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SCIENTIFIC INVESTIGATIONS

Efficacy and safety of esmirtazapine in adult outpatients with chronic primary insomnia: a randomized, double-blind placebo-controlled study and open-label extension

Neely Ivgy-May, PhD[1]; Goeran Hajak, MD[2]; Gonnie van Osta, MSc[1]; Sabine Braat, MSc[3]; Qing Chang, MD, PhD[1]; Thomas Roth, PhD[4]

[1]Merck & Co., Inc., Kenilworth, New Jersey; [2]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Social Foundation Bamberg, Bamberg, Germany; [3]MSD, Oss, The Netherlands; [4]Henry Ford Hospital, Detroit, Michigan

Study Objectives: Esmirtazapine (1.5–4.5 mg) has demonstrated short-term sleep-promoting effects in nonelderly outpatients with chronic insomnia. This phase 3, randomized, double-blind study (NCT00631657) and its open-label extension (NCT00750919) investigated efficacy and safety of long-term esmirtazapine treatment in adult outpatients with chronic insomnia.

Methods: Participants were randomized to receive esmirtazapine 4.5 mg or placebo for 6 months; those receiving esmirtazapine were then rerandomized to esmirtazapine or placebo for an additional 7 days. Participants could enter the 6-month open-label extension with esmirtazapine 4.5 mg. The primary objective of the double-blind study was to assess long-term efficacy of esmirtazapine vs placebo on self-reported total sleep time. Assessing long-term safety and tolerability were secondary and primary objectives of the double-blind and extension studies, respectively.

Results: Overall, 457 participants received treatment in the double-blind study (esmirtazapine, n = 342; placebo, n = 115) and 184 participants (prior esmirtazapine, n = 136; prior placebo, n = 48) received esmirtazapine in the extension. In the double-blind study, a 48.7-minute increase in average nightly total sleep time was observed for esmirtazapine vs placebo (95% confidence interval, 35.0–62.5; $P < .0001$) at months 4–6. There was no evidence of residual effects on next-day alertness or daytime functioning and no evidence of rebound insomnia or withdrawal symptoms upon treatment discontinuation. Esmirtazapine was generally well tolerated; somnolence and weight gain were the most common adverse events.

Conclusions: Esmirtazapine improved sleep duration vs placebo over at least 6 months. There was no evidence of next-day residual effects or of withdrawal symptoms or rebound insomnia following abrupt treatment discontinuation.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: A 6-Month Efficacy and Safety Study of Org 50081 in Adult Patients With Chronic Primary Insomnia (21106/P05701/MK-8265-002); URL: https://clinicaltrials.gov/ct2/show/NCT00631657; Identifier: NCT00631657; and Registry: ClinicalTrials.gov; Name: Twenty-Six Week Extension Trial of Org 50081 (Esmirtazapine) in Outpatients With Chronic Primary Insomnia (176003/P05721/MK-8265-007); URL: https://clinicaltrials.gov/ct2/show/NCT00750919); Identifier: NCT00750919.

Keywords: chronic insomnia, clinical trial, efficacy, esmirtazapine, long-term, outpatients, safety

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Esmirtazapine has demonstrated short-term efficacy in nonelderly phase 2 and 3 trial participants with insomnia. However, given the chronic nature of insomnia, longer-term studies are required to confirm the efficacy and safety of esmirtazapine.

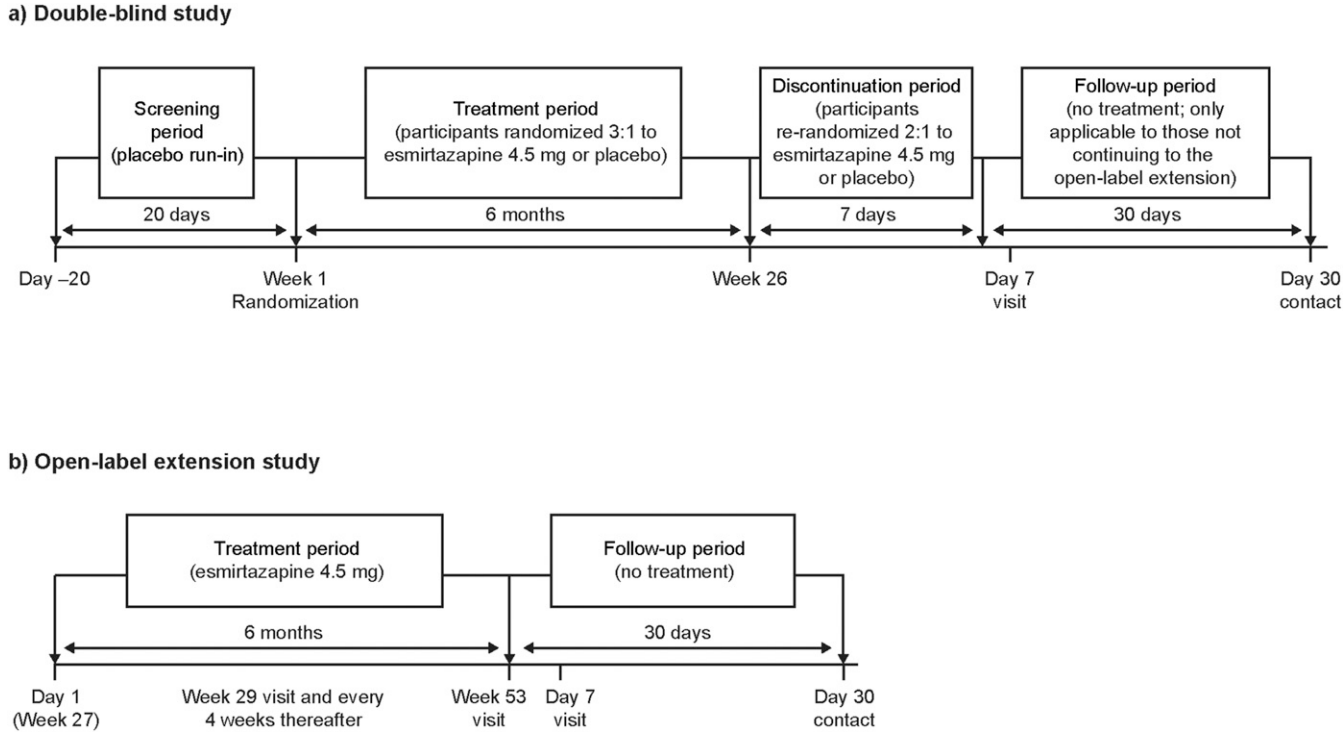
Study Impact: In this long-term trial in participants with chronic insomnia, esmirtazapine significantly improved total sleep time over placebo, with effects maintained through at least 6 months. Esmirtazapine was generally well tolerated, and there was no evidence of withdrawal effects or rebound insomnia after abrupt treatment discontinuation.

INTRODUCTION

Insomnia is characterized by difficulty initiating or maintaining sleep or a reduced quality of sleep despite adequate opportunity and a suitable environment for sleep.[1] It is the most frequent sleep disorder reported by the general population[1] and seems to affect around 20% of adults (based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]).[2] Individuals affected by insomnia report impaired daytime functioning, including reduced social and occupational functioning, leading to a lower overall quality of life and an increased risk of new or recurrent psychiatric disorders.[3–5] Moreover, objective short sleep duration has been linked to an increased risk of other illnesses such as hypertension and type 2 diabetes.[6,7]

A number of sleep-promoting agents are commonly used to treat insomnia in clinical practice. These include agents that specifically target γ-aminobutyric acid type A receptors, such as the benzodiazepines temazepam and triazolam and other benzodiazepine receptor agonists such as zolpidem, zaleplon,

Figure 1—Study design.



and eszopiclone.[8] Although effective in promoting sleep, γ-aminobutyric acid type A modulators elicit global inhibitory effects in the central nervous system, which makes them liable to a host of side effects (eg, rebound insomnia, memory failures, and abuse potential[9,10]). In addition to γ-aminobutyric acid type A modulators, histaminic H_1 receptor antagonists are also known to have hypnotic actions.[11] Of these, doxepin was the first antidepressant (at low, nonantidepressant doses) to be approved by the Food and Drug Administration for the treatment of insomnia.[12] However, doxepin has a highly circumscribed effect, which limits its effect on sleep to the middle and end of night.[9] Other hypnotic agents approved for the treatment of insomnia include melatonin agonists such as ramelteon, which are limited to improving sleep onset, and the orexin receptor antagonist suvorexant.[8,12]

The antidepressant mirtazapine, which is indicated for the treatment of major depressive disorder, has been shown to also have sleep-promoting effects in both healthy volunteers[13] and patients with major depressive disorder accompanied by sleep complaints.[14] Mirtazapine is a racemic mixture of R(−) and S(+) enantiomers, which acts by blocking 5-HT_2 and 5-HT_3 receptors, thereby enhancing 5-HT_{1A}–mediated transmission and modulating noradrenergic and serotonergic neurotransmission.[15] Esmirtazapine, the maleic acid salt of the S(+) enantiomer of mirtazapine, has a shorter half-life than the racemic mixture, indicating that it could be associated with a reduced risk of next-day residual sedative effects. The short-term efficacy and safety of esmirtazapine (1.5, 3.0, and 4.5 mg) has been investigated in phase 2/3 trials involving nonelderly (aged 18–65 years) individuals with insomnia.[16–18] Compared with placebo, esmirtazapine provided significant improvements in total sleep time (TST), sleep latency (SL), sleep quality, and satisfaction with sleep duration, as well as a significant reduction in wake time after sleep onset (WASO). Furthermore, esmirtazapine was generally well tolerated, with minimal residual daytime effects and no signs of rebound insomnia.

Given the chronic nature of insomnia, long-term studies are needed to confirm the efficacy and safety of treatments observed in short-term studies. Here, we report results from a 6-month, phase 3, randomized, double-blind, placebo-controlled study and its 6-month open-label extension involving adult outpatients with chronic insomnia who received esmirtazapine 4.5 mg or placebo. The primary objective of the double-blind study was to demonstrate the efficacy of esmirtazapine vs placebo on total sleep time, with an investigation of long-term safety and tolerability as a key secondary objective. The primary objective of the open-label extension was to investigate the safety and tolerability of long-term treatment with esmirtazapine.

METHODS

Study design

The 6-month, double-blind, randomized, phase 3, placebo-controlled, parallel-group study (Sponsor Protocol P05701; NCT00631657) comprised a 7- to 20-day single-blind placebo run-in period (washout), during which participants were assessed for their eligibility to enter the trial (**Figure 1**). This was followed by a 6-month double-blind active treatment period, at the start of which (day 1) participants were randomized in a 3:1 ratio

using an Interactive Voice Response system to receive either esmirtazapine 4.5 mg or placebo. Study drug was to be taken once daily as an oral tablet in the evening, 30 minutes before going to bed. After 6 months, participants who were treated with esmirtazapine and who completed the double-blind study were rerandomized 1:2 to receive double-blind treatment of either esmirtazapine 4.5 mg or placebo, respectively, for an additional 7-day period to assess the effect of abrupt discontinuation of esmirtazapine. Those participants receiving placebo as part of the double-blind study continued to receive placebo for the additional 7 days.

Participants who completed the double-blind study were eligible for inclusion in the 6-month open-label extension (Sponsor Protocol P05721; NCT00750919), where all participants received esmirtazapine 4.5 mg (**Figure 1**). Any participants not continuing in the open-label extension had a follow-up visit 7 days after discontinuation to assess serious adverse events (SAEs) and adverse events (AEs). A telephone call took place 30 days after discontinuation to follow up on any new or ongoing SAEs.

The trial was carried out in compliance with the ethical principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice, as well as applicable local regulatory requirements. All participants gave written informed consent before trial enrollment. The clinical development of esmirtazapine was discontinued in 2010.

Study population

Eligible participants (aged ≥18 to <65 years) must have been diagnosed with chronic primary insomnia according to DSM-IV-TR criteria[19] and must have experienced the following for at least 1 month, based on their medical history, for ≥3 nights per week: TST ≤ 6.5 hours; WASO ≥ 60 minutes; and SL ≥ 30 minutes. Participants had to have a normal bedtime within 21:00 to 01:00 hours, with variations not exceeding 2 hours for 5 out of 7 nights. In the week preceding randomization, participants must have independently completed an electronic sleep diary (LogPad) and daily morning questionnaires for at least 6 out of 7 days. Study selection criteria were fulfilled during the screening period.

Participants were excluded if they had the following: other sleep disorders based on DSM-IV-TR criteria[19]; sleep disturbances comorbid with significant medical or DSM-IV-TR psychiatric illness; a current diagnosis (DSM-IV-TR) of major depressive disorder or had been diagnosed and treated for major depressive disorder within the last 2 years; and a history of bipolar disorder or attempted suicide or a family history of attempted suicide. Participants were also excluded if they drank more than 2 alcoholic drinks per day, smoked more than 15 cigarettes per day and/or could not abstain from smoking during the night, or had a caffeine intake greater than 500 mg per day.

The washout period for pretrial medication for the double-blind study was required to be at least 5 times the elimination half-life of the active compound. Concomitant medications with a clear influence on sleep were not allowed during the studies and were discontinued from the screening visit onwards. Any concomitant medication was to be recorded on the medication electronic case report form by the investigator or other designated individual, including medication used up to 30 days prior to screening.

Randomization

Given that participants receiving active treatment provide more relevant information on safety than those receiving placebo, a randomization ratio of 3:1 (esmirtazapine:placebo) was used to maximize exposure to esmirtazapine while maintaining sufficient data to allow comparison between treatment groups.

Endpoints: double-blind study

The primary efficacy outcome of TST was measured by subjective self-reported TST during months 4–6. Key secondary efficacy outcomes were SL and WASO, and other sleep maintenance parameters included number of awakenings (NAW), sleep quality, and satisfaction with sleep duration.

Self-reported efficacy outcomes were recorded using the LogPad electronic sleep diary. Sleep diaries were recorded daily during screening, during the 6-month treatment period, and during the discontinuation period. A morning questionnaire, completed approximately 0.5–1 hours after arising, consisted of 6 questions that assessed compliance, TST, SL, WASO, and NAW. During screening, week 2, every fourth week after week 2, and discontinuation, the daily diary included 4 additional morning questions that assessed quality of sleep, satisfaction with sleep duration, and alertness at awakening (to assess residual effects using a visual analog scale). Participants who recorded morning questionnaire information for at least 6 out of 7 days immediately preceding the randomization visit met the LogPad compliance inclusion criteria. In addition, an evening questionnaire, completed approximately 1–2 hours before going to bed (during screening, week 2, 4-week intervals for 7 days until week 26, and the 7-day discontinuation period), assessed energy, ability to work/function, and napping during the day.

At baseline, week 6, week 14 (month 4), and week 26 (month 6) or discontinuation, symptom severity was assessed using the Insomnia Severity Index (ISI). A clinician with at least 3 years of clinical experience who was blinded to treatment completed the 7-point Investigator Global Rating-Severity of symptoms scale (a greater reduction in score indicated a greater reduction in symptom severity) and the 7-point Investigator Global Rating-Change rating of the therapeutic effect of the treatment regimen compared with the start of double-blind treatment (not completed at baseline; lower scores indicated a greater therapeutic effect).

Safety and tolerability were assessed by monitoring AEs, clinical and physical examinations, vital signs, routine laboratory parameters, and electrocardiograms. Residual effects on alertness were assessed by a visual analog scale for feeling of tiredness or alertness; this was assessed at awakening and later when the LogPad diary was completed, as well as in the evening using a visual analog scale for daytime energy levels and daytime functioning. The effects of discontinuation of esmirtazapine treatment at the end of the double-blind 6-month treatment period were assessed by measuring rebound insomnia.

Discontinuation effects were recorded using the LogPad diary, the benzodiazepine withdrawal symptoms questionnaire, and assessment of AEs.

Endpoints: open-label extension study

Safety outcomes included monitoring of AEs, physical examinations, vital signs, routine laboratory parameters, and electrocardiograms.

Long-term exploratory efficacy endpoints included TST, WASO, SL, NAW, assessment of sleep quality, satisfaction with sleep duration (morning diary), and a napping assessment (evening questionnaire). Participants completed their morning diary daily throughout the study, with 4 additional morning questions and 4 evening questions completed during week 29 and every fourth week after that including during the 7-day follow-up period. ISI, Investigator Global Rating-Severity of symptoms scale, and Investigator Global Rating-Change were measured at weeks 33, 41, and 53. ISI scores were based on a validation report by Bastien et al.[20]

Statistical methods

Sample size

The sample size of 440 participants (330 esmirtazapine; 110 placebo) for the double-blind study was based on 90% power and 2-sided 5% level of significance to observe an increase of 25 minutes for the self-reported TST in favor of esmirtazapine, assuming an equal standard deviation (SD) of 70 minutes[21] in both arms and assuming no correlation between baseline and postbaseline TST (conservative). A difference of 25 minutes was considered the minimally clinically relevant increase. No correction for lost to follow up was included because of the method of statistical analysis.

Statistical analyses in the double-blind study

All efficacy analyses were performed for the intention-to-treat population; this consisted of all randomized participants with a baseline TST value and at least 1 postbaseline TST value. All efficacy data were analyzed based on treatment group as randomized. Superiority of esmirtazapine to placebo (primary hypothesis) was examined using analysis of covariance on the change from baseline (average of all available pretreatment data) to month 4–6 (average of weekly means of weeks 14–26) TST scores, with treatment and (pooled) center as fixed effects and baseline TST (an average of nonmissing values from the 7-day run-in period) as a covariate. The weekly mean of weeks 1–26 was obtained as the average of nonmissing daily diary data of that week (if ≤3 nonmissing days) or the weighted average of nonmissing daily diary data of the previous and that week (if >3 nonmissing days); the latter implied the mean of the previous week was carried forward (last observation carried forward) if no data were available. The estimate of the treatment difference between esmirtazapine and placebo (difference of the least-squares means of change from baseline) and associated 95% confidence interval (CI) were presented along with the test for treatment difference.

The key secondary efficacy variables, change from baseline in month 4–6 average SL and WASO with esmirtazapine vs placebo, were analyzed similarly. The multiplicity adjustment strategy for the primary and key secondary efficacy hypotheses was made using a fixed sequential procedure, whereby TST was analyzed first, followed by SL analysis and subsequent WASO analysis if the preceding hypothesis was rejected at the 2-sided .05 α level. To evaluate the robustness of the results of TST, SL, and WASO to the underlying missing-data assumption of the last observation carried forward approach, the observed case data were analyzed using a mixed-model approach. All other efficacy data in the double-blind study were summarized using descriptive statistics.

The safety analysis during the double-blind study was performed for the all-subjects-as-treated (AST) population, which consisted of all participants who received at least 1 dose of study medication. All safety data were analyzed based on treatment group as treated and summarized using descriptive statistics.

The special safety analysis during the 7-day discontinuation period was performed for the all-subjects-treated-after-completion group, which consisted of all participants who had received at least 1 dose of double-blind trial medication during the discontinuation phase. All parameters were analyzed based on treatment group (placebo-placebo, esmirtazapine-placebo, esmirtazapine-esmirtazapine) as treated and summarized using descriptive statistics.

Statistical analyses in the open-label extension study

The analysis was performed for the AST population, which comprised all participants who received at least 1 dose of study medication during the 6-month open-label treatment period. If a treatment week had ≤3 nonmissing diary entries, data from the previous and current weeks were taken into account using weighted means. If no diary data were available, the data were considered missing and not imputed. For the observed case, data were not carried forward for analysis if a participant discontinued; only missing values while receiving treatment were imputed (if at least one entry was recorded). Although all participants received esmirtazapine during the extension phase, participants were grouped according to the treatment received during the double-blind study (placebo or esmirtazapine). All safety and exploratory efficacy data captured during the open-label extension phase were characterized using descriptive statistics.

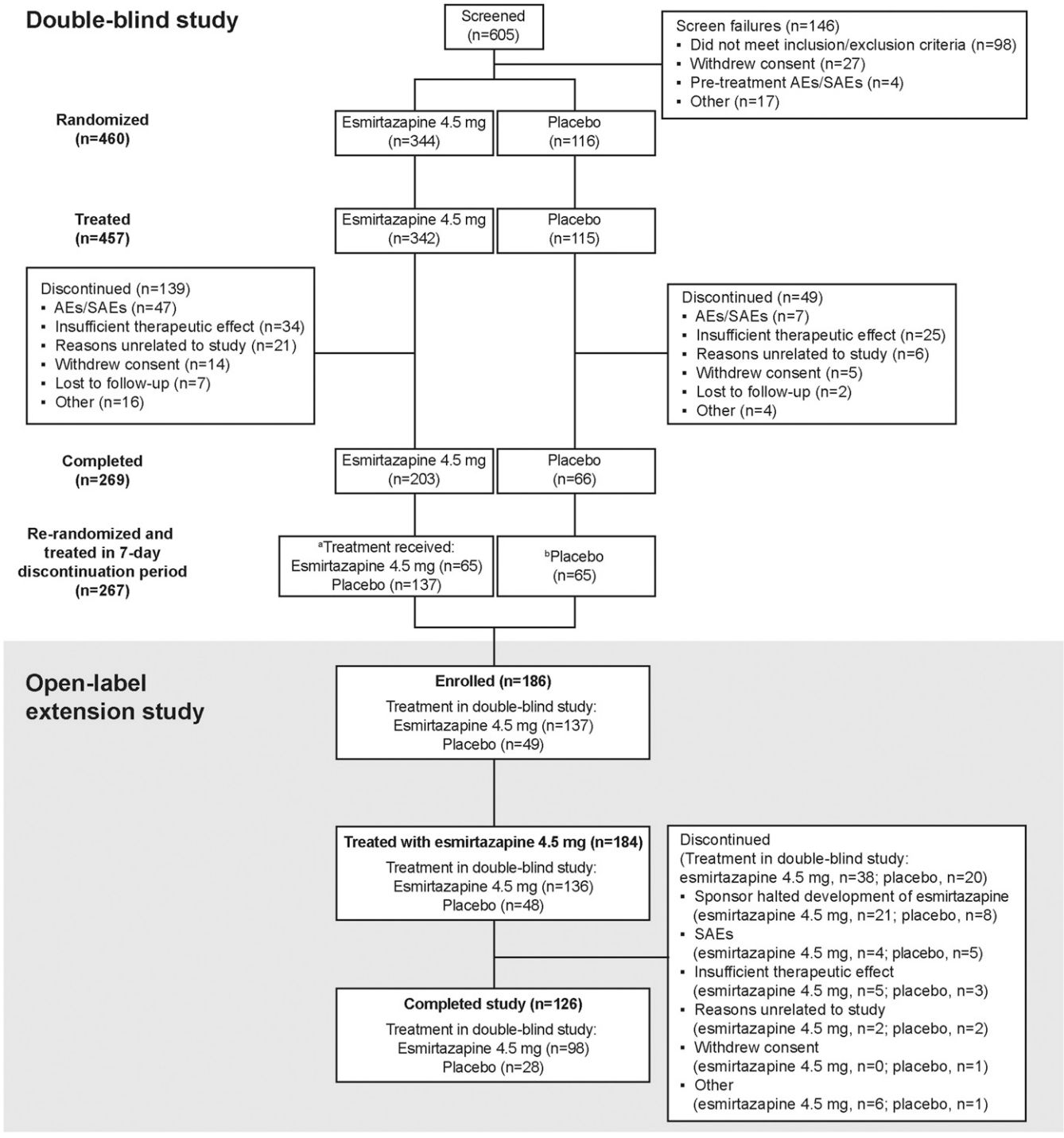
RESULTS

Double-blind study

Study population

The double-blind study was conducted between March 24, 2008 and December 9, 2009 at 48 centers in Asia, Canada, Europe, Latin America, and the United States. Of 605 participants screened, 460 were randomized and 457 were treated; 342 participants received esmirtazapine and 115 participants received placebo (**Figure 2**). All 457 participants were included in both the AST and intention-to-treat populations. The 6-month double-blind treatment period was completed by 203 of 342 (59.4%) participants who received esmirtazapine and 66 of 115 (57.4%) participants who received placebo. For esmirtazapine,

Figure 2—Participant disposition.



[a]One participant was randomized for the discontinuation period, although they did not complete the 6-month treatment period; this participant was not treated. An additional participant was randomized but not treated during the discontinuation period. [b]During the discontinuation period, one participant receiving placebo in the double-blind study did not continue to receive placebo. AE = adverse event, SAE = serious adverse event.

the main reasons for early discontinuation were experiencing an AE/SAE (47 of 139 [33.8%] discontinued participants) or insufficient therapeutic effect (34 of 139 [24.5%] discontinued participants). For placebo, the main reason for early discontinuation was insufficient therapeutic effect (25 of 49 [51.0%] discontinued participants). Overall, mean compliance with medication for the double-blind period was greater than 98% in both treatment groups (esmirtazapine, 99.4%; placebo, 98.5%); at each week, compliance was greater than 94% for each group. A LogPad compliance of 100% was reported for both the esmirtazapine and placebo groups. Participants who recorded morning questionnaire information for at least 6 out of 7 days

Table 1—Participant demographics and sleep parameters at screening.

Variables	Esmirtazapine 4.5 mg	Placebo	Total
Demographics (AST population)	**n = 342**	**n = 115**	**n = 457**
Sex, n (%)			
Male	132 (38.6)	44 (38.3)	176 (38.5)
Female	210 (61.4)	71 (61.7)	281 (61.5)
Mean age, years (SD)	47.4 (11.4)	49.0 (11.1)	47.8 (11.3)
Mean BMI, kg/m^2 (SD)	25.6 (4.3)	24.9 (4.1)	25.4 (4.3)
Race, n (%)			
White	244 (71.3)	86 (74.8)	330 (72.2)
Asian	68 (19.9)	22 (19.1)	90 (19.7)
Black or African American	23 (6.7)	5 (4.3)	28 (6.1)
Other[a]	7 (2.0)	2 (1.7)	9 (2.0)
Sleep parameters, median (minimum, maximum; ITT population)	**n = 342**	**n = 115**	
TST, min	314 (0, 546)	309 (45, 523)	
SL, min	64 (0, 377)	70 (12, 309)	
WASO, min	77 (0, 311)	80 (1, 346)	
Number of awakenings	1.8 (0, 8)	1.9 (0, 12)	
Quality of sleep	40.4 (0, 79)	38.4 (6, 78)	
Satisfaction with sleep duration	39.1 (0, 85)	37.0 (4, 78)	
Daytime naps	0 (0, 1)	0 (0, 1)	
ISI total score	18.0 (2, 28)	18.0 (5, 28)	
IGR total score	5.0 (3, 7)	5.0 (3, 7)	

[a]Includes Native Hawaiian or other Pacific Islander. AST = all-subjects-as-treated, BMI = body mass index, IGR = Investigator Global Rating, ISI = Insomnia Severity Index, ITT = intention-to-treat, SD = standard deviation, SL = sleep latency, TST = total sleep time, WASO = wake time after sleep onset.

immediately preceding the randomization visit met the LogPad compliance inclusion criteria. The mean (SD) duration of exposure to 6-month double-blind treatment was 134.6 (65.0) days for esmirtazapine and 128.1 (67.9) days for placebo.

Of the 203 participants who received esmirtazapine during, and completed, the double-blind study, 65 participants were randomized to esmirtazapine, and 137 participants were randomized to receive placebo during the 7-day discontinuation period. A total of 65 of 66 participants randomized to receive placebo during the double-blind study continued to receive placebo during the discontinuation period.

Treatment groups were comparable for demographics and baseline characteristics and sleep parameters (**Table 1** and **Table 2**). The proportion of participants with a body mass index categorized as obese (>30 kg/m^2) or overweight (25–30 kg/m^2) was smaller in the placebo group compared with esmirtazapine (44.3% and 51.8%, respectively).

Efficacy

Primary endpoint, TST: At the end of the double-blind study, the change from baseline in TST at months 4–6 was statistically significantly higher for esmirtazapine compared with placebo (treatment effect, 48.7 minutes; 95% CI, 35.0–62.5; $P < .0001$; **Table 2**). The improvement over placebo was apparent from the first week of treatment and was sustained over the 6-month double-blind treatment period (**Figure 3**). Sensitivity analysis with respect to missing data (mixed model using observed case) provided similar findings (49.9 minutes; 95% CI, 35.6–64.1; $P < .0001$; **Table S1** in the supplemental material).

Key secondary efficacy endpoints, SL and WASO: At the end of the double-blind study, the estimated treatment effect for SL at months 4–6 was a 4.9-minute (95% CI, –12.6 to 2.8; $P = .2145$) greater decrease from baseline for esmirtazapine compared with placebo (**Table 2**). For WASO, the decrease from baseline was 25.0 minutes (95% CI, –34.5 to –15.4) greater at months 4–6 for esmirtazapine compared with placebo (**Table 2**). Because of the fixed sequential testing procedure, these differences are nominally not statistically significant. Sensitivity analysis with respect to missing data (mixed model using observed case) provided similar findings (SL: –6.1 minutes; 95% CI, –12.6 to 0.3; WASO: –22.1 minutes; 95% CI –31.0 to –13.2; **Table S1**).

Additional efficacy endpoints: While no formal statistical analyses were conducted for the additional efficacy endpoints, numerically greater decreases for NAW per night and increases in quality of sleep last night and satisfaction with duration of sleep last night from baseline to months 4–6 were observed in the esmirtazapine group compared with the placebo group. The frequency of daytime napping was similar between the groups, with minimal change from baseline (**Table 3**).

Table 2—Six-month efficacy of esmirtazapine 4.5 mg and placebo during the double-blind study: primary and key secondary endpoints (intention-to-treat population).

	n	Baseline Mean (SD)	Months 4–6[a] Mean (SD)	Change From Baseline at Months 4–6[a] Mean (SD)	Treatment Effect[b]		
					Estimate	95% CI	*P*[c]
TST, min							
Esmirtazapine	342	307.2 (78.5)	373.0 (85.6)	65.9 (71.9)	48.7	35.0–62.5	<.0001
Placebo	115	301.4 (80.5)	320.7 (85.7)	19.3 (62.1)			
SL, min							
Esmirtazapine	342	75.4 (52.1)	45.7 (43.2)	–29.7 (47.3)	–4.9	–12.6 to 2.8	.2145
Placebo	115	79.1 (53.4)	52.2 (38.9)	–26.9 (46.8)			
WASO, min							
Esmirtazapine	342	88.8 (61.5)	42.5 (52.4)	–46.4 (57.7)	–25.0	–34.5 to –15.4	Data not shown
Placebo	115	87.9 (52.5)	67.1 (53.4)	–20.8 (51.4)			

[a]Based on last observation carried forward; for 101 (30%) participants in the esmirtazapine group and 39 (34%) participants in the placebo group, data for months 4–6 were imputed using data from before month 4. [b]Based on the primary last observation carried forward analysis; estimates represent the difference between least-square means for esmirtazapine vs placebo. [c]A fixed-sequence multiple-testing procedure was applied (TST → SL → WASO); testing was stopped if $P > .05$ and, consequently, the *P* value for WASO is not shown. CI = confidence interval, SD = standard deviation, SL = sleep latency, TST = total sleep time, WASO = wake time after sleep onset.

At the last recording, the mean change from baseline [SD] in ISI total score was greater for esmirtazapine (n = 286; –6.8 [6.6]) compared with placebo (n = 92; –3.6 [5.3]). The percentages of ISI responders (41.0% vs 17.7%), defined as participants with a decrease of > 7 points from baseline total score, and ISI remitters at endpoint (33.9% vs 16.7%), defined as participants with a postbaseline ISI total score < 8, were also higher in the esmirtazapine group vs the placebo group, respectively. Similarly, the mean change [SD] from baseline in Investigator Global Rating-Severity of symptoms scale rating was greater (ie, greater decrease in severity) for esmirtazapine (n = 296; –1.7 [1.4]) vs placebo (n = 97; –1.0 [1.4]; **Table 3**). Mean Investigator Global Rating-Change scores in the esmirtazapine group (n = 296; 2.3 [1.3]) were lower (ie, greater overall therapeutic effect) compared with placebo (n = 98; 2.9 [1.4]).

Safety and tolerability

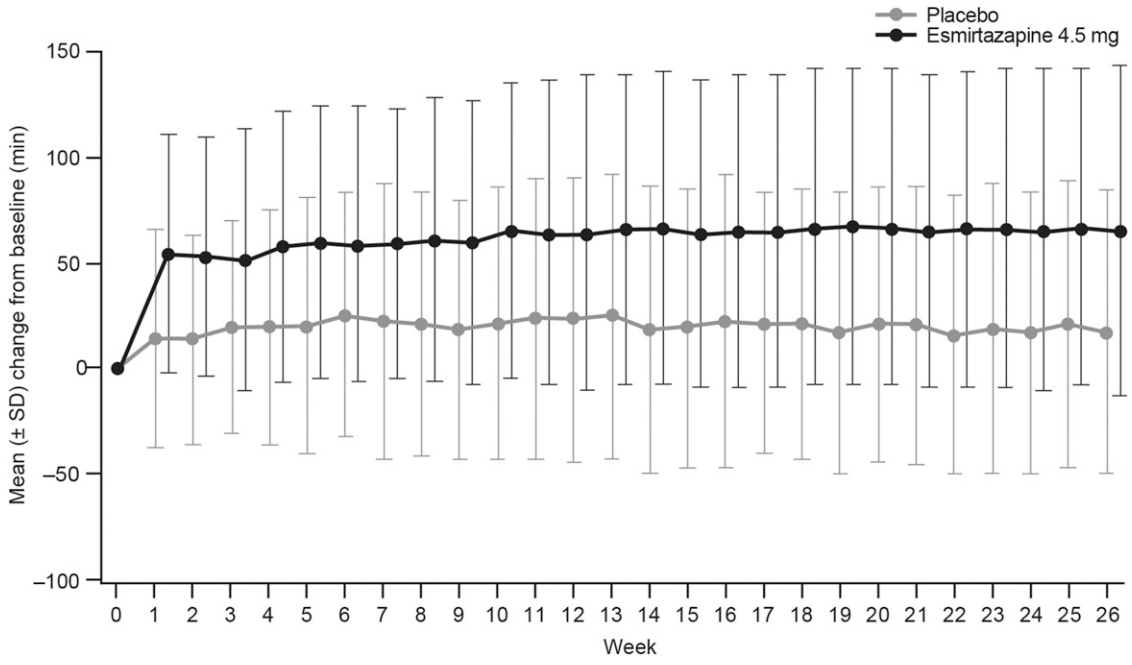
Drug-related AEs were experienced by 48.1% of participants overall: 53.8% of participants received esmirtazapine and 31.3% received placebo (**Table 4**). At least 1 SAE was reported for 2.3% (n = 8) of participants in the esmirtazapine group (retinal vein occlusion, osteoarthritis, synovial rupture, coronary artery disease, bunion operation, intervertebral disc protrusion, infectious mononucleosis, pancreatitis, sudden visual loss, concussion, road traffic accident, nerve compression, and facial bones fracture) and for 1.7% (n = 2) participants in the placebo group (fall, cartilage injury, and limb injury); no SAEs were considered by the investigator to be related to the study drug. In total, 13.7% (n = 47) of participants receiving esmirtazapine discontinued from the study because of AEs compared with 6.1% (n = 7) of participants receiving placebo. No deaths were reported during the study, and esmirtazapine was not associated with clinically relevant changes in electrocardiogram or vital signs. There was a small increase in the incidence of participants with a postbaseline increase in fasting glucose and fasting triglycerides and a small increase in fasting triglycerides over time (data not shown); other clinical laboratory results were similar with esmirtazapine and placebo.

AEs that occurred with an incidence of at least 2% during treatment with esmirtazapine and at least twice the incidence compared with placebo were weight gain (17.0% vs 3.5%), somnolence (14.9% vs 3.5%), increased appetite (9.9% vs 0.9%), dizziness (7.9% vs 3.5%), arthralgia (3.5% vs 1.7%), constipation (2.9% vs 0.0%), restless legs syndrome (2.9% vs 0.9%), hypertension (2.6% vs 0.9%), and increased γ-glutamyl transferase (2.3% vs 0.0%). An increase in body weight was observed with esmirtazapine (mean [SD] gain of 1.5 [2.5] kg vs 0.6 [2.3] kg with placebo at end of double-blind study); this appeared to plateau after approximately 12 weeks of esmirtazapine treatment (**Figure S1**). The percentage of participants with body weight above the safety range (ie, increase of ≥7% from baseline) was higher for esmirtazapine than placebo (9.0% vs 1.9% at the last visit).

Residual effects

There was no evidence of residual effects on alertness or daytime functioning with esmirtazapine based on visual analog

Figure 3—Mean weekly change from baseline in total sleep time during the double-blind study by treatment group[a] (intention-to-treat population).



[a]Based on last observation carried forward. SD = standard deviation.

Table 3—Six-month efficacy of esmirtazapine 4.5 mg and placebo during the double-blind study: additional secondary endpoints (intention-to-treat population).

	Baseline				Months 4–6[a]				Change From Baseline at Months 4–6[a]			
	Esmirtazapine 4.5 mg (n = 342)		Placebo (n = 115)		Esmirtazapine 4.5 mg (n = 342)		Placebo (n = 115)		Esmirtazapine 4.5 mg (n = 342)		Placebo (n = 115)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Number of awakenings	342	2.0 (1.3)	115	2.2 (1.6)	342	1.3 (1.2)	115	1.8 (1.8)	342	–0.7 (1.2)	115	–0.4 (0.9)
Quality of sleep	342	40.5 (15.2)	115	38.1 (16.6)	332	56.5 (21.2)	109	44.5 (19.1)	332	16.1 (19.5)	109	5.8 (14.0)
Satisfaction with duration of sleep	342	39.1 (15.3)	115	37.0 (17.2)	332	57.3 (21.0)	109	44.9 (19.9)	332	18.3 (20.1)	109	7.2 (15.9)
Daytime naps	341	0.1 (0.2)	115	0.1 (0.2)	327	0.1 (0.2)	106	0.2 (0.2)	326	–0.0 (0.2)	106	0.0 (0.2)
ISI total score	331	17.5 (4.5)	111	18.3 (5.0)	295	10.9 (6.4)[b]	96	14.1 (6.1)[b]	286	–6.8 (6.6)[b]	92	–3.6 (5.3)[b]
IGR severity of illness rating	342	4.7 (1.0)	114	4.8 (0.9)	200	2.7 (1.3)[b]	65	3.4 (1.4)[b]	200	–2.1 (1.4)[b]	65	–1.4 (1.4)[b]

[a]Based on last observation carried forward. [b]Mean (SD) and change from baseline at 6 months or discontinuation. ISI total score is the sum of all ISI items ranging from 0 to 28, where a lower value is better. IGR severity: 1 = normal; 2 = very mild; 3 = mild; 4 = moderate; 5 = marked; 6 = severe; 7 = extremely severe. IGR = Investigator Global Rating, ISI = Insomnia Severity Index, SD = standard deviation.

scales (**Figure S2**). In general, an increase in feeling at awakening, daytime energy level, and daytime functioning were noted in both treatment groups relative to baseline, with a higher magnitude of improvement in participants treated with esmirtazapine. Mean change from baseline increased during the first 3 months of treatment and remained relatively stable from months 4 to 6 of the treatment period.

Withdrawal effects

No significant changes in the benzodiazepine withdrawal symptoms questionnaire total score were observed during the 7-day discontinuation period compared with week 26, and there was no difference between treatment groups. In addition, individual item scores showed no difference between esmirtazapine and placebo, suggesting a lack of withdrawal effect on treatment discontinuation (**Table S2**).

In participants who received esmirtazapine and then switched to placebo during the 7-day discontinuation period, there was no evidence of rebound insomnia based on the TST results (**Figure S3a**). During the entire 7-day discontinuation period, no worsening in TST compared with baseline was observed, and the mean increase from pretreatment baseline TST was higher for participants who were treated with esmirtazapine compared with those who were treated with placebo throughout. Similarly, there

Table 4—Incidence of adverse events by treatment group in the double-blind study and open-label extension study (AST population).

	Double-Blind Study		Open-Label Extension Study[a]	
	Esmirtazapine 4.5 mg (n = 342)	Placebo (n = 115)	Prior Esmirtazapine 4.5 mg (n = 136)	Prior Placebo (n = 48)
AEs, n (%)	253 (74.0)	75 (65.2)	92 (67.6)	35 (72.9)
Drug-related AEs,[b] n (%)	184 (53.8)	36 (31.3)	36 (26.5)	22 (45.8)
Severe AEs, n (%)	26 (7.6)	3 (2.6)	8 (5.9)	3 (6.3)
Serious AEs,[c] n (%)	8 (2.3)	2 (1.7)	3 (2.2)	0 (0.0)
AEs leading to discontinuation,[d] n (%)	47 (13.7)	7 (6.1)	4 (2.9)	5 (10.4)
AEs occurring in ≥2% of participants in any treatment group in the double-blind study, n (%)				
Weight increased	58 (17.0)	4 (3.5)	8 (5.9)	3 (6.3)
Somnolence	51 (14.9)	4 (3.5)	3 (2.2)	7 (14.6)
Nasopharyngitis	35 (10.2)	14 (12.2)	11 (8.1)	8 (16.7)
Headache	30 (8.8)	14 (12.2)	6 (4.4)	4 (8.3)
Increased appetite	34 (9.9)	1 (0.9)	1 (0.7)	7 (14.6)
Dizziness	27 (7.9)	4 (3.5)	3 (2.2)	0 (0.0)
Dry mouth	20 (5.8)	5 (4.3)	3 (2.2)	2 (4.2)
Fatigue	18 (5.3)	7 (6.1)	4 (2.9)	2 (4.2)
Upper respiratory tract infection	13 (3.8)	5 (4.3)	7 (5.1)	2 (4.2)
Arthralgia	12 (3.5)	2 (1.7)	7 (5.1)	2 (4.2)
Cough	8 (2.3)	3 (2.6)	1 (0.7)	0 (0.0)
Nausea	7 (2.0)	4 (3.5)	3 (2.2)	1 (2.1)
Peripheral edema	9 (2.6)	2 (1.7)	3 (2.2)	1 (2.1)
Restless legs syndrome	10 (2.9)	1 (0.9)	1 (0.7)	0 (0.0)
Back pain	7 (2.0)	3 (2.6)	5 (3.7)	4 (8.3)
Constipation	10 (2.9)	0 (0.0)	1 (0.7)	2 (4.2)
Hypertension	9 (2.6)	1 (0.9)	0 (0.0)	0 (0.0)
Insomnia	6 (1.8)	4 (3.5)	18 (13.2)	5 (10.4)
Hypercholesterolemia	7 (2.0)	2 (1.7)	0 (0.0)	0 (0.0)
Gastroenteritis	5 (1.5)	3 (2.6)	5 (3.7)	0 (0.0)
γ-Glutamyl transferase increased	8 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)

[a]All participants received esmirtazapine during the open-label extension study. [b]Relationship to study drug according to investigator: 'definite', 'probable', 'possible'. [c]Includes a window of 30 days after last investigational medicinal product intake. [d]Includes 3 participants who discontinued during the 6-month treatment period because of AEs, which started during pretreatment and continued after the participants were randomized and started treatment. AE = adverse event, AST = all-subjects-as-treated.

were no signs of rebound insomnia based on SL or WASO (**Figures S3b and c**). Values collected during the 7-day discontinuation period were similar to those observed during the double-blind period, suggesting the efficacy of esmirtazapine may have been sustained during the 7-day discontinuation period.

Open-label extension

Study population

The open-label extension study was conducted between October 7, 2008 and April 16, 2010 at 36 of the 48 centers involved in the double-blind study. In total, 186 participants were enrolled into the extension study, and 184 received treatment with esmirtazapine (AST population; **Figure 2**). Of these, 136 participants had received esmirtazapine and 48 had received placebo during the double-blind study. A total of 126 (68.5%) participants completed the extension study, and 58 (31.5%) participants discontinued prematurely. The main reason for early discontinuation was the decision by the sponsor to halt the clinical development of esmirtazapine (n = 21 prior esmirtazapine; n = 8 prior placebo).

The study population in the extension study was generally similar to that in the double-blind study (**Table 5**). As in the double-blind study, fewer participants were categorized as obese or overweight in the prior placebo group compared with the prior esmirtazapine group (31.2% vs 55.8%). The mean duration of exposure (SD) in the 6-month open-label extension phase was 156.1 ± 47.5 days. Overall mean compliance with medication for the open-label extension period was 99.5%.

Table 5—Demographics and baseline characteristics for participants included in the open-label extension study (AST population).

Variables	Prior Treatment in the Double-Blind Phase		Total, n = 184
	Esmirtazapine 4.5 mg, n = 136	Prior Placebo, n = 48	
Sex, n (%)			
Male	58 (42.6)	15 (31.3)	73 (39.7)
Female	78 (57.4)	33 (68.8)	111 (60.3)
Mean age, years (SD)	47.9 (11.3)	47.3 (11.9)	47.8 (11.5)
Mean BMI, kg/m^2 (SD)	26.0 (4.4)	23.6 (4.0)	25.4 (4.4)
Race, n (%)			
White	98 (72.1)	30 (62.5)	128 (69.6)
Asian	33 (24.3)	15 (31.3)	48 (26.1)
Black or African American	3 (2.2)	1 (2.1)	4 (2.2)
Other[a]	2 (1.5)	2 (4.2)	4 (2.2)

[a]Includes Native Hawaiian or other Pacific Islander. AST = all-subjects-as-treated, BMI = body mass index, SD = standard deviation.

Safety and tolerability

Drug-related AEs were experienced by 31.5% of participants: 26.5% of participants in the prior esmirtazapine group and 45.8% of participants in the prior placebo group (**Table 4**). SAEs were reported by 3 participants, all from the prior esmirtazapine group: intervertebral disc degeneration, strabismus correction, and acute myocardial infarction. The acute myocardial infarction was considered possibly related to study medication by the investigator, who considered an acute occlusion of anterior-descending coronary artery as part of the acute myocardial infarction SAE (previously the participant did not have symptoms of blood vessel disease). During the study, 9 participants discontinued because of an AE. Of these, 4 of 136 (2.9%) participants had previously received esmirtazapine and 5 of 48 participants had previously received placebo (10.4%). Overall, the incidences of drug-related AEs and AEs leading to discontinuation were similar for the original esmirtazapine group during the double-blind study vs the placebo-esmirtazapine group during the extension study (**Table 4**). No deaths were reported during the study, and esmirtazapine was not associated with clinically relevant changes in electrocardiograms, vital signs, or laboratory safety tests.

Commonly reported AEs (reported by at least 2% participants during the double-blind study) are shown in **Table 4**. During the extension study, participants who previously received placebo in the double-blind study had a markedly higher incidence of increased appetite (14.6%) and somnolence (14.6%) compared with those who received esmirtazapine in both the double-blind study and extension (increased appetite: 0.7%; somnolence: 2.2%). However, incidence of these AEs was similar to rates reported during the double-blind period for participants who received esmirtazapine (increased appetite: 9.9%; somnolence: 14.9%). For participants who previously received esmirtazapine during the double-blind study, there were 2 AEs in which the incidence at least doubled during the open-label extension. These were gastroenteritis (2.2% in the double-blind study and 5.9% in the double-blind plus the extension study) and insomnia (0% in the double-blind study and 13.2% in the double-blind plus the extension study).

The weekly average weight of participants who previously received placebo during the double-blind study increased after starting treatment with esmirtazapine during the extension study (**Figure S1**).

Efficacy

For participants who continued to receive esmirtazapine from the double-blind study, TST increases were sustained during the extension phase (**Figure S4**). For participants who previously received placebo during the double-blind study, weekly average TST increased over time, and by the end of the extension, their scores were comparable with those who had previously received esmirtazapine during the double-blind study.

No clear change in SL pattern was seen over time throughout the extension study when comparing those previously treated with esmirtazapine vs those previously treated with placebo during the double-blind study (**Figure S5**). In contrast, a similar pattern to that observed for TST was shown for WASO, suggesting a sustained positive effect with esmirtazapine.

DISCUSSION

The studies reported here evaluated the long-term (ie, up to 12 months) efficacy and safety of esmirtazapine compared with placebo in outpatients with chronic insomnia. The 4.5-mg dose of esmirtazapine was chosen because previous phase 2/3 studies suggested that the likely therapeutic dose range of esmirtazapine is between 1.5 and 4.5 mg.[16–18] Therefore, the higher dose of esmirtazapine was selected to investigate long-term efficacy and safety.

During the double-blind study, there were significant increases in average TST (95% CI) for months 4–6 of 48.7 (35.0–62.5) minutes for participants receiving esmirtazapine vs placebo. The benefits of esmirtazapine compared with placebo in terms of improving TST were observed from week 1. No statistically significant decreases in SL were observed with esmirtazapine vs placebo (secondary endpoint), suggesting the increase in TST may be caused by sleep maintenance rather than reducing

latency to sleep time. A decrease in WASO was observed (–25.0; 95% CI, –34.5 to –15.4); however, this was not considered statistically significant in the formal statistical analysis due to the lack of significant effect on SL in the fixed sequential statistical testing procedure. Previous studies showed statistically significant decreases in SL and WASO compared with placebo after 2 and 6 weeks of treatment with esmirtazapine 4.5 mg in participants with primary insomnia.[16,17] It is possible that an increase in time spent in bed also contributed to the observed increases in TST; however, this was not evaluated in this study. Improvements were observed in other endpoints, including a decrease in NAW per night and increases in quality of sleep and satisfaction with duration of sleep. The mean change from baseline in ISI total score was greater for participants receiving esmirtazapine vs placebo, as was the percentage of ISI responders and remitters and the mean change from baseline in Investigator Global Rating-Severity of symptoms scale rating, suggesting a greater shift from more severe to less severe insomnia for esmirtazapine compared with placebo. Esmirtazapine was also associated with a greater therapeutic effect than placebo based on the Investigator Global Rating-Change scores.

Although the open-label extension study was not powered to investigate long-term efficacy of esmirtazapine compared with placebo, exploratory analyses indicated that the increase in TST observed for participants receiving esmirtazapine seemed to be maintained during the extension study. Moreover, participants who had previously received placebo during the double-blind study experienced increases in TST during the extension study similar to those who received esmirtazapine throughout the double-blind study.

Effects of esmirtazapine on TST and WASO were generally consistent with results obtained in the shorter-term phase 2/3 studies of esmirtazapine in nonelderly adults with primary insomnia.[16–18] In the current study, the effects of esmirtazapine on TST and WASO were maintained throughout the 6-month double-blind study, and exploratory results based on the 6-month extension suggested these effects were maintained for up to 1 year. Although decreases in SL were observed in the previous studies, no definitive decrease in SL was observed in the current study.

Esmirtazapine has a shorter half-life (10 hours) compared with the R(−) enantiomer and racemic mixture of mirtazapine (both ~18 hours), indicating that it may be associated with a reduced risk of next-day residual sedative effects. In both the double-blind and extension study, esmirtazapine was generally well tolerated. Most AEs were mild or moderate, and no new safety issues were identified. Weight gain was the most common AE in the double-blind study (17.0% for esmirtazapine vs 3.5% for placebo), and the percentage of participants with body weight above the safety range (ie, a change of ≥7% from baseline) was higher for esmirtazapine vs placebo from week 6. Weight gain appeared to plateau at approximately 12 weeks among participants receiving esmirtazapine. During the extension, 5.9% of participants who had continued with esmirtazapine from the double-blind study reported an increase in weight. Weight gain is a known side effect of mirtazapine when used to treat depression,[22,23] and this has been attributed to blocking H_1 and/or 5-HT_{2C} receptors.[24,25] Somnolence was reported in 14.9% of esmirtazapine participants in the double-blind study and in a similar proportion (14.6%) of participants who switched from placebo to esmirtazapine in the extension study. Among participants continuing esmirtazapine in the extension, somnolence was reported in only 2.2%. Together with the finding that drug-related AEs and AEs leading to discontinuation were observed at a similar overall frequency for the esmirtazapine group during the double-blind study and the placebo-esmirtazapine group during the extension study, these results are consistent with the general occurrence of drug-related AEs close to the start of treatment, with participants who have just switched being most likely to experience an AE.

Abrupt discontinuation of esmirtazapine after 6 months of treatment was not associated with emergence of withdrawal symptoms or rebound insomnia. Previous studies of esmirtazapine doses of 4.5 mg or lower over 2 or 6 weeks similarly did not identify evidence of withdrawal symptoms or rebound insomnia after treatment.[16,17] The current study provides evidence that even long-term treatment with esmirtazapine is not associated with rebound insomnia.

Several factors limit the interpretation of our studies. The use of objective sleep endpoints measured using polysomnography would have strengthened the study. The safety and tolerability data from our studies cover a 12-month period, and different patterns could emerge after a longer duration of use or in a less restrictive population. Because the study stopped prematurely, collection of the open-label extension data was not completed; furthermore, the extension study was not powered to assess efficacy.

This study did not evaluate periodic leg movements or obstructive sleep apnea as potential confounding variables. Given that weight gain and sedation were common AEs in this study and a previous 6-week study of esmirtazapine[16] and that mirtazapine may increase periodic leg movements, which are associated with awakenings/arousals and may contribute to sleep disturbance[26] and may reduce apnea-hypopnea index in patients with obstructive sleep apnea,[27] these factors could be evaluated as confounding variables in future studies.

In conclusion, esmirtazapine 4.5 mg provided sleep-promoting, primarily sleep maintenance, effects that were greater than those observed with placebo among adults with chronic insomnia. These benefits were maintained for at least 6 months, with no evidence of next-day residual effects. The safety and tolerability profile of esmirtazapine in this longer-term study was generally consistent with that seen in previous short-term studies of esmirtazapine, with no evidence of withdrawal effects or rebound insomnia after the abrupt discontinuation of treatment. Since this study was conducted, the sponsor (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) discontinued further development of esmirtazapine.

ABBREVIATIONS

AE, adverse event
AST, all-subjects-as-treated

CI, confidence interval
DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ISI, Insomnia Severity Index
NAW, number of awakenings
SAE, serious adverse event
SD, standard deviation
SL, sleep latency
TST, total sleep time
WASO, wake time after sleep onset

REFERENCES

1. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med.* 2008;4(5):487–504.
2. Roth T, Coulouvrat C, Hajak G, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psychiatry.* 2011;69(6):592–600.
3. Kucharczyk ER, Morgan K, Hall AP. The occupational impact of sleep quality and insomnia symptoms. *Sleep Med Rev.* 2012;16(6):547–559.
4. Thase ME. Correlates and consequences of chronic insomnia. *Gen Hosp Psychiatry.* 2005;27(2):100–112.
5. Drake CL, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety.* 2003;18(4):163–176.
6. Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep*. 2009;32(4):491–497.
7. Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care*. 2009;32(11):1980–1985.
8. Buysse DJ. Insomnia. *JAMA*. 2013;309(7):706–716.
9. Krystal AD. New developments in insomnia medications of relevance to mental health disorders. *Psychiatr Clin North Am.* 2015;38(4):843–860.
10. Roehrs T, Roth T. Insomnia pharmacotherapy. *Neurotherapeutics*. 2012;9(4): 728–738.
11. Stahl SM. Selective histamine H1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. *CNS Spectr.* 2008;13(12):1027–1038.
12. Asnis GM, Thomas M, Henderson MA. Pharmacotherapy treatment options for insomnia: a primer for clinicians. *Int J Mol Sci.* 2015;17(1):E50.
13. Aslan S, Isik E, Cosar B. The effects of mirtazapine on sleep: a placebo controlled, double-blind study in young healthy volunteers. *Sleep*. 2002;25(6): 677–679.
14. Winokur A, Sateia MJ, Hayes JB, Bayles-Dazet W, MacDonald MM, Gary KA. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. *Biol Psychiatry.* 2000;48(1):75–78.
15. de Boer T. The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. *Int Clin Psychopharmacol.* 1995;10(suppl 4): 19–23.
16. Ivgy-May N, Ruwe F, Krystal A, Roth T. Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a randomized, 6-week sleep laboratory trial. *Sleep Med.* 2015;16(7):838–844.
17. Ivgy-May N, Roth T, Ruwe F, Walsh J. Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a 2-week randomized outpatient trial. *Sleep Med.* 2015;16(7):831–837.
18. Ruwe F, IJzerman-Boon P, Roth T, Zammit G, Ivgy-May N. A phase 2 randomized dose-finding study with esmirtazapine in patients with primary insomnia. *J Clin Psychopharmacol.* 2016;36(5):457–464.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Press; 2000.
20. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297–307.
21. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26(7): 793–799.
22. Masand PS, Gupta S. Long-term side effects of newer-generation antidepressants: SSRIS, venlafaxine, nefazodone, bupropion, and mirtazapine. *Ann Clin Psychiatry*. 2002;14(3):175–182.
23. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressive agents for depression. *Cochrane Database Syst Rev.* 2011;12: CD006528.
24. Chiu HW, Li TC. Rapid weight gain during mirtazapine treatment. *J Neuropsychiatry Clin Neurosci.* 2011;23(1):E7.
25. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord.* 1998;51(3):267–285.
26. Fulda S, Kloiber S, Dose T, et al. Mirtazapine provokes periodic leg movements during sleep in young healthy men. *Sleep*. 2013;36(5):661–669.
27. Carley DW, Olopade C, Ruigt GS, Radulovacki M. Efficacy of mirtazapine in obstructive sleep apnea syndrome. *Sleep*. 2007;30(1):35–41.

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List of investigators: ***Argentina:*** A Garay*, CEMIC, Buenos Aires; C Podesta*, Neuraxis, Buenos Aires; ***Belgium:*** P De Deyn*, Algemeen Ziekenhuis Middelheim, Antwerpen; M Ossemann*, Cliniques Universitaires de Mont Godinne, Yvoir; A Volckaert*, Hopital de Jolimont, Haine Saint Paul; ***Canada:*** H Conter, MSHJ Research Assoc. Inc, Halifax; B Lasko, Manna Research, Toronto; MFJ O'Mahony, London Road Diagnostic Clinic & Medical Centre, Sarnia; ***Chile:*** G Vergara, Centro de Estudios y Tratamiento de Enfermedades Psiquiatricas, Santiago; ***France:*** C Monaca*, Hopital Roger Salengro - CHRU Lille, Lille; ***Germany:*** I Eisensehr, Neurologie in der Sendlinger Strasse, Muenchen; I Fietze, ASR Advanced Sleep Research GmbH, Berlin; S Happe, Klinikum Bremen Ost GmbH – Institut fur Klinische Neurophysiologie, Bremen; D Riemann*, Universitaetsklinikum Freiburg, Freiburg; ***Hungary:*** L Csiba, University of Debrecen, Debrecen; M Schulz-Varszegi, SomnoCenter Szeged, Szeged; Z Szakacs, Zoltan, SomnoCenter AEK, Budapest; ***Italy:*** P Girardi*, Sapienza University, Rome; M Zucconi*, Instituto Scientifico Universitario San Raffaele, Milano; ***Mexico:*** M Reyes-Zuniga, Instituto Nacional de Enfermedades, Mexico City; ***The Netherlands:*** A de Weerd, Slaapcentrum SEIN Zwolle, Zwolle; TJ Tacke, Stichting Streekziekenhuis Midden-Twente, Hengelo; ***Poland:*** K Kubiak, Poradnia Zdrowia Psychicznego, Warsaw; D Malicki, Prywatne Centrum Medyczne Luxmed, Lublin; E Rudnik, Poradnia Zaburzen Snu, Zaklad Psychiatrii Biologicznej, Akademickie Centrum Kliniczne, Gdansk; ***South Korea:*** SB Hong, Samsung Medical Center, Seoul; S-C Hong, The Catholic University of Korea, Suwon; I-Y Yoon, Seoul National University Bundang Hospital, Seongnam; ***Sweden:*** L Grote, Somnlaboratoriet Avd. for lungmedicin och allergologi, Sahlgrenska Universitetssjukhuset, Göteborg; L Haggstrom, Brain and Body AB Psykiatrimott Affecta, Halmstad; J Hedner, Somnkliniken, Carlanderska sjukhset, Göteborg; L Leissner, Universitetssjukhuset Örebro, Orebro; ***Taiwan:*** C-J Hong, Taipei Veterans General Hospital, Taipei; Y-S Huang, Chang Gung Memorial Hospital-Linkou, Taoyuan County; ***Thailand:*** R Nivataphand, Chulalongkorn Hospital, Bangkok; N Wongpakaran, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai; ***United Kingdom:*** I Smith, Papworth Hospital, Cambridge; R Stott*, QinetiQ, Farnborough; ***United States:*** B Bortnick, Comprehensive NeuroScience, Inc., Atlanta, GA; AC Bowen, Chester County Primary Care, West Chester, PA; A Dahdul, FutureCare Studies, Inc., Springfield, MA; E Gfeller, Florida Clinical Research Center LLC, Maitland, FL; B Harris*, PsyPharma Clinical Research Inc., Phoenix, AZ; JA Hoekstra, National Clinical Research, Inc.,

Richmond, VA; WP Jennings*, Radiant Research San Antonio, San Antonio, TX; S Kabeli, Vermont Medical Sleep Disorders Center, Essex Junction, VT; A Klymiuk, KRK Medical Research, Dallas, TX; DW Mayleben, Community Research & Sleep Management Institute, Crestview Hills, KY; JD McDavid, Summit Research Network, Seattle, WA; M Scharf*, Tri-State Sleep Disorders Center, Cincinnati, OH; HM Thomas*, Clinical Trials Technology Inc., Prairie Village, KS; JA Tornabene, Wenatchee Valley Clinic, Wenatchee, WA. *These investigators did not participate in the extension study.

SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Neely Ivgy-May, PhD, Merck & Co., Inc., 2000 Galloping Hill Rd., Kenilworth, NJ 07033; Tel: (972) 52 672-6671; Fax: (973) 767-8100; Email: mayneely@gmail.com

DISCLOSURE STATEMENT

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