
Nausea	13 (4.3)
Oropharyngeal pain	13 (4.3)
Nasal congestion	12 (4.0)
Upper respiratory tract infection	12 (4.0)
Sinusitis	11 (3.6)
Insomnia	10 (3.3)
Influenza	10 (3.3)
Toothache	9 (3.0)
Pharyngitis streptococcal	8 (2.6)
Abdominal discomfort	7 (2.3)
Hallucination, visual	7 (2.3)
Contusion	6 (2.0)
Influenza-like illness	6 (2.0)
Urinary tract infection	6 (2.0)
AEs of special interest	
Dizziness	30 (9.9)
Skin reactions	13 (4.3)
Hallucinations	10 (3.3)
Suicidality[b]	3 (1.0)

[a] 2 mg for children aged 6–11 y, 3 mg for adolescents aged 12–17 y.

[b] C-SSRS interviews identified suicidal ideation in one additional patient.

dysgeusia, and dizziness. The overall rate of AEs was similar to those reported in a previous study of zolpidem in a comparable patient population,[13] although there was some variation in the specific profile.

As with zolpidem,[13] eszopiclone failed to demonstrate efficacy in children and adolescents with ADHD-related insomnia. It is unclear whether these medications were not effective because the studied population was pediatric, because the population had ADHD, or for other reasons. Studies of these agents in children without ADHD and in adults with ADHD may be informative.

Hypotheses to explain the current negative findings include temporal variability in sleep parameters (associated with the study design or with ADHD-related instability of the sleep–wake system) that may have obscured possible treatment effects; developmental changes in physiologic functioning of the γ-aminobutyric acid $(GABA)_A$ receptor, which may affect response to GABA-ergic agents in children; and involvement of neurotransmitters other than GABA in the pathophysiology of ADHD-related insomnia in the pediatric population. The failure of zolpidem[13] and eszopiclone studies to produce greater improvement than placebo in sleep parameters for patients with ADHD-associated insomnia suggests that the benzodiazepine binding site on the $GABA_A$ receptor may be the wrong pharmacologic target for this population. One hypothesis implicating a different therapeutic target is that pediatric insomnia in ADHD may be attributable to a melatonin-mediated, circadian-based sleep delay. Children with ADHD have a stronger circadian evening preference than control subjects.[21] This observation is consistent with the demonstrated delay in evening increases of endogenous melatonin levels in nonmedicated children with ADHD.[22] An evening circadian tendency is associated with both parental reports of sleep-onset delay and PSG-measured sleep-onset latency in children with ADHD.[21] Consistent with these findings, melatonin has demonstrated efficacy for improving sleep-onset latency and total sleep time in 2 studies in this population.[23,24]

CONCLUSIONS

Eszopiclone did not significantly reduce LPS compared with placebo at 12 weeks in children with ADHD-related insomnia who were unresponsive to behavioral interventions. The most frequent treatment-emergent AEs were headache, dysgeusia, and dizziness. The open-label study demonstrated that eszopiclone was generally well tolerated for up to 1 year. The overall AE profile was generally consistent with that of eszopiclone in adults. However, several patients discontinued treatment because of hallucinations, and suicidal ideation was noted in 1% to 2% of eszopiclone-treated patients. Study design limitations, such as the absence of an adaptation night and intrinsic characteristics of pediatric ADHD-related insomnia, may have contributed to the negative findings. Future studies are needed to elucidate the underlying pathophysiology of insomnia in this patient population and to identify effective treatments.

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