RESEARCH ARTICLE

A Phase II Dose-Ranging Study Evaluating the Efficacy and Safety of the Orexin Receptor Antagonist Filorexant (MK-6096) in Patients with Primary Insomnia

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Abstract

Background: Filorexant (MK-6096) is an orexin receptor antagonist; here, we evaluate the efficacy of filorexant in the treatment of insomnia in adults.
Methods: A double-blind, placebo-controlled, randomized, two 4-week–period, adaptive crossover polysomnography study was conducted at 51 sites worldwide. Patients (18 to <65 years) with insomnia received 1 of 4 doses of oral filorexant (2.5, 5, 10, 20mg) once daily at bedtime during one period and matching placebo in the other period in 1 of 8 possible treatment sequences. Polysomnography was performed on night 1 and end of week 4 of each period. The primary endpoint was sleep efficiency at night 1 and end of week 4. Secondary endpoints included wakefulness after persistent sleep onset and latency to onset of persistent sleep.
Results: A total of 324 patients received study treatment, 315 received ≥1 dose of placebo, and 318 ≥1 dose of filorexant (2.5mg, n=79; 5mg, n=78; 10mg, n=80; 20mg, n=81). All filorexant doses (2.5/5/10/20mg) were significantly superior to placebo in improving sleep among patients with insomnia as measured by sleep efficiency and wakefulness after persistent sleep onset on night 1 and end of week 4. The 2 higher filorexant doses (10/20mg) were also significantly more effective than placebo in improving sleep onset as measured by latency to onset of persistent sleep at night 1 and end of week 4. Filorexant was generally well tolerated.
Conclusions: Orexin receptor antagonism by filorexant significantly improved sleep efficiency in nonelderly patients with insomnia. Dose-related improvements in sleep onset and maintenance outcomes were also observed with filorexant.

Keywords: dose-ranging study, filorexant, insomnia, orexin receptor antagonist, sleep efficiency

Clinical Trial Registry: clinicaltrials.gov: NCT01021852.

Introduction

Insomnia, defined as difficulty in initiating or maintaining sleep despite adequate opportunity for sleep, affects between 10% and 30% of the population overall and is associated with significant impairments in health, productivity, and quality of life (Mai and Buysse, 2008; Schutte-Rodin et al., 2008; Sarsour et al., 2011; Ishak et al., 2012; Morin and Benca, 2012). Recent data also suggest that patients with chronic insomnia may be hyperaroused, experiencing increased metabolic rate, body temperature, and heart rate and elevated levels of norepinephrine and catecholamines (Bonnet and Arand, 2010). For several decades, the pharmacological treatment of insomnia has been dominated by benzodiazepine receptor agonists; however, although effective at promoting sleep onset and less frequently sleep maintenance, these agents have limitations for many patients, including next-day residual effects and dependence in at-risk populations. Furthermore, for a sizeable proportion of patients with insomnia, the condition often goes unrecognized and untreated (Morin and Benca, 2012).

The orexin (hypocretin) signaling system originates in the lateral hypothalamus and is a central promoter of wakefulness and arousal. In preclinical studies, genetic depletion of orexin signaling resulted in the development of narcoleptic phenotypes (Lin et al., 1999; Sakurai et al., 2010; Gotter et al., 2012), and specific pharmacological blockade of orexin OX1 and OX2 receptors was associated with the development of somnolence (Brisbare-Roch et al., 2007; Winrow et al., 2011). Several orexin receptor antagonists (ORAs) have been developed, with similar affinities for the 2 orexin receptors, OX1 and OX2 (Winrow and Renger, 2014). In proof of concept studies, the ORAs suvorexant (MK-4305, Belsomra) administered daily for 4 weeks (Herring et al., 2012), almorexant (singe-dose) (Hoever et al., 2012), and SB649868 (single-dose) (Bettica et al., 2012) were shown to be effective and well tolerated for the treatment of sleep disturbances in adult patients with insomnia. Suvorexant also significantly improved sleep onset and maintenance in phase 3 studies in patients with insomnia and has recently been approved in the US and Japan for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance (Belsomra (suvorexant) Package Insert 2014; Michelson et al., 2014; Herring et al., 2016).

Filorexant (MK-6096) is a dual ORA with a relatively short half-life ($t_{1/2}$; 3–6 hours). In preclinical studies in rodents and dogs, filorexant increased nonrapid eye movement (REM) and REM sleep (Coleman et al., 2012; Winrow et al., 2012). Filorexant has also demonstrated sleep-promoting effects in a polysomnography (PSG) study in healthy subjects (Sun et al., 2011a). Based on these findings and its relatively short $t_{1/2}$, which suggests potential for a low incidence of next-day residual effects compared with placebo, filorexant was considered a suitable candidate for further clinical evaluation in the treatment of insomnia. Here, we report the results of a phase 2b dose-ranging study evaluating filorexant for the treatment of insomnia in adults.

Methods

Study Design and Treatment

This was a double-blind, placebo-controlled, randomized, 2-period, adaptive crossover PSG study conducted between December 2009 and February 2011 at 51 sites within the US, Germany, United Kingdom, Spain, Finland, and Japan (clinicaltrials.gov: NCT01021852; Merck protocol 6096-011). The study comprised a 3-week screening period and two 4-week, double-blind treatment periods separated by an intervening 2-week washout period (comprising 3 days of single-blind placebo followed by 11 days off study treatment) (supplementary Figure 1).

Each patient received 1 of 4 doses of oral filorexant (2.5, 5, 10, or 20 mg) once daily at bedtime during one period and matching placebo in the other period in 1 of 8 possible treatment sequences. Each treatment period comprised 29 ± 3 days of treatment and included an overnight PSG visit on the first and last nights of the treatment period, with a clinic office visit on day 15. Filorexant or matching placebo was administered approximately 30 minutes before bedtime on PSG nights and immediately (within 5 to 10 minutes) before bedtime on non-PSG nights. On the day following a PSG night, patients were awakened (or allowed to get out of bed if already awake) after 8 hours of PSG recording. Patients completed an electronic sleep diary each morning and evening.

Patients

Men and women (aged 18 to <65 years) were eligible for inclusion in the study if they had a diagnosis of primary insomnia (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria) and reported, on at least 3 of 7 nights each week during the 4 weeks prior to the start of screening (day -21): a total sleep time (TST) of ≤6.5 hours, sleep latency of ≥30 minutes, ≥1 hour of wakefulness after sleep onset (WASO), and spending 6.5 to 9 hours in bed each night. Patients were also required to have a regular bedtime between 9 PM and 12 AM and be willing to refrain from napping during the study, limit their alcohol consumption to 2 drinks/d (at least 3 hours before going to bed) on non-PSG visit days, refrain from drinking alcohol at least 24 hours before a PSG visit, and limit their caffeine consumption to ≤600 mg caffeine/d. In addition, patients were required to have latency to onset of persistent sleep (LPS) >20 minutes on both the screening PSG (day -14) and baseline PSG (day -7) nights, and mean WASO ≥60 minutes on the combined screening and baseline PSG nights where neither night is ≤45 minutes. Patients were excluded from the study if they had evidence of ongoing depression, history of bipolar disorder or a psychotic disorder, or other concomitant medical conditions, including a history or diagnosis of narcolepsy, idiopathic cataplexy, circadian rhythm sleep disorder, parasomnia, or sleep-related breathing disorder.

All patients were required to give written informed consent prior to inclusion in the study. The study protocol was approved by the relevant International Review Board/Independent Ethics Committee at each participating center and was conducted in accordance with the standards established by the Declaration of Helsinki and in compliance with all local and/or national regulations and directives.

Investigational medications, fluoxetine, and specific moderate and strong cytochrome P450 3A inhibitors and specific strong cytochrome P450 3A inducers (supplementary Table 1) were withdrawn at least 4 weeks before the screening visit.

Efficacy Endpoints

The primary endpoint was mean change from baseline in sleep efficiency (SE), derived from TST as a percentage of total time in bed (fixed at 8 hours for this study), on both night 1 and end of week 4, as measured by PSG. Secondary endpoints (measured by PSG) were mean change from baseline in WASO and LPS both on

night 1 and end of week 4. Sleep stage scoring was performed visually in 30-second epochs by a central reader (Rechtschaffen A, Kales A, eds., 1968; Iber et al., 2007). Exploratory endpoints evaluated other PSG sleep parameters (TST, number of awakenings) and the sleep architecture of filorexant compared with placebo, as measured by duration and percentages in stages 1, 2, 3, 4 (stages 3 and 4 were combined as slow wave sleep) and REM sleep on night 1 and week 4.

Exploratory subjective sleep measures included subjective TST (sTST) and subjective time to sleep onset (sTSO), as reported by patients in electronic morning diaries; and patient-reported insomnia, as measured by the Insomnia Severity Index (ISI), freshness (sFresh), and quality of sleep (sQual) visual analog scales. Next-day function measures included the patient-reported Sheehan Disability Scale (SDS).

Safety and Tolerability

Safety was assessed through the collection of adverse event (AE) data and routine laboratory tests performed at clinic visits (including hematology, chemistry, and urinalysis), electrocardiography, and vital signs assessments. AEs of clinical interest included cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, sleep-onset paralysis, falls, excessive daytime sleepiness, complex sleep-related behaviors, selected events associated with potential for abuse, and suicidal ideation and/or behaviors.

Next-day residual effects were assessed using the Digit Symbol Substitution Test (DSST) performed in the morning (within 30 minutes to 1 hour following lights on) after each PSG assessment (night 1 and week 4). Acute withdrawal effects were measured based on analysis of patients reporting 3 or more emergent or worsening symptoms of 20 in a single day on the Tyrer Withdrawal Symptom Questionnaire (WSQ) (Tyrer et al.,

1990) completed for the first 3 nights of the single-blind washout period, or 3 or more symptoms across the first 3 days, after the end of treatment period 1. Rebound insomnia was measured using sTSO and sTST assessments for each of the first 3 nights of the washout period. The Columbia Suicide Severity Rating Scale was administered by trained raters at baseline prior to treatment period 1 and at each visit during periods 1 and 2 to provide a detailed assessment of suicidal ideation and behaviors.

Statistical Methods

Based on a planned sample size of 272 patients (68 in each filorexant dose group) completing Periods 1 and 2, the study had approximately 99% power to detect a difference of 8.33 percentage points in SE at both time points (night 1 and end of week 4) for a particular filorexant dose (a difference of 8.33 percentage points in SE corresponds to a 40-minute difference in TST when time in bed is fixed at 8 hours).

Efficacy analyses were conducted using the full analysis set population (all randomized patients who received at least one dose of study treatment and had a post-dose assessment of the primary efficacy measure in either treatment period). Patients were analyzed according to the treatment sequence to which they were randomized for the efficacy analyses.

The primary (SE) and secondary endpoints (WASO and LPS) at night 1 and the end of 4 weeks of treatment were compared between each dose of filorexant and placebo using a fixed-effects repeated-measures model including terms for baseline value (prerandomization), geographic region (Japan vs ex-Japan), gender, treatment, sequence, period, time (as a categorical variable), and treatment-by-time and period-by-time interactions for each dose. An unstructured covariance matrix was used for within-subject correlation assuming
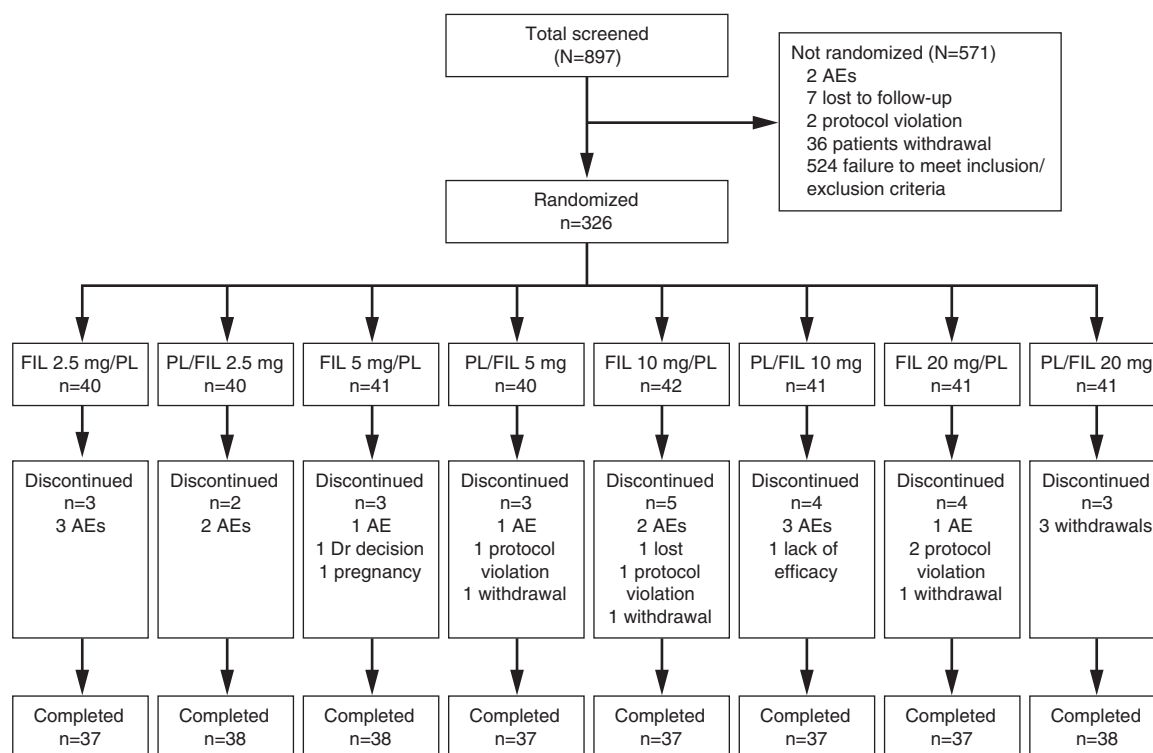

Figure 1. Patient disposition. AE, adverse event; FIL, filorexant; PL, placebo.

independence for between-subject correlation. The model was used to provide an estimate of treatment effect for the comparison of each filorexant dose with placebo. Least-squares mean differences between filorexant and placebo with 95% CI and *P* values (based upon a normal approximation) were computed. Exploratory efficacy analyses for continuous endpoints were evaluated using a similar model. To account for the multiple dose comparisons to placebo for the primary efficacy hypothesis, a fixed sequential testing procedure was used to assess statistical significance at both timepoints (night 1 and week 4), starting with the highest filorexant dose. Since both night 1 and week 4 results had to be positive for each endpoint and filorexant dose comparison with placebo, no adjustment was required for multiple timepoints. Filorexant doses that were statistically significant for the primary endpoint (at both timepoints) were tested in a similar fashion for the first secondary endpoint (WASO), and filorexant doses that were statistically significant for both SE and WASO (at both timepoints) were tested in a similar fashion for the second secondary endpoint (LPS). The same mixed effects model used to evaluate primary and secondary endpoints was used to evaluate DSST. WSQ was assessed via point estimates with 95% CIs provided for comparisons of treatment vs placebo.

A prespecified interim analysis was conducted when approximately 50% of patients had completed the study to evaluate for futility and also to determine if evaluation of a lower (1 mg) or higher (40 mg) dose of filorexant was warranted.

The all-patients-as-treated population was used for safety analyses (all randomized patients who received at least one dose of study treatment).

Results

Patients

A total of 326 patients were randomized to treatment, and 2 patients discontinued from the study without taking study drug. Of the 324 patients who received study drug, 315 received at least 1 dose of placebo and 318 received at least 1 dose of filorexant (2.5 mg, n = 79; 5 mg, n = 78; 10 mg, n = 80; 20 mg, n = 81). Figure 1

Table 1. Patient Demography and Baseline Characteristics

	Filorexant 2.5 mg (n = 79)[a]	Filorexant 5 mg (n = 78)[a]	Filorexant 10 mg (n = 80)[a]	Filorexant 20 mg (n = 81)[a]	Placebo (n = 315)[a]
Sex, n (%)					
Male	30 (38.0)	29 (37.2)	30 (37.5)	31 (38.3)	117 (37.1)
Female	49 (62.0)	49 (62.8)	50 (62.5)	50 (61.7)	198 (62.9)
Age, mean (SD), years	47.3 (11.8)	46.4 (10.6)	45.4 (10.5)	48.3 (11.2)	46.9 (10.8)
BMI, mean (SD), kg/m^2	25.5 (4.6)	26.1 (3.8)	25.9 (4.5)	25.6 (4.0)	25.7 (4.2)
Race					
White	54 (68.4)	54 (69.2)	51 (63.8)	62 (76.5)	216 (68.6)
Black	10 (12.7)	8 (10.3)	9 (11.3)	5 (6.2)	33 (10.5)
Asian	14 (17.7)	14 (17.9)	18 (22.5)	12 (14.8)	58 (18.4)
Other[b]	1 (1.3)	2 (2.6)	2 (2.5)	2 (2.5)	8 (2.5)
ISI					
Total score	15.7 (4.7)	15.7 (4.9)	14.9 (4.5)	15.1 (3.7)	15.3 (4.5)
PSG sleep					
SE, %	64.8 (11.0)	65.5 (13.4)	67.6 (13.1)	65.0 (15.1)	65.9 (12.8)
WASO, min	112.1 (42.7)	105.1 (47.1)	101.1 (50.4)	114.1 (54.0)	106.8 (46.3)
LPS, min	64.1 (33.7)	67.0 (46.6)	63.0 (37.0)	61.2 (43.1)	64.3 (40.3)
TST, min	310.9 (52.8)	314.3 (64.1)	324.4 (63.0)	312.0 (72.3)	316.1 (61.6)
NAW	13.8 (6.1)	13.3 (7.0)	14.0 (5.8)	13.7 (6.6)	13.8 (6.4)
Sleep architecture, min					
Stage 1	38.7 (20.5)	38.3 (19.8)	44.6 (20.7)	41.6 (22.8)	40.9 (21.2)
Stage 2	183.1 (44.4)	192.4 (50.3)	188.7 (48.0)	182.3 (52.0)	186.9 (48.4)
Stages 3 + 4 (SWS)	41.5 (26.1)	32.7 (25.4)	38.5 (29.4)	41.2 (35.4)	38.6 (29.4)
REM	55.1 (21.3)	56.1 (25.3)	59.5 (23.7)	54.8 (24.1)	56.6 (23.3)
Latency to REM	90.7 (63.8)	80.0 (55.1)	87.3 (61.6)	87.1 (60.8)	84.7 (58.3)
Subjective sleep, min					
sTSO	64.1 (31.5)	67.5 (36.5)	63.6 (32.0)	63.1 (40.7)	64.4 (34.1)
sTST	322.2 (58.3)	326.1 (56.8)	330.8 (57.1)	318.1 (59.0)	323.7 (59.0)
SDS					
Total score	9.8 (8.1)	9.4 (8.5)	10.1 (7.7)	8.8 (6.4)	9.5 (7.7)
Work	3.2 (2.8)	3.1 (2.7)	3.3 (2.5)	3.1 (2.3)	3.2 (2.6)
Social	2.7 (2.5)	2.7 (2.8)	3.1 (2.6)	2.8 (2.3)	2.8 (2.5)
Family	3.0 (2.7)	2.9 (2.7)	3.4 (2.7)	2.9 (2.4)	3.0 (2.6)
Residual effects					
DSST, correct	57.7 (14.2)	56.3 (14.8)	59.3 (13.7)	54.7 (13.5)	57.3 (14.3)

Abbreviations: BMI, body mass index; DSST, Digit Symbol Substitution Test; ISI, Insomnia Severity Index; LPS, latency to persistent sleep; NAW, number of awakenings; PSG, polysomnography; REM, rapid eye movement; SDS, Sheehan Disability Scale; SE, sleep efficiency; sTSO, subjective time to sleep onset; sTST, subjective total sleep time; SWS, slow-wave sleep; TSO, time to sleep onset; TST, total sleep time; WASO, wakefulness after sleep onset.
[a]n = all patients treated; baseline means for efficacy measures based upon patients included in analyses at night 1 for PSG and DSST endpoints, Week 1 for subjective sleep endpoints, and week 4 for ISI and SDS.
[b]Multiracial or American Indian/Alaskan native.

shows patient disposition by treatment sequence. A total of 299 patients completed the study and 27 discontinued, primarily due to AEs (n = 13).

Patient baseline characteristics were similar across treatment groups (Table 1). Of the 324 patients treated, 62.3% were female, 68.8% were white, and mean age was 46.9 years.

Efficacy

All doses of filorexant (2.5, 5, 10, and 20 mg) were significantly more effective than placebo in improving sleep as measured by the primary endpoint of SE both on night 1 and at the end of week 4. Mean change in SE from baseline was 18.3% to 25.0% with filorexant vs 10.2% with placebo on night 1, and 16.8% to 22.4% with filorexant vs 12.5% with placebo at week 4 (Table 2). The differences in least-squares means for SE between filorexant and placebo at night 1 and week 4 were statistically significantly in favor of filorexant for all doses (night 1, P < .001;

week 4, P ≤ .004), with an indication of a dose-response effect at night 1 (Figure 2).

All doses of filorexant (2.5, 5, 10, and 20 mg) were also significantly more effective than placebo in improving sleep maintenance as measured by the secondary endpoint of WASO on night 1 and at the end of week 4. Results for the secondary efficacy endpoint of LPS were also statistically significantly in favor of the 10- and 20-mg filorexant doses on night 1 and at the end of week 4. While results for the lower filorexant doses (2.5 and 5 mg) suggested beneficial effects at night 1 and week 4 for LPS (nominal P values ≤ .06), these were not considered statistically significant according to the multiplicity strategy (Table 2; Figure 2).

Placebo-subtracted results for exploratory objective PSG and sleep architecture measures are summarized in Table 3. All doses of filorexant showed improvements from baseline in TST compared with placebo at night 1 and week 4, ranging from 80.6 to 120.1 minutes (vs 48.6 and 59.3 minutes with placebo).

Table 2. Summary of Primary and Secondary Efficacy Endpoints: SE, WASO, and LPS (Full Analysis Set)

Endpoint	n	Baseline Mean (SD)	Treatment Mean (SD)	Change from Baseline Mean (SD)	95% CI
SE (%)					
Night 1					
Placebo	313	65.9 (12.8)	76.1 (13.3)	10.2 (15.1)	8.6, 11.9
Filorexant 2.5 mg	79	64.8 (11.0)	83.1 (9.9)	18.3 (11.9)	15.6, 21.0
Filorexant 5 mg	78	65.5 (13.4)	85.8 (9.0)	20.3 (16.3)	16.6, 24.0
Filorexant 10 mg	80	67.6 (13.1)	87.5 (7.7)	19.9 (12.1)	17.2, 22.6
Filorexant 20 mg	80	65.0 (15.1)	90.0 (8.6)	25.0 (14.0)	21.9, 28.1
Week 4					
Placebo	300	65.7 (12.9)	78.2 (12.6)	12.5 (15.3)	10.7, 14.2
Filorexant 2.5 mg	76	64.5 (11.1)	81.3 (11.5)	16.8 (11.2)	14.2, 19.4
Filorexant 5 mg	76	65.6 (13.5)	84.5 (8.9)	19.0 (15.7)	15.4, 22.5
Filorexant 10 mg	76	68.0 (12.1)	85.9 (9.0)	17.9 (13.2)	14.9, 20.9
Filorexant 20 mg	75	65.7 (14.7)	88.1 (7.3)	22.4 (14.8)	19.0, 25.9
WASO (mins)					
Night 1					
Placebo	313	106.8 (46.3)	78.9 (53.3)	-27.9 (57.3)	-34.3, -21.6
Filorexant 2.5 mg	79	112.1 (42.7)	54.8 (40.7)	-57.3 (44.6)	-67.3, -47.3
Filorexant 5 mg	78	105.1 (47.1)	47.4 (34.5)	-57.6 (54.7)	-70.0, -45.3
Filorexant 10 mg	80	101.1 (50.4)	40.7 (28.7)	-60.5 (43.4)	-70.1, -50.8
Filorexant 20 mg	80	114.1 (54.0)	35.0 (31.0)	-79.1 (55.9)	-91.6, -66.7
Week 4					
Placebo	300	107.7 (46.5)	72.1 (46.8)	-35.6 (56.9)	-42.1, -29.1
Filorexant 2.5 mg	76	112.7 (43.2)	62.2 (49.7)	-50.5 (45.1)	-60.8, -40.2
Filorexant 5 mg	76	104.0 (46.7)	52.6 (36.8)	-51.5 (51.1)	-63.1, -39.8
Filorexant 10 mg	76	98.7 (40.6)	47.9 (38.4)	-50.8 (47.8)	-61.7, -39.9
Filorexant 20 mg	75	114.3 (55.2)	41.2 (27.8)	-73.2 (53.6)	-85.5, -60.8
LPS (mins)					
Night 1					
Placebo	313	64.3 (40.3)	41.5 (38.2)	-22.8 (48.4)	-28.2, -17.4
Filorexant 2.5 mg	79	64.1 (33.7)	30.6 (25.7)	-33.5 (39.1)	-42.3, -24.8
Filorexant 5 mg	78	67.0 (46.6)	26.1 (24.0)	-40.9 (44.4)	-50.9, -30.9
Filorexant 10 mg	80	63.0 (37.0)	22.7 (23.2)	-40.3 (39.5)	-49.1, -31.5
Filorexant 20 mg	80	61.2 (43.1)	17.2 (20.2)	-44.0 (39.1)	-52.7, -35.3
Week 4					
Placebo	300	63.9 (40.6)	37.3 (41.1)	-26.6 (51.7)	-32.5, -20.7
Filorexant 2.5 mg	76	65.0 (34.0)	33.0 (26.6)	-32.0 (38.1)	-40.7, -23.3
Filorexant 5 mg	76	67.3 (47.2)	25.3 (23.7)	-42.0 (51.1)	-53.7, -30.3
Filorexant 10 mg	76	63.6 (37.6)	24.1 (19.2)	-39.6 (38.6)	-48.4, -30.7
Filorexant 20 mg	75	57.7 (36.5)	20.9 (27.5)	-36.8 (42.5)	-46.6, -27.1

Abbreviations: CI, confidence interval; LPS, latency to onset of persistent sleep; SD, standard deviation; SE, sleep efficiency; WASO, wakefulness after persistent sleep onset.
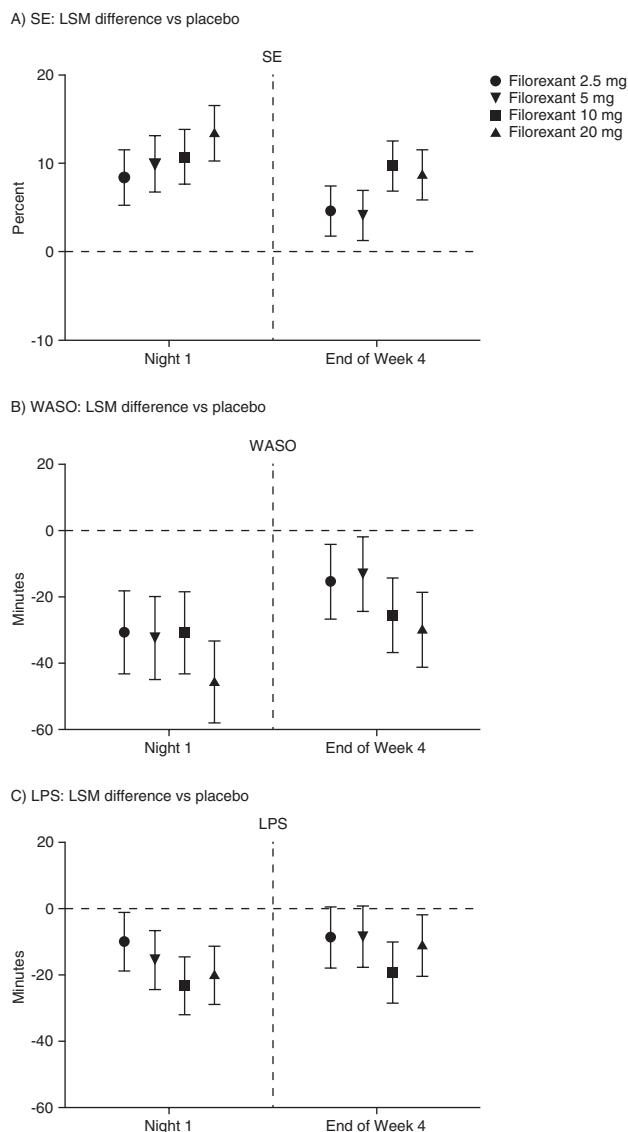
A) SE: LSM difference vs placebo

B) WASO: LSM difference vs placebo

C) LPS: LSM difference vs placebo

Figure 2. Difference in least-squares means between filorexant and placebo at night 1 and week 4 for (A) sleep efficiency (SE), (B) wakefulness after sleep onset (WASO), and (C) latency to persistent sleep (LPS). Footnote (A): night 1, $P<.001$ for all doses; week 4, $P\leq.001$ for filorexant 2.5, 10, and 20 mg and $P=.004$ for filorexant 5 mg. Footnote (B): night 1, $P<.001$ for all doses; week 4, $P=.006$ for filorexant 2.5 mg, $P=.020$ for filorexant 5 mg, $P<.001$ for filorexant 10 and 20 mg. Footnote (C): night 1, $P=.022$ for filorexant 2.5 mg, $P<.001$ for filorexant 5, 10, and 20 mg; week 4, $P=.055$ for filorexant 2.5 mg, $P=.060$ for filorexant 5 mg, $P<.001$ for filorexant 10 mg, $P=.015$ for filorexant 20 mg. LPS, latency to persistent sleep; LSM, least-squares mean; SE, sleep efficiency; WASO, wakefulness after sleep onset.

Filorexant generally had no notable effect on number of awakenings after onset of persistent sleep (Table 3). Analysis of sleep architecture endpoints generally showed numerical increases in time spent in most sleep stages (stage 1, stage 2, slow-wave sleep, and REM sleep) with filorexant vs placebo. However, increases in TST compared with placebo were mainly due to increases in the durations of stage 2 and REM sleep. When the percentage of time in each sleep stage (rather than minutes in each stage) was analyzed, only the percentage of REM sleep showed nominally significant increases compared with placebo for most of the filorexant doses (night 1: 2.5% to 3.3%; week 4: -0.8% to 2.1%). In terms of latency to REM sleep, numerically shorter latencies

(reductions of 5.5 to 31.7 minutes vs placebo) were observed for most filorexant doses compared with placebo. All differences were nominally significant at night 1 with the exception of the 2.5-mg dose; however, the only difference that was nominally significant at week 4 was 20 mg.

In terms of exploratory patient-reported outcome measures, filorexant doses of 5, 10, and 20 mg provided improvements compared with placebo at week 1 and week 4 for sTSO, sTST, sQual, and sFresh measures. Results for sTST and sTSO were suggestive of a dose response, with higher doses of filorexant generally achieving greater benefit. Improvement in insomnia, as assessed by ISI, was observed with all doses of filorexant compared with placebo, showing greatest benefit with the 2 highest doses (10 and 20 mg). Except for filorexant 2.5 mg, all doses suggested improvement compared with placebo in the total score of the SDS, with associated improvements in the individual domains of work, social, and family life/home reported (Table 3).

Safety and Tolerability

Filorexant was generally well tolerated in patients with insomnia treated for up to 4 weeks (Table 4). A dose-related increase in the overall rate of AEs was observed with filorexant; the AE rate for filorexant 2.5 and 5 mg was comparable with placebo, whereas the higher doses of filorexant (10 and 20 mg) were associated with an increased incidence of AEs.

The most common AE among patients treated with filorexant compared with placebo was somnolence, which was also the most commonly reported drug-related AE (ie, considered by the investigator to be related to study medication). Fourteen patients discontinued treatment due to an AE and of these patients, 7 were in the filorexant treatment group (2.5 mg: headache n=2, fatigue n=1, periorbital cellulitis n=1; 5 mg: atrial fibrillation n=1; 10 mg: upper respiratory tract infection n=1, acute cholecystitis n=1). All patients recovered following discontinuation of study medication.

Three patients reported serious AEs occurring during treatment with filorexant (2.5 mg: periorbital cellulitis; 5 mg: atrial fibrillation and syncope; 10 mg: acute cholecystitis); none of these serious AEs were considered by the investigator to be related to filorexant. Two serious AEs occurred posttreatment. One case of acute cholecystitis occurred 10 days after the last dose of placebo in treatment period 2, and one case of completed suicide (death) occurred during the washout period, 8 days after the last dose of placebo during treatment period 1. This was the only death reported during the study, and it was not considered by the investigator to be related to study drug. No suicidal ideation and/or behavior were reported during the treatment phase based on reported AEs or Columbia Suicide Severity Rating Scale assessments.

AEs that were prespecified as events of clinical interest occurred in 7 patients. One patient reported 3 episodes of sleep-onset paralysis, which were confirmed by the adjudication committee (1 episode on filorexant 10 mg and 2 on placebo). Two patients reported excessive daytime sleepiness (filorexant 20 mg and placebo), 2 patients reported falls (both on placebo), and 2 cases of drug administration error/events associated with potential drug abuse (filorexant 2.5 mg and 5 mg) were reported.

By objective assessment, no pattern was observed indicative of next-day residual effects as measured by the number of correct responses on the DSST (Table 5). No statistically significant differences were observed between the filorexant and placebo groups in terms of baseline-adjusted number of correct responses at either night 1 or week 4.

Table 3. Summary of Exploratory Efficacy Endpoints (Full Analysis Set)[a]

PSG endpoints[a]	Night 1				Week 4			
	2.5 mg	5 mg	10 mg	20 mg	2.5 mg	5 mg	10 mg	20 mg
TST, min	40.4 (25.4, 55.3)[b]	48.1 (33.1, 63.1)[b]	53.1 (38.3, 67.9)[b]	64.2 (49.4, 78.9)[b]	23.4 (9.9, 37.0)[b]	19.9 (6.4, 33.5)[c]	45.6 (32.1, 59.2)[b]	42.2 (28.6. 55.9)[b]
NAW	0.1 (-1.4, 1.6)	-1.2 (-2.8, 0.3)	-0.6 (-2.0, 0.9)	-3.0 (-4.4, -1.5)[b]	1.3 (-0.2, 2.7)	-0.5 (-2.0, 0.9)	-0.5 (-1.9, 0.9)	0.4 (-1.1, 1.8)
Sleep architecture								
Stage 1, min	1.9 (-1.8, 5.6)	2.7 (-1.0, 6.5)	7.1 (3.4, 10.8)[b]	1.8 (-1.9, 5.4)	7.3 (3.3, 11.2)[b]	-0.2 (-4.1, 3.7)	3.6 (-0.3, 7.6)	3.1 (-0.8, 7.1)
Stage 1, %	-0.8 (-1.8, 0.3)	-0.7 (-1.7, 0.3)	0.0 (-1.0, 1.0)	-1.6 (-2.6, -0.6)[c]	0.9 (-0.3, 2.0)	-0.5 (-1.7, 0.6)	-0.8 (-1.9, 0.3)	-0.3 (-1.4, 0.8)
Stage 2, min	15.8 (5.1, 26.5)[c]	15.5 (4.8, 26.3)[c]	20.0 (9.4, 30.6)[b]	34.3 (23.7, 44.9)[b]	13.8 (3.1, 24.5)[d]	7.4 (-3.3, 18.0)	24.0 (13.3, 34.8)[b]	23.5 (12.8, 34.3)[b]
Stage 2, %	-2.0 (-3.7, -0.2)[d]	-3.3 (-5.1, -1.6)[b]	-3.2 (-4.9, -1.5)[b]	-1.2 (-2.9, 0.6)	-0.2 (-1.9, 1.6)	-1.1 (-2.8, 0.7)	-0.8 (-2.6, 0.9)	-0.1 (-1.8, 1.7)
SWS, min	3.8 (-2.5, 10.1)	11.1 (4.8, 17.3)[b]	4.4 (-1.7, 10.5)	7.8 (1.5, 14.2)[d]	0.8 (-5.5, 7.1)	1.4 (-4.9, 7.7)	2.5 (-3.8, 8.9)	3.5 (-3.2, 10.1)
SWS, %	-0.5 (-2.0, 1.1)	1.3 (-0.3, 2.8)	-0.2 (-1.7, 1.3)	0.0 (-1.5, 1.6)	-0.5 (-2.0, 1.1)	-0.2 (-1.7, 1.4)	-0.7 (-2.2, 0.9)	-0.4 (-2.1, 1.2)
REM, min	19.1 (11.7, 26.5)[b]	18.6 (11.2, 26.0)[b]	22.3 (15.0, 29.6)[b]	21.6 (14.4, 28.9)[b]	0.8 (-5.5, 7.2)	11.3 (4.9, 17.7)[b]	16.3 (10.0, 22.7)[b]	11.3 (4.9, 17.7)[b]
REM, %	3.3 (1.7, 4.8)[b]	2.5 (1.0, 4.1)[b]	3.1 (1.6, 4.6)[b]	2.6 (1.1, 4.1)[b]	-0.8 (-2.2, 0.6)	1.5 (0.1, 2.9)[d]	2.1 (0.7, 3.5)[c]	0.6 (-0.8, 2.0)
Latency to REM, min	-14.0 (-28.4, 0.5)	-26.1 (-40.6, -11.5)[b]	-25.4 (-39.7, -11.1)[b]	-31.7 (-46.0, -17.5)[b]	-5.5 (-18.3, 7.3)	-10.6 (-23.4, 2.3)	-11.8 (-24.6, 1.0)	-25.6 (-38.4, -12.8)[b]

Patient-reported endpoints[a]	Week 1				Week 4			
	2.5 mg	5 mg	10 mg	20 mg	2.5 mg	5 mg	10 mg	20 mg
Subjective sleep								
sTST, min	5.3 (-6.1, 16.7)	19.2 (7.6, 30.7)[c]	20.1 (8.7, 31.5)[b]	30.1 (19.1, 41.2)[b]	14.1 (3.3, 25.0)[d]	25.7 (14.7, 36.7)[b]	30.7 (19.8, 41.6)[b]	38.0 (27.4, 48.6)[b]
sTSO, min	-8.0 (-15.4, -0.6)[d]	-12.0 (-19.5, -4.5)[c]	-17.6 (-25.0, -10.2)[b]	-16.9 (-24.1, -9.7)[b]	-9.4 (-16.0, -2.7)[c]	-14.0 (-20.8, -7.3)[b]	-17.1 (-23.8, -10.5)[b]	-18.2 (-24.7, -11.7)[b]
sQual, 4-point scale[e]	0.1 (0.0, 0.2)	0.1 (0.0, 0.3)[d]	0.2 (0.1, 0.3)[b]	0.2 (0.1, 0.3)[b]	0.1 (0.0, 0.2)	0.2 (0.1, 0.4)[b]	0.3 (0.2, 0.4)[b]	0.3 (0.2, 0.4)[b]
sFresh, 5-point scale[f]	0.1 (-0.1, 0.2)	0.2 (0.0, 0.3)[d]	0.2 (0.0, 0.4)[d]	0.2 (0.0, 0.3)[d]	0.1 (0.0, 0.3)	0.2 (0.0, 0.4)[d]	0.3 (0.1, 0.4)[c]	0.3 (0.1, 0.4)[c]
ISI								
Total score	-	-	-	-	-1.5 (-2.6, -0.4)[c]	-2.3 (-3.3, -1.2)[b]	-3.0 (-4.1, -2.0)[b]	-3.4 (-4.4, -2.3)[b]
SDS								
Total score	-	-	-	-	-1.1 (-2.5, 0.2)	-1.4 (-2.7, -0.1)[d]	-1.8 (-3.1, -0.4)[c]	-1.8 (-3.1, -0.5)[c]
Work	-	-	-	-	-0.2 (-0.7, 0.3)	-0.5 (-1.0, 0.0)[d]	-0.4 (-0.9, 0.1)	-0.6 (-1.1, -0.1)[d]
Social	-	-	-	-	-0.4 (-0.9, 0.1)	-0.3 (-0.8, 0.1)	-0.6 (-1.0, -0.1)[d]	-0.6 (-1.1, -0.1)[d]
Family	-	-	-	-	-0.1 (-0.6, 0.4)	-0.6 (-1.1, -0.1)[d]	-0.7 (-1.2, -0.2)[c]	-0.5 (-1.0, 0.0)[d]

Abbreviations: CI, confidence interval; ISI, Insomnia Severity Index; NAW, number of awakenings after onset of persistent sleep; REM, rapid eye movement; SDS, Sheehan Disability Scale; sFresh, patient-reported freshness of sleep; sQual, patient-reported quality of sleep; sTST, subjective total sleep time; sTSO, subjective time to sleep onset; SWS, slow-wave sleep (stage 3 and 4); TSO, time to sleep onset; TST, total sleep time; VAS, visual analog scale.

[a]Data presented are difference (95% CI) between filorexant and placebo in least-squares mean changes from baseline.

[b]P≤.001.

[c]P≤.01.

[d]P≤.05 vs placebo.

[e]Response options were: 1=poor, 2=fair, 3=good, 4=excellent, in response to the question, "How would you describe the quality of your sleep last night?"

[f]Response options were: 0=not at all, 1=a little, 2=moderately, 3=quite a bit, 4=extremely, in response to the question, "How refreshed do you feel this morning?"

Table 4. Summary of AEs (All Patients as Treated)

| | Placebo (n=315) | Filorexant | | | | |
		2.5 mg (n=79)	5 mg (n=78)	10 mg (n=80)	20 mg (n=81)	Total (n=318)
Number (%) of patients						
With ≥1 AE	82 (26.0)	21 (26.6)	20 (25.6)	26 (32.5)	28 (34.6)	95 (29.9)
With drug-related AEs	29 (9.2)	9 (11.4)	8 (10.3)	14 (17.5)	20 (24.7)	51 (16.0)
With SAEs	0 (0)	1 (1.3)	1 (1.3)	1 (1.3)	0 (0)	3 (0.9)
With drug-related SAEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued due to AEs	7 (2.2)	4 (5.1)	1 (1.3)	2 (2.5)	0 (0)	7 (2.2)
Common AEs (≥3% incidence in any treatment group)						
Somnolence	9 (2.9)	1 (1.3)	2 (2.6)	5 (6.3)	11 (13.6)	19 (6.0)
Headache	12 (3.8)	3 (3.8)	3 (3.8)	5 (6.3)	3 (3.7)	14 (4.4)
Fatigue	1 (0.3)	2 (2.5)	1 (1.3)	0 (0)	3 (3.7)	6 (1.9)
Diarrhea	3 (1.0)	0 (0)	1 (1.3)	3 (3.8)	0 (0)	4 (1.3)
Common drug-related AEs (≥2% incidence in any treatment group)						
Somnolence	9 (2.9)	1 (1.3)	2 (2.6)	5 (6.3)	11 (13.6)	19 (6.0)
Headache	6 (1.9)	2 (2.5)	1 (1.3)	2 (2.5)	1 (1.2)	6 (1.9)
Fatigue	1 (0.3)	2 (2.5)	1 (1.3)	0 (0)	2 (2.5)	5 (1.6)
Irritability	0 (0)	0 (0)	2 (2.6)	2 (2.5)	1 (1.2)	5 (1.6)
Abnormal dreams	1 (0.3)	0 (0)	1 (1.3)	1 (1.3)	2 (2.5)	4 (1.3)

AE, adverse event; SAE, serious adverse event.

Table 5. Digit Symbol Substitution Test: Number of Correct Responses

	Differences between Filorexant and Placebo in LSM[a]	95% CI	P Value
Night 1			
Filorexant			
2.5 mg	0.2	(-2.2, 2.6)	0.865
5 mg	1.6	(-0.7, 4.0)	0.177
10 mg	0.9	(-1.4, 3.3)	0.435
20 mg	-1.7	(-4.1, 0.6)	0.143
Week 4			
Filorexant			
2.5 mg	-1.2	(-3.6, 1.2)	0.337
5 mg	0.2	(-2.2, 2.6)	0.852
10 mg	1.1	(-1.3, 3.5)	0.387
20 mg	0.0	(-2.3, 2.4)	0.980

Abbreviation: CI, confidence interval; LSM, least-squares mean.
[a]Data presented are difference (95% CI) between filorexant and placebo LSM changes from baseline.

Table 6. Patients reporting ≥3 of 20 emergent or worsening symptoms on the Tyrer Withdrawal Symptom Questionnaire for the first 3 nights after the end of treatment Period 1

| | Across Nights 1–3 after the end of treatment Period 1 | | |
	Difference in proportion of patients with withdrawal between filorexant and placebo (%)	95% CI	P Value
Filorexant			
2.5 mg	-3.18	(-12.7, 12.8)	0.687
5 mg	-3.77	(-13.0, 11.4)	0.724
10 mg	-4.75	(-13.6, 9.2)	0.786
20 mg	-2.05	(-11.6, 12.6)	0.631

CI, confidence interval.

Evaluation of sTST and sTSO for evidence of rebound insomnia upon stopping filorexant showed no clear, consistent pattern across the doses in the proportion of patients reporting any worsening in sTST or sTSO on the first 3 nights of the washout period compared with baseline. The proportion of patients reporting any worsening in sTST during this time was numerically greater for the filorexant 20 mg group than for placebo only on night 1 (P=.014; night 2, P=.939; night 3, P=.086), and for either night 1, 2, or 3 (P=.013). The proportion of patients reporting any worsening in sTSO during this time was also greater for filorexant 10 mg on nights 1 and 2 (P=.006 and P=.046, respectively) and for filorexant 20 mg on night 1 (P<.001).

There was no evidence of acute withdrawal following discontinuation of filorexant, as measured by the Tyrer WSQ, with a similar low proportion of patients demonstrating withdrawal effects in the filorexant (8.1% to 10.8%) and placebo (12.9%) treatment groups across nights 1 to 3 of the washout period (Table 6).

Discussion

The current dose-ranging study was designed to evaluate filorexant as a treatment for insomnia in adults. All doses of filorexant investigated (2.5, 5, 10, and 20 mg) were significantly superior to placebo in improving sleep among patients with insomnia as measured by SE (primary endpoint) and WASO on night 1 and at the end of week 4. The 2 higher doses of filorexant (10 and 20 mg) were significantly more effective than placebo in improving sleep onset as measured by LPS at night 1 and at the end of week 4, although the study was not powered to detect minimally clinically meaningful treatment effects on LPS. Filorexant also increased TST, primarily due to increases in the duration of sleep bout duration, with no overall effect on the NAW. Latency to REM sleep was numerically decreased by filorexant in a dose-dependent manner, and the percentage of time spent in REM sleep was minimally increased relative to placebo. Filorexant also had a beneficial effect on subjective assessments of sleep

variables, including sTST, sTSO, sQual, and sFresh, improved insomnia as assessed by the ISI, and improved daytime function based on changes in the SDS. Together, these findings provide further validation of the orexin receptor pathway as an important and effective mechanistic target for the treatment of insomnia. These results add to earlier evidence from preclinical studies and a PSG sleep study in healthy volunteers showing that antagonism of orexin receptors by filorexant produces sleep-promoting effects (Sun et al., 2011a; Winrow et al., 2012).

Suvorexant is the first ORA to be approved by the U.S. FDA for the treatment of insomnia, having demonstrated improvements in PSG and patient-reported sleep endpoints on the first night after dosing and after 4 weeks, and 1 year, of treatment in patients with insomnia (Herring et al., 2012, 2016; Michelson et al., 2014). Although the current study was not designed as a comparative study, filorexant generally demonstrated improvements in PSG and patient-reported sleep endpoints that were comparable with those typically achieved with suvorexant in nonelderly patients with insomnia (Herring et al., 2012).

Overall, treatment with filorexant was generally well tolerated with no important safety concerns. The observed safety profile of filorexant was similar to that reported with compounds in the same class, such as suvorexant (Herring et al., 2012, 2016; Michelson et al., 2014), SB649868 (Bettica et al., 2012), and almorexant (Hoever et al., 2012; Cruz et al., 2014) in healthy subjects and patients with insomnia. Somnolence was the most common AE reported with filorexant. Serious AEs were uncommon during treatment and none were considered related to filorexant. Significant residual or rebound effects were not reported.

The current study incorporated some important design considerations. The 4-week dosing duration for each treatment period allowed both an acute (night 1) and more chronic (end of week 4) assessment of filorexant efficacy and tolerability. This design allowed the evaluation of immediate and sustained efficacy, both of which are fundamental requirements for insomnia therapies. Furthermore, the washout duration of 14 days (3 days of single-blind placebo followed by 11 days off study drug) provided an estimated 67 half-lives (based upon a $t_{1/2}$ for filorexant of 5 hours) of pharmacokinetic clearance for filorexant. This provided an adequate buffer for the clearance of any potentially associated pharmacodynamic effects prior to night 1 of the subsequent 4-week treatment period (period 2) and minimized the likelihood of a carryover effect of treatment between the 2 treatment periods. There was no evidence of significant sequence effects. Further studies are required to evaluate the long-term safety and efficacy of filorexant and also its safety and efficacy in the elderly.

The relatively short apparent $t_{1/2}$ of filorexant (approximately 3 to 6 hours) suggests the possibility of a unique clinical profile compared with that of other known ORA receptor antagonists (Sun et al., 2011b). For instance, a compound with a shorter $t_{1/2}$ may offer an improved residual effect profile, but, perhaps, at the expense of maintaining sleep throughout the night. In this trial, while a dose-related effect was observed for somnolence, the incidence of somnolence at the 2 lower doses was similar to placebo, and sustained maintenance effects were noted across the full filorexant dose range. However, without data from a study specifically designed to make cross-compound comparisons between doses ultimately deemed clinically acceptable for regulatory approval (suvorexant is approved in the US for insomnia at a dose of 10 to 20 mg once daily and is currently the only FDA-approved ORA), comparisons in this regard would be speculative.

In conclusion, this study has shown that filorexant, a shorter-acting dual ORA, is well tolerated and promotes the initiation and maintenance of sleep in patients with insomnia, achieving consistent improvements in sleep time, as determined by both PSG and patient report.

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