RAPID PUBLICATION

Sustained Efficacy of Eszopiclone Over 6 Months of Nightly Treatment: Results of a Randomized, Double-Blind, Placebo-Controlled Study in Adults with Chronic Insomnia

Andrew D. Krystal, MD, MS[1]; James K. Walsh, PhD[2]; Eugene Laska, PhD[3]; Judy Caron, PhD[4]; David A. Amato, PhD[4]; Thomas C. Wessel, MD, PhD[4]; Thomas Roth, PhD[5]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; [2]Sleep Medicine and Research Center, St. John's/St. Luke's Hospitals and Department of Psychology, Saint Louis University, St. Louis, MO; [3]Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, and New York University School of Medicine, New York, NY; [4]Research and Development, Sepracor, Inc, Marlborough, MA; [5]Henry Ford Sleep Disorders Center, Detroit, MI

Study Objectives: To determine the long-term efficacy of eszopiclone in patients with chronic insomnia.
Design: Randomized, double-blind, multicenter, placebo-controlled.
Setting: Out-patient, with monthly visits.
Patients: Aged 21 to 69 years meeting DSM IV criteria for primary insomnia and reporting less than 6.5 hours of sleep per night, and/or a sleep latency of more than 30 minutes each night for at least 1 month before screening.
Interventions: Eszopiclone 3 mg (n = 593) or placebo (n = 195), nightly for 6 months
Measurements and Results: Efficacy was evaluated weekly using an interactive voice-response system. Endpoints included sleep latency; total sleep time; number of awakenings; wake time after sleep onset; quality of sleep; and next-day ratings of ability to function, daytime alertness, and sense of physical well-being. At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in sleep latency, wake time after sleep onset, number of awakenings, number of nights awakened per week, total sleep time, and quality of sleep compared with placebo ($P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo ($P \leq 0.002$). There was no evidence of tolerance, and the most common adverse events were unpleasant taste and headache.
Conclusions: Throughout 6 months, eszopiclone improved all of the components of insomnia as defined by DSM-IV, including patient ratings of daytime function. This placebo-controlled study of eszopiclone provides compelling evidence that long-term pharmacologic treatment of insomnia is efficacious.
Key Words: chronic insomnia, sleep initiation and maintenance disorders, tolerance, long-term, next-day function, non-benzodiazepine, wakefulness after sleep onset, sleep, awakenings, eszopiclone
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INTRODUCTION

AN ESTIMATED 2.5% OF THE UNITED STATES POPULATION TAKE HYPNOTIC MEDICATIONS FOR INSOMNIA IN ANY GIVEN YEAR, AND, OF THESE, ABOUT 23% TAKE HYPNOTICS ON A NIGHTLY BASIS FOR 4 MONTHS OR LONGER.[1] Clinical research studies of hypnotics, on the other hand, have a median duration of medication use of approximately 1 week.[2] The results of only a small number of longer, randomized, double-blind, placebo-controlled studies have been reported, including those of 2 studies with durations of 5 weeks[3,4] and 1 with a duration of 8 weeks[5] of nightly hypnotic use.

Long-term nightly use of hypnotic medications has traditionally been discouraged for a number of reasons, including (1) the belief that tolerance develops for the sleep-promoting properties of hypnotics; (2) the belief that the abuse liability of hypnotics is high and increases with duration of use; and (3) the belief that insomnia is a symptom (rather than a disorder) that remits with treatment of the underlying medical or psychiatric disorder, negating the need for long-term insomnia treatment. The assumptions and data underlying those beliefs have recently been questioned.[6]

Despite perceptions to the contrary, abuse liability of current hypnotics by insomniacs is low and is largely limited to individuals involved with multi-drug use. Dose escalation by patients is infrequent.[1] Self-administration studies suggest a pattern of hypnotic use consistent with therapy-seeking behavior rather than with misuse or abuse.[7] To our knowledge, there is no evidence that indicates that longer duration of hypnotic use is related to increased misuse or abuse.

Tolerance to the sleep-promoting effects of hypnotics has not been observed in double-blind investigations of nightly use lasting up to 5 weeks.[3,4] That is, the improvements in sleep observed during the first few nights of treatment are maintained for the duration of the study, without dose escalation. Whether tolerance develops after longer periods of hypnotic use has not been systematically studied and remains an important clinical question.

The view that insomnia is always secondary to other conditions is not consistent with available data. First, epidemiologic studies indicate that about 20% of individuals who report having chronic insomnia do not have a medical or psychiatric explanation for their sleep complaint, and are viewed as having a primary insomnia disorder.[8,9] Secondly, physiologic indications of hypothalamic-pituitary-adrenal axis hyperarousal have been delineated as characteristic of primary insomnia,[10] suggesting a pathophysiology that is distinct from that of other insomnia disorders (eg, restless legs syndrome) or circadian-mediated insomnias, such as delayed sleep-phase syndrome or shift-work sleep disorder. Therefore,

Disclosure Statement
Drs. Andrew Krystal, James K. Walsh, and Thomas Roth are consultants, investigators and advisory board members to Sepracor. Dr. Eugene Laska is a consultant to Sepracor. Drs. Judy Caron, David Amato, and Thomas Wessel are Sepracor employees.

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Address correspondence to: Andrew D. Krystal, MD, MS, Box 3309, Duke University Medical Center, Durham, NC 27710; Tel: 919-681-8788; Fax: 919-681-8744; E-mail: krystal@phy.duke.edu

insomnia appears to be a persistent primary disorder in a substantial segment of chronic insomniacs. Moreover, it is clear that many individuals with secondary insomnia continue to experience sleep disturbance despite treatment of the primary condition.[11] These considerations, coupled with evidence of the morbidity of untreated insomnia, suggest that treatment directed specifically at insomnia is needed.[2]

The need for effective long-term insomnia treatment, the widespread nightly use of hypnotic medication for months or years without supporting scientific data, and the changing views regarding abuse liability and tolerance development with more-recently developed agents provided the impetus to conduct a long-term study of nightly pharmacologic treatment of insomnia with eszopiclone.

Racemic zopiclone is used widely in many countries at a usual dose of 7.5 mg (3.75 mg each of (S)- and (R)-zopiclone). The investigational drug employed in this study was eszopiclone 3 mg, a non-benzodiazepine, cyclopyrrolone that is the (S)-isomer of racemic zopiclone.[12] (S)-zopiclone is responsible for the hypnotic effects of zopiclone, whereas the (R)-isomer has no hypnotic properties.[13] Eszopiclone appears rapidly in the systemic circulation and achieves peak concentrations about 1 hour after the dose is taken, with a half-life of approximately 5 to 7 hours.[12,14,15] Preliminary reports have indicated that 3 mg of eszopiclone is efficacious in reducing sleep latency and improving sleep-maintenance difficulties in a model of transient insomnia[16] and in a 6-week study of chronic insomnia.[17] The possibility that eszopiclone affects both aspects of hypnotic efficacy (sleep induction and sleep maintenance) is particularly important for chronic insomnia because it appears that the type of complaint frequently changes over time.[18]

The objective of this study was to determine the safety and efficacy of eszopiclone 3 mg administered nightly to patients with chronic insomnia for 12 months. The first 6 months of the study used a randomized, double-blind, placebo-controlled design, followed by a 6-month open-label extension that was available to all patients. This manuscript describes results of the first 6 months of the study. We employed measures of sleep initiation, sleep maintenance, quality of sleep, and next-day function as outcome measures, all of which are the core features that define insomnia.[19]

METHODS

This study was conducted at 70 sites in the United States following approval of the protocol by each site's Institutional Review Board. Informed consent was obtained from potential study patients prior to any study-related procedures.

Patient Recruitment and Selection

Men and women between 21 and 65 years of age were recruited through media advertisements and from patient databases. Preliminary information about the study was conveyed to prospective participants via telephone. Those who qualified on the basis of the telephone screening were scheduled for an initial screening visit, which included medical, sleep, and medication history and physical, mental, and neurological examinations. Patients receiving a DSM IV diagnosis of primary insomnia and reporting a usual total sleep time less than 6.5 hours per night and/or a usual sleep latency of more than 30 minutes each night for at least 1 month prior to screening were eligible for randomization, provided they did not (1) meet criteria for a DSM-IV Axis I psychiatric diagnosis other than primary insomnia, sexual and gender-identity disorders, or Axis II personality disorders (excluded by medical history); (2) have a history of substance abuse or substance dependence; (3) consume more than 2 alcoholic beverages per day or more than 14 per week; (4) use any psychotropic, hypnotic, or other medications known to affect sleep or to be contraindicated for use with hypnotics; or (5) use over-the-counter analgesics that contain caffeine or herbal supplements, including products with herbs, melatonin, or St. John's Wort.

Study Procedures

During the randomization visit, instruction was provided to participants regarding the use of an interactive voice response system (IVRS) to collect study data. At that time, the patient provided baseline data through IVRS for all study questions with regard to the previous week of sleep, just as it was to be performed from home throughout the study. The IVRS system was selected because it provides accurate entries that are time-stamped, in contrast to paper diaries. Several IVRS computer-administered versions of clinician-administered rating scales are widely used and have been validated over a range of psychopharmacologic trials.[20]

During participation each subject telephoned the IVRS once each week on a regularly scheduled day between 8 PM and midnight (± 1 day) to report average nightly values during that week for (1) sleep latency, (2) wake time after sleep onset (WASO), (3) total sleep time, and (4) number of awakenings. In addition, patients provided estimates for (5) the number of nights during which they awakened that week, (6) sleep quality, (7) daytime ability to function, (8) daytime alertness, and (9) sense of physical well-being (the last 4 measures being rated on a scale of 0-10). Daytime ability to function captured the patient's ability to concentrate or think clearly over the past week (ratings from poor to excellent), while daytime alertness captured feelings of alertness during the week (very sleepy to wide awake and alert). Sense of physical well-being was graded on a scale of poor to excellent. For the first 6-months, patients were instructed to take the double-blind medication at bedtime each night. All patients who completed the double-blind period entered the open-label extension and received eszopiclone 3 mg in the same manner. Monthly study visits were scheduled for safety and compliance assessments and for medication refills. Additionally, a termination visit occurred 5 to 7 days after the last dose of study medication during which

Table 1—Patient disposition

	Placebo No. (%)	Eszopiclone 3 mg No. (%)
Randomized*	196	595
Completed study	111 (56.6)	360 (60.5)
Discontinued study	85 (43.4)	235 (39.5)
Reason for discontinuation		
Adverse Event	14 (7.1)	76 (12.8)
Protocol Violation	7 (3.6)	17 (2.9)
Voluntary Withdrawal	51 (26.0)	82 (13.8)
Lost to follow-up	8 (4.1)	52 (8.7)
Other	5 (2.6)	8 (1.3)

*1 patient in the placebo group and 2 patients in the eszopiclone group were randomized and assigned to treatment groups but discontinued participation prior to receiving the study drug.

Table 2—Baseline demographics

Demographics	Placebo	Eszopiclone
Age, yr		
Mean (SD)	43.2 (11.1)	44.3 (11.4)
Median	44.0	45.0
Range	21-65	21-69
Race, no. (%)		
Caucasian	153 (78.5)	469 (79.1)
African American	27 (13.8)	77 (13.0)
Other	15 (7.7)	47 (7.9)
Women, no. (%)	125 (64.1)	373 (62.9)
Men, no. (%)	70 (35.9)	220 (37.1)
Body mass index, (kg/m^2)		
Mean (SD)	27.8 (6.5)	29.5 (7.2)*
Median	26.5	28.1
Range	15-49	17-59
Weight, (kg)		
Mean (SD)	79.1 (21.8)	84.5 (22.2)*
Median	75.8	81.6
Range	42-171	37-168

*$P < .05$

the patient was specifically queried for adverse events that occurred upon drug discontinuation.

Statistical Analysis

A sample size of 800 patients was planned, utilizing a 3:1 (eszopiclone:placebo) randomization ratio. This sample-size target was based upon the expected attrition rate of 50% over the course of the study and the desire to obtain 6 months of eszopiclone exposure in at least 300 patients.

Measures of efficacy included sleep latency, total sleep time, WASO, number of awakenings, number of nights awakened, quality of sleep, and next-day function. Treatment comparisons were performed using an analysis of variance (ANOVA) model with treatment and site as fixed effects using the SAS MIXED procedure. These analyses were conducted using ranked data because it was thought a priori that most of the endpoints would not be normally distributed. Medians are presented here because they are the most appropriate measure of central tendency for ranked variables. Monthly values, which reflect the average of 4 weeks of information per subject (which reduces variability), were analyzed. All tests were 2-tailed and were conducted at the 5% level of significance.

Analyses were performed on 3 study populations for each dependent measure: (1) the Intent-to-Treat (ITT) population comprised all randomized patients. If a patient's data were incomplete, a last observation carried forward (LOCF) approach was used to impute values. This method ensured that subjects who discontinued early, including those in whom treatment failed, were included in the analysis and preserved the integrity of the randomization procedure. This population and imputation method was specified in the protocol. Two other populations were examined to enhance the interpretability of the results: (2) the population of Observed Cases up to month *t*, comprised all randomized patients for whom data were collected at month *t* for $t = 1, 2, \ldots, 6$ and (3) the Completers population, comprised those patients who completed 6 months of double-blind treatment.

In the protocol, the primary measure was specified to be the average sleep latency over the last 3 months (Months 4-6) of the double-blind period, and the key secondary measure was the average total sleep time during the same period. The averages were to be computed using LOCF. Because they are far more informative, however, we have instead analyzed 7 time points (Week 1, and Months 1-6) and 9 different endpoints. This raises the possibility that the Type I error (the probability of erroneously rejecting a true null hypothesis) is inflated merely by chance. We protected against this possibility, known as the problem of multiplicity, by constraining the familywise error rate to be less than 0.05. The familywise error rate is the probability that among a set of tests of null hypotheses (in this case, 63 of them), even 1 of the hypotheses is erroneously rejected. This can be accomplished by using the Bonferroni method, which treats all endpoints as if they were independent of one another and simply divides the nominal significance level by the number of treatment comparisons. In this study, the familywise error rate is controlled at the .05 level if the observed *P* value is less than .0008 (.05/63). The Bonferroni adjustment is a very conservative procedure because of the high degree of dependence between the monthly assessments of the same endpoint, as well as correlations between the different endpoints.

Table 3—Summary of efficacy results for Intent-to-Treat population using last observation carried forward technique

			Placebo		Eszopiclone 3 mg				
Sleep Category	Endpoint	Timepoint	Mean (SD)	Median	Mean (SD)	Median	*t* value	df	*P* value
Sleep Induction	Sleep latency, min	Baseline	96.1 (94.7)	75.0	90.6 (79.6)	60.0	-0.50	696	.6137
		Week 1	85.4 (81.1)	60.0	48.2 (56.4)	30.0	-6.92	457	< .0001
		Month 1	71.3 (59.8)	52.5	44.3 (36.5)	31.3	-6.38	650	< .0001
		Month 2	65.4 (56.9)	50.0	45.1 (46.2)	30.0	-5.20	661	< .0001
		Month 3	63.2 (57.1)	45.0	46.3 (53.9)	30.0	-4.79	663	< .0001
		Month 4	64.3 (59.8)	45.0	47.8 (49.8)	30.0	-4.29	663	< .0001
		Month 5	66.6 (74.6)	43.8	45.3 (45.4)	30.0	-4.06	665	< .0001
		Month 6	63.1 (57.9)	45.0	47.0 (50.6)	30.0	-4.15	665	< .0001
Sleep Maintenance	WASO, min	Baseline	70.7 (72.8)	45.0	83.2 (120.7)	60.0	1.03	696	.3038
		Week 1	69.0 (120.8)	45.0	48.2 (102.4)	20.0	-5.39	457	< .0001
		Month 1	62.8 (77.2)	36.7	47.4 (77.7)	23.8	-5.11	650	< .0001
		Month 2	58.8 (71.8)	35.0	44.4 (64.5)	22.5	-3.87	661	.0001
		Month 3	56.1 (67.2)	36.4	42.2 (70.1)	20.0	-4.77	663	< .0001
		Month 4	51.1 (63.3)	31.3	42.3 (56.9)	21.5	-3.11	663	.0020
		Month 5	58.5 (85.2)	34.4	42.5 (65.1)	21.3	-4.50	665	< .0001
		Month 6	48.2 (59.4)	30.0	44.2 (74.2)	21.0	-2.96	665	.0032
	Awakenings/night, no.	Baseline	3.5 (2.8)	3.0	3.2 (2.3)	3.0	-1.26	696	.2098
		Week 1	2.8 (2.1)	2.0	2.2 (1.7)	2.0	-3.23	457	.0013
		Month 1	2.8 (2.6)	2.5	2.1 (1.4)	2.0	-4.52	650	< .0001
		Month 2	2.8 (2.8)	2.3	2.0 (1.5)	1.9	-4.29	661	< .0001
		Month 3	2.6 (2.7)	2.0	1.9 (1.5)	1.7	-4.21	663	< .0001
		Month 4	2.6 (2.6)	2.2	1.9 (1.5)	1.6	-4.40	663	< .0001
		Month 5	2.5 (2.7)	2.0	1.9 (1.6)	1.5	-4.17	665	< .0001
		Month 6	2.6 (2.7)	2.0	1.9 (1.5)	1.6	-4.10	665	< .0001
	Nights Awakened/wk, no.	Baseline	5.6 (1.8)	7.0	5.3 (2.0)	6.0	-1.57	696	.1172
		Week 1	5.2 (2.2)	6.5	4.3 (2.4)	4.0	-3.88	457	.0001
		Month 1	5.0 (1.9)	5.5	4.1 (2.2)	4.0	-4.89	650	< .0001
		Month 2	4.9 (2.1)	5.3	3.9 (2.3)	3.8	-5.03	661	< .0001
		Month 3	4.8 (2.2)	5.3	3.9 (2.4)	4.0	-4.39	663	< .0001
		Month 4	4.7 (2.3)	5.3	3.9 (2.4)	4.0	-4.01	663	< .0001
		Month 5	4.7 (2.2)	5.3	3.9 (2.5)	4.0	-4.22	665	< .0001
		Month 6	4.7 (2.4)	5.2	3.9 (2.5)	4.0	-3.86	665	.0001
Sleep Duration	Total sleep time, min	Baseline	303.6 (78.3)	300.0	302.4 (123.2)	300.0	-1.29	696	.1986
		Week 1	322.3 (73.8)	330.0	372.5 (85.7)	375.0	6.66	457	< .0001
		Month 1	333.1 (69.8)	337.5	373.9 (67.5)	375.0	6.60	650	< .0001
		Month 2	339.1 (79.8)	345.0	379.7 (68.9)	385.0	6.92	661	< .0001
		Month 3	341.7 (69.6)	348.8	378.2 (70.5)	382.5	6.23	663	< .0001
		Month 4	345.6 (73.6)	360.0	375.6 (72.1)	379.4	4.77	663	< .0001
		Month 5	338.4 (77.9)	340.6	377.8 (71.7)	382.5	6.02	665	< .0001
		Month 6	339.3 (77.1)	345.0	378.3 (72.3)	382.5	6.17	665	< .0001

WASO refers to wake time after sleep onset.

RESULTS

Patients

A total of 1194 patients were screened. Of these, 791 met all eligibility criteria and returned to the clinic for randomization to either eszopiclone 3 mg or placebo; however, 3 patients discontinued the study before taking the study drug. Thus, 788 were randomly assigned and received treatment, and 471 (approximately 60% in each group) completed the double-blind portion of the trial (Table 1).

The 2 treatment groups had similar demographic characteristics and sleep histories, although weight and body mass index were slightly but significantly greater in the eszopiclone group (Table 2). The mean age (SD) was 44 (±11) years, most patients

were Caucasian (79%), and there were more women (63%) than men in the study. The 9 sleep and daytime ratings collected at baseline with IVRS for the 2 treatment groups were not significantly different (Tables 3 and 4).

There were similar, not statistically different, discontinuation rates in the eszopiclone and placebo groups (39.5% and 43.4%, respectively; Table 1), and survival analysis indicated that the rate of discontinuation was not different ($P = .2$; Figure 1). The rates of discontinuations due to adverse events was 7.1% in the placebo group and 12.8% in the eszopiclone group ($P < .05$), while the rate of voluntary withdrawals was 26.0% in the placebo group compared with 13.8% for the eszopiclone group ($P < .001$). Adherence to the treatment regimen during the double-blind period was calculated using the number of doses taken (determined by tablets counts obtained at the sites each month) divided by the number of doses to be taken (calculated as the number of days on study), multiplied by 100. The mean adherence rate was 94.4% and 90.6% for eszopiclone and placebo, respectively, and the mean number of tablets taken each week was 6.6 for eszopiclone and 6.3 for placebo.

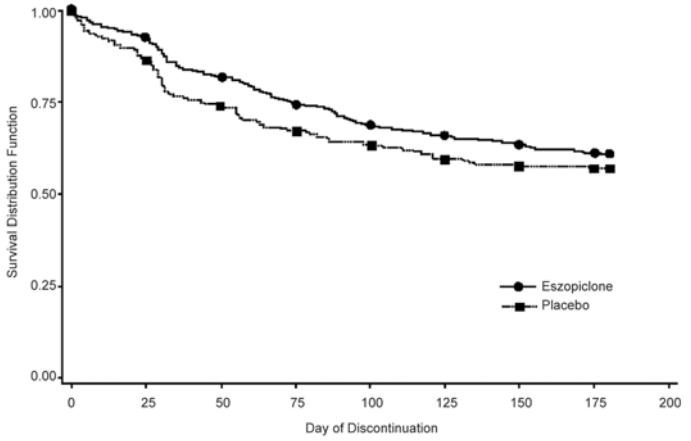

Figure 1—Kaplan-Meier plot of time to discontinuation over the treatment period. There was no significant difference in the rate of discontinuation for patients receiving eszopiclone compared with those receiving placebo ($P = 0.2$).

Efficacy Results

Data from Week 1 were examined as a measure of short-term efficacy and sustained efficacy was assessed monthly throughout the trial. There were statistically significant treatment differences in sleep onset at the first measured time point ($P < .0001$; Table 3), and this effect was maintained for 6 months (Figure 2A). During the first week, the median sleep latency per night was 30 minutes for the eszopiclone group and 60 minutes for placebo. After 6 months of treatment, the median sleep latency per night was 30 minutes for the eszopiclone group and 45 minutes for placebo ($P < .0001$).

Treatment effects were also evident in measures of sleep maintenance. During the first week of treatment, patients taking eszopiclone reported a median nightly WASO of 20 minutes, compared with 45 minutes for the placebo group ($P < .0001$; Table 3). This effect was maintained consistently over the treatment period (median WASO at Month 6: 21 vs 30 minutes for eszopiclone and placebo, respectively; $P = .0032$), and was significant throughout the study (Figure 2B). A similar finding was noted in 2 other measures of sleep maintenance: number of awakenings per night and number of nights per week when there was at least 1 awakening (Table 3). Differences between eszopiclone and placebo groups were statistically significant at every time point. After 6 months of treatment, the median number of nightly awakenings was 2.0 for patients receiving placebo and 1.6 for eszopiclone ($P < .0001$), while the median number of nights patients were awakened each week was 5.2 nights for placebo compared with 4.0 nights for eszopiclone ($P = .0001$).

Improvements in sleep onset and sleep maintenance contributed to increased median total sleep time, which was approximately 30-40 minutes longer per night for patients who received eszopiclone compared with those who received placebo. At baseline, patients in both groups reported a median total sleep time of 300 minutes (Table 3). This median was increased by 75 minutes during the first week of treatment for the eszopiclone group (median total sleep time: eszopiclone 375, placebo 330 minutes; $P < .0001$; Table 3). At the first month and every month thereafter, these effects on total sleep time were maintained and were highly significant, with median total sleep times of 382 minutes for the eszopiclone group and 345 minutes for the placebo group at Month 6 ($P < .0001$). The findings for quality of sleep were similar. At baseline, the score for sleep quality for the 2 treatment groups was

Table 4—Summary of sleep quality and ratings of next day functioning for Intent-to-Treat population using Last Observation Carried Forward technique.

			Placebo		Eszopiclone 3 mg				
Category	Endpoint	Timepoint	Mean (SD)	Median	Mean (SD)	Median	*t* value	df	*P* value
Sleep Quality	Sleep quality*	Baseline	3.5 (2.0)	4.0	3.5 (2.0)	4.0	-0.56	696	.5782
		Week 1	4.4 (2.2)	4.0	6.0 (2.2)	6.0	7.29	457	< .0001
		Month 1	5.0 (1.7)	5.3	6.2 (1.8)	6.3	8.11	650	< .0001
		Month 2	5.3 (1.7)	5.5	6.4 (1.7)	6.5	7.37	661	< .0001
		Month 3	5.3 (1.7)	5.5	6.4 (1.7)	6.5	7.71	663	< .0001
		Month 4	5.5 (1.7)	5.7	6.4 (1.8)	6.5	5.74	663	< .0001
		Month 5	5.3 (1.8)	5.5	6.4 (1.7)	6.5	6.73	665	< .0001
		Month 6	5.5 (1.8)	5.5	6.4 (1.8)	6.5	5.94	665	< .0001
Next-day function	Daytime ability to function*	Baseline	5.6 (1.8)	6.0	5.6 (2.1)	5.0	0.12	696	.9032
		Week 1	5.6 (2.0)	6.0	6.8 (1.9)	7.0	6.02	457	< .0001
		Month 1	6.1 (1.7)	6.3	6.8 (1.6)	7.0	5.23	650	< .0001
		Month 2	6.2 (1.6)	6.5	6.9 (1.6)	7.0	4.55	661	< .0001
		Month 3	6.2 (1.7)	6.5	6.8 (1.7)	7.0	4.52	663	< .0001
		Month 4	6.3 (1.6)	6.5	6.8 (1.7)	7.0	4.08	663	< .0001
		Month 5	6.1 (1.7)	6.3	6.8 (1.7)	7.0	4.74	665	< .0001
		Month 6	6.2 (1.8)	6.3	6.8 (1.7)	7.0	4.29	665	< .0001
	Daytime alertness*	Baseline	4.7 (2.0)	5.0	4.6 (2.1)	5.0	-0.57	696	.5659
		Week 1	4.9 (2.2)	5.0	6.1 (2.1)	6.0	5.70	457	< .0001
		Month 1	5.5 (1.6)	5.8	6.3 (1.7)	6.3	5.30	650	< .0001
		Month 2	5.7 (1.6)	6.0	6.5 (1.8)	6.6	5.60	661	< .0001
		Month 3	5.8 (1.6)	6.0	6.4 (1.8)	6.8	5.06	663	< .0001
		Month 4	5.8 (1.7)	6.0	6.4 (1.7)	6.7	4.42	663	< .0001
		Month 5	5.7 (1.7)	6.0	6.5 (1.7)	6.7	5.26	665	< .0001
		Month 6	5.9 (1.7)	6.0	6.5 (1.7)	6.8	4.58	665	< .0001
	Sense of physical well-being*	Baseline	5.9 (2.0)	6.0	5.9 (2.1)	6.0	-0.20	696	.8387
		Week 1	5.7 (2.1)	6.0	6.6 (2.0)	7.0	4.97	457	< .0001
		Month 1	6.1 (1.7)	6.3	6.6 (1.6)	6.8	4.18	650	< .0001
		Month 2	6.1 (1.7)	6.1	6.7 (1.7)	7.0	4.40	661	< .0001
		Month 3	6.1 (1.7)	6.3	6.7 (1.7)	7.0	4.11	663	< .0001
		Month 4	6.2 (1.7)	6.3	6.6 (1.7)	6.8	3.14	663	.0017
		Month 5	6.1 (1.7)	6.3	6.6 (1.7)	6.8	3.89	665	.0001
		Month 6	6.1 (1.8)	6.3	6.7 (1.7)	6.9	3.81	665	.0002

*Higher numbers indicate more positive ratings

the same (median score = 4 out of 10 for each group; Table 4). After 1 week of treatment, patients who received eszopiclone reported a 50% increase in sleep quality (median score = 6), while the score for patients receiving placebo remained unchanged. The 2 groups were significantly different, and this effect was maintained for the study duration ($P < .0001$; Table 4). At 6 months, the median sleep quality scores were 5.5 for the placebo group and 6.5 for eszopiclone ($P < .0001$).

At baseline, the median ratings for next-day function measures were approximately 5 to 6 for each group for each measure (Table 4). After 1 week and for the duration of the study, there were significant differences in all measures ($P < .002$; Table 4). During the first week, the eszopiclone group experienced a 40% improvement over baseline in patient ratings of daytime ability to function and approximately a 20% improvement in patient ratings of daytime alertness and sense of physical well-being, while there was no change in the placebo group. An improvement of 5% to 25% was noted in these parameters at the end of the treatment period for placebo patients, compared with approximately 20% to 40% improvement for the eszopiclone group.

The medians and *P*-values reported above were all the results of the analysis of the ITT population using an ANOVA of the ranked transformed measures. The same effects were found whether the population analyzed was the ITT population, the Completers, or the Observed Cases (Figures 2A and 2B), or whether ANOVA on the ranked data, ANOVA on the log-transformed data, or the Wilcoxon rank-sum test was used to analyze the data, demonstrating the robustness of the findings. Even after Bonferroni adjustment for multiplicity on the 63 variables (utilizing the planned analytical method on the ITT population with LOCF), virtually all comparisons remained statistically significant. That is, the familywise error rate for all of the statistical statements made is less than 0.05. Similar numeric differences between eszopiclone and placebo groups were also noted in all efficacy parameters among subjects who discontinued the study (data not shown), suggesting that the effect of eszopiclone was not driven by a high dropout rate among non-responders. In short, tolerance to eszopiclone did not develop in any of the endpoints measured, and the statistically significant treatment effects were maintained throughout the study.

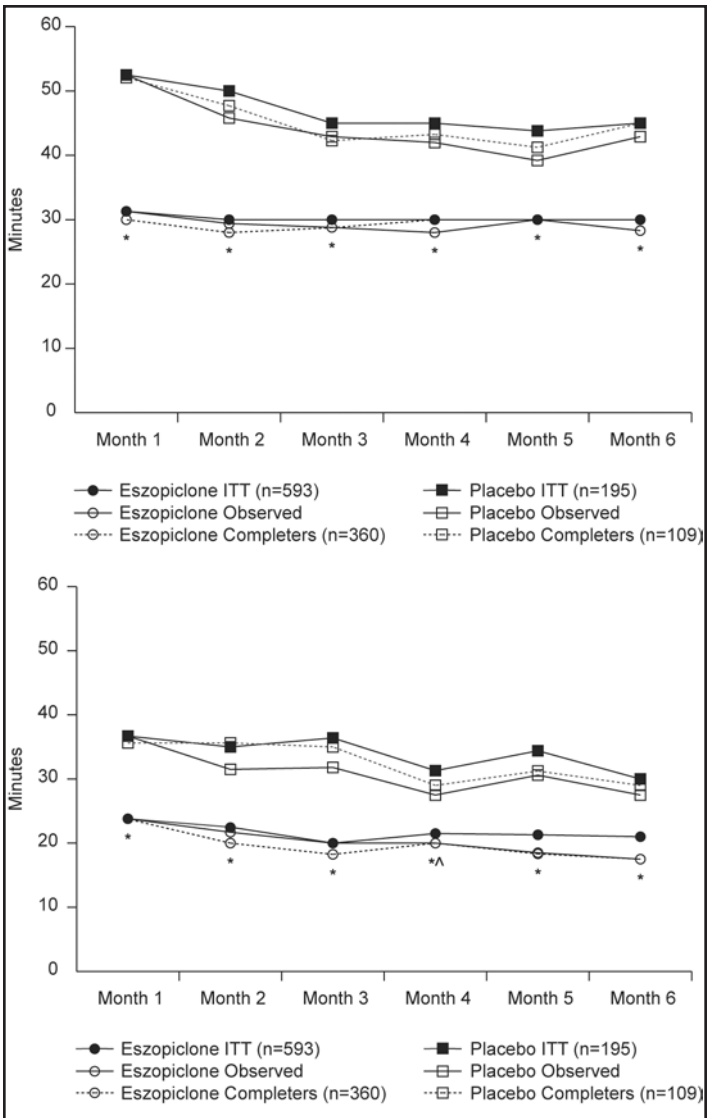

Figure 2A—Median sleep latency in minutes over the treatment period for the Intent to Treat (ITT) group, Observed cases, and Completers. *$P < .005$ for all comparisons.

Figure 2B—Median sleep maintenance (time awake after sleep onset in minutes [WASO]) over the treatment period for the Intent to Treat (ITT) group, Observed cases, and Completers. *$P < .05$ for all comparisons, except ^$P = .07$ for Observed case at Month 4.

Safety Results

Analysis of clinical laboratory studies, vital signs, electrocardiograms, and findings on physical examination indicated that there was no evidence of significant drug-related safety issues for the 6-month treatment period. Tolerability data are presented in Table 5. All adverse events with a frequency of at least 5%, regardless of causality, are provided; these events may be clinically relevant for the physician when they are treatment related. Over the 6-month study period, all-causality adverse event rates were 81.1% for the eszopiclone group, compared with 70.8% for the placebo group. The majority of adverse events in each group were mild or moderate in severity (placebo, 89.2%; eszopiclone, 87.7%), and the most common adverse events were unpleasant taste, headache, infection, pain, nausea, and pharyngitis. The vast majority of infections (approximately 85% in each group) were due to mild to moderate symptoms of the common cold that were not associated with fever or alterations in white blood cell count, and none resulted in discontinuation from the study or were considered to be treatment related. For most of these adverse events, the duration of events was the same or shorter within the eszopiclone group, and the severity was generally mild or moderate. The percentage of subjects with adverse events that the investigator considered to be of *"unknown"* relationship to treatment were similar in both groups, 6.2% for placebo and 6.4% for eszopiclone, while the percentage with adverse events considered *"possibly related"* were 25.1% and 29.5%, respectively. The percentage of patients who had adverse events considered *"probably"* or *"definitely related"* to study drug were 7.2% and 22.6%, respectively, and the majority of this difference was accounted for by unpleasant taste, an event that led to discontinuing participation in the study in 0.5% of patients taking placebo and 1.7% of patients taking eszopiclone.

Table 5—Summary of all adverse events reported with a frequency ≥ 5% in any group.

	Placebo (n = 195) No. (%)	**Eszopiclone 3 mg** (n = 593) No. (%)
Abdominal pain	11 (5.6)	48 (8.1)
Accidental injury	11 (5.6)	43 (7.3)
Asthenia	11 (5.6)	26 (4.4)
Back pain	6 (3.1)	45 (7.6)
Diarrhea	14 (7.2)	45 (7.6)
Dizziness	6 (3.1)	58 (9.8)
Dry mouth	3 (1.5)	39 (6.6)
Dyspepsia	13 (6.7)	41 (6.9)
Headache	37 (19.0)	116 (19.6)
Infection	13 (6.7)	94 (15.9)
Nausea	11 (5.6)	67 (11.3)
Pain	12 (6.2)	67 (11.3)
Pharyngitis	10 (5.1)	59 (9.9)
Rash	6 (3.1)	31 (5.2)
Rhinitis	9 (4.6)	42 (7.1)
Sinusitis	11 (5.6)	25 (4.2)
Somnolence	5 (2.6)	54 (9.1)
Unpleasant taste	11 (5.6)	155 (26.1)

Over the 6-month period, the rate of discontinuation due to adverse events was 12.8% in the eszopiclone group and 7.1% in the placebo group ($P < .05$), and the most common reasons were somnolence (2.2% for eszopiclone, 1.5% for placebo), depression (2.0% and 0%, respectively), unpleasant taste (1.7% and 0.5%), headache (0% and 2.0%), asthenia (1.0% and 1.5%), and insomnia (0% and 1.5%). Rates of discontinuation due to severe events were low in both groups (placebo, 0.5%; eszopiclone, 0.3%). The 2 groups had a similar low incidence of serious adverse events, regardless of causality (placebo, 1.0%; eszopiclone, 2.9%), and the most common serious adverse events observed were similar in proportion: gastrointestinal disorder (1 placebo, 3 eszopiclone; 0.5% per group) and chest pain (1 placebo, 3 eszopiclone; 0.5% per group). Serious adverse events that were considered to be *"possibly related"* to treatment occurred in 0.34% of patients (2/593) taking eszopiclone over the 6-month treatment period, 2.53% of patients (15/593) had serious adverse events considered to be *"unrelated"* to treatment, and none had a serious adverse event that was considered to be *"definitely related"* to treatment.

Following discontinuation of the drug (after either 6 or 12 months of nightly use), there were similar overall rates of *"new"* events (those not seen during the treatment period, or a worsening of an event) in the placebo (10.7%) and eszopiclone (11.2%) groups. There were no reports of seizures, hallucinations, or perceptual-disturbance events that are commonly reported as withdrawal symptoms following termination of sedative-hypnotic medications; there was 1 report of anxiety in the eszopiclone group. These data provide an indication that there were no clinically significant withdrawal symptoms following discontinuation of eszopiclone after 6 or 12 months of nightly use.

The higher incidence of unpleasant taste in the eszopiclone group raised the concern that some patients may have been aware of their treatment assignment, leading to bias. However, significant treatment differences were maintained following removal of data from patients with gustatory adverse events from the analysis. Additionally, when comparing patients who received eszopiclone and reported unpleasant taste with those who received eszopiclone but did not report unpleasant taste, we found very similar results, with no significant differences in any of the parameters. There were also similar rates of adherence (99% for those with gustatory side effects, and 93% for those without) and completion (58% and 67%, respectively). These data present strong evidence that gustatory side-effects did not have a significant impact on the results of this study.

DISCUSSION

The results of this study demonstrate that nightly use of eszopiclone 3 mg, resulted in statistically significant differences in patient-reported measures of sleep onset, sleep maintenance, sleep quality, and next-day function compared with placebo in patients with chronic insomnia. These differences were apparent during the first week of treatment and were maintained throughout 6 months of double-blind treatment, with no evidence of tolerance. This study provides compelling evidence of effective long-term pharmacologic treatment of primary insomnia. The findings increase the period of sustained efficacy that has been demonstrated in large, randomized, double-blind placebo-controlled studies from approximately 1 month[2-4] to 6 months. This has important clinical implications in light of growing evidence of the significant morbidity of untreated chronic insomnia, the unremitting nature of insomnia, and the common practice of long-term pharmacologic management that has been carried out without empirical support for the sustained benefit of the treatment.[1,9]

This evidence for sustained efficacy contrasts with the commonly held view that hypnotics are ineffective in the long-term treatment of insomnia. While there is a belief that this long-held view has experimental support,[21] the limited data available prior to the current study—data that consists primarily of 2 placebo-controlled studies exceeding 5 weeks in duration—do not provide a basis for this conclusion. Morin and colleagues[5] reported that 20 patients who took temazepam 7.5 to 30 mg (individually titrated) on an average of 75% of nights during an 8-week treatment period experienced significantly greater improvement in sleep (at the end of the treatment period) on both polysomnographic and subjective measures compared with 20 patients who received placebo. In another study, 50 subjects receiving lormetazepam 2 mg had significantly shorter sleep-onset latency, as recorded in sleep diaries, compared with 25 patients receiving placebo after 6-months of nightly treatment. In the same study, 25 subjects took nitrazepam 5 mg without benefit for sleep latency, and, while both medications led to initial improvement in sleep quality compared with placebo, this difference was no longer evident after 6 months.[22] An epidemiologic study of 532 patients reporting long-standing insomnia and chronic use of medication to help their sleep found that 67% of patients rated their sleep quality as improved.[21] The current study provides the first data derived from a large, randomized, double-blind, placebo-controlled study with which to empirically assess long-term efficacy, and it provides evidence that eszopiclone has sustained efficacy over 6 months of nightly treatment.

One of the major methodologic challenges of long-term clinical trials is to retain a sufficient number of patients to enable a meaningful comparison of treatments at the end of the trial and to determine how to statistically handle patients who discontinue their participation in the study. In some instances, excessive rates of dropout may make it impossible to test the study hypotheses.[23] If not appropriately analyzed, a differential dropout rate due to non-response can lead to an erroneous conclusion of sustained efficacy. We hypothesized a dropout rate of 50% when we were designing the study, and the actual rate was 40.3%. It is remarkable that the active treatment and placebo had approximately the same rate of discontinuation (Table 1 and Figure 1; $P = 0.2$). The placebo group had more voluntary withdrawals (presumably due to lack of efficacy) and fewer discontinuations because of adverse events.

In order to definitively establish that hypnotic efficacy was maintained throughout the 6-month treatment, and was not the result of nonresponsive patients prematurely discontinuing their participation in the study, we performed several statistical analyses. The same results were obtained when the analyses were performed on the Observed Cases population (all randomly assigned patients for whom data were collected at month *t*) and the Completers population (comprising those patients who completed 6 months of double-blind treatment). Further, in both treatment groups, those who dropped out and those who remained in the study experienced a similar degree of improvement during the time they remained in the study. When analyzing the ITT population (comprising of all randomized patients), we used the LOCF technique to impute the values of missing data. This technique does so by assuming that the value at dropout would have remained the same until the end of the trial. That is, it assumes that patients who drop out for lack of efficacy would continue to have no response through the remainder of the trial and those who have a good response but are lost to follow-up would have continued to have a favorable response were they to have stayed in the trial. Although it has its shortcomings, this method of imputation has the desirable property that it retains all subjects and preserves the randomization. The results of the analyses based on this approach were essentially the same as the other 2 analyses described above. The consistency of these 3 analyses provides robust evidence that efficacy was maintained (ie, tolerance did not occur) in all measures of sleep and next-day function over 6 months of nightly treatment with eszopiclone.

The primary aim of this study was, broadly, to determine the feasibility of long-term efficacy trials in insomnia and, specifically, to determine the long-term efficacy of eszopiclone in the management of chronic insomnia. However, some issues related to long-term therapy could not be easily addressed within the design of the current study and remain unanswered. For example, while the present data support the continued efficacy of eszopiclone, and, hence, a decreased likelihood of dose escalation, formal placebo-controlled trials are needed to evaluate discontinuation effects and drug-seeking behavior. The absence of polysomnography data, in addition to patient reports, is a limitation of this study. For example, subjective self-assessments are more likely to be influenced in

the event of "unblinding" because of side effects in the active-drug condition, whereas objective measures would presumably be less susceptible to such bias. Our reanalysis of data in patients with gustatory adverse events found no evidence that this type of bias occurred. Nevertheless, polysomnography measures over the 6 months would have provided additional important information, and the use of polysomnography should be considered in future studies evaluating long-term efficacy. However, we would expect the same study results with polysomnography measures given that, in a recent 6-week, placebo-controlled study, eszopiclone 3 mg was found to have very similar effects on both polysomnographic and subjective measures of sleep onset and sleep maintenance in patients with chronic insomnia.[17]

It is notable that the sustained efficacy of eszopiclone was evident simultaneously in measures of sleep initiation, maintenance, and quality. Evidence of efficacy has been previously reported in studies of shorter duration for all of these measures (sleep maintenance in terms of awakenings) for the benzodiazepines flurazepam, estazolam, and temazepam.[2-4,24] On the other hand, nonbenzodiazepines such as zaleplon and zolpidem usually have significant effects on sleep-onset measures, but not on sleep-maintenance variables.[3,4] Improving both sleep onset and maintenance may be a particularly important attribute for treatments of chronic insomnia given recent evidence that the type of sleep difficulty changes over time in many individuals with chronic insomnia.[18]

Another important finding of this study is that sustained improvement in all of these measures of sleep was accompanied by perceived improvements in daytime function. Though it would have been valuable to have objective measures of next-day functioning to corroborate these findings, these results add to the growing body of evidence of the relationship between chronic sleep disturbance and functional impairment[6,19] and provide an indication that effective treatment of chronic insomnia may improve the associated deficits. This is worthy of further study.

The use of eszopiclone led to improvements in sleep and daytime function without causing clinically significant side effects. There was no evidence for any systematic adverse effects with eszopiclone that led to discontinuation or that represent a safety risk unique to longer-term treatment. Following discontinuation, patients were queried for adverse events 5 to 7 days later. There were no significant adverse events that occurred following abrupt discontinuation of eszopiclone at the end of the open-label phase or for those that discontinued at any time during the study. This suggests that after taking eszopiclone for 6 months (in 86 patients) and 12 months (in 296 patients), there was no evidence of significant withdrawal symptoms.

As the longest and largest placebo-controlled investigation of the pharmacologic treatment of insomnia to date, this study has implications for the design of future studies of insomnia treatment. For example, the observed dropout rate of 40%; the use of convenient, time-stamped data-collection systems, such as IVRS; or offering open-label treatment following the randomization phase should be considered. Perhaps most importantly, this study demonstrates the feasibility of conducting long-term efficacy studies for the pharmacologic management of insomnia and establishes that eszopiclone is an effective long-term treatment for chronic insomnia.

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