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Original Article

Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data

W. Joseph Herring [a, *], Kathryn M. Connor [a], Ellen Snyder [a], Duane B. Snavely [a], Charles M. Morin [b], Christopher Lines [a], David Michelson [a]

[a] Merck & Co., Inc., 2000 Galloping Hill Rd, Kenilworth, NJ, 07033, USA
[b] Université Laval, 2325 Rue des Bibliothèques, Pavillon FAS, Québec, G1V 0A6, Canada

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ABSTRACT

Objective: Suvorexant is an orexin receptor antagonist that is approved in the US, Japan and Australia for the treatment of insomnia. Using outcomes from the Insomnia Severity Index (ISI) in the core registration studies, we explored suvorexant effects on sleep problems and their impact on daytime function.
Methods: Data were pooled from two similar Phase 3, randomized, double-blind, placebo-controlled, parallel-group, three-month trials in elderly (≥65 years) and non-elderly (18–64 years old) insomnia patients. Age-adjusted (non-elderly/elderly) dose-regimes of 40/30 mg and 20/15 mg were evaluated. The ISI, a 7-item self-rated questionnaire with each item rated on 0–4 scale (higher score corresponds to increasing severity), was administered to patients as an exploratory assessment in both studies at baseline and one and three months after randomization.
Results: The analysis included 1824 patients. Suvorexant improved change-from-baseline ISI total scores to a greater extent than placebo (Month three: 20/15 mg = −6.2, 40/30 mg = −6.7, placebo = −4.9, *p*-values for both active arms vs. placebo <0.001) and resulted in a greater proportion of responders than placebo using a variety of definitions (eg, ≥6-point improvement from baseline at Month three: 20/15 mg = 55.5%, 40/30 mg = 54.9%, placebo = 42.2%, *p*-values for both active arms vs. placebo <0.001). Additionally, the "impact of insomnia" component, which assesses the impact of insomnia on daytime function/quality-of-life, was improved to a greater extent by suvorexant than placebo.
Conclusions: Suvorexant 20/15 mg and 40/30 mg improved sleep to a greater extent than placebo as assessed by the ISI in patients with insomnia. Improvement in sleep onset/maintenance as well as a reduction of the impact of sleep problems on daytime function contributed to the overall improvement observed in ISI total score.
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1. Introduction

Suvorexant is a first-in-class orexin receptor antagonist approved for treating insomnia in the US, Japan and Australia. at doses up to 20 mg. Suvorexant blocks orexin-mediated wake signaling [1–3], a mechanism distinct from GABA-A receptor modulator sleep medicines (eg. zolpidem, zaleplon, eszopiclone, temazepam etc.), which act via GABA inhibition, inducing broad central nervous system depressant effects [4].

The key primary and secondary endpoints used in the two pivotal Phase 3 placebo-controlled trials of suvorexant included patient-reported and polysomnography (PSG) measures of sleep maintenance and sleep onset. Furthermore, suvorexant was found to improve both patient-reported and PSG sleep measures [5,6]. The Insomnia Severity Index (ISI) was included as an additional exploratory assessment. The ISI is a brief instrument that was designed to assess the severity of both nighttime and daytime aspects of insomnia [7,8]. Its psychometric properties have been described and it has been increasingly used as a measure of treatment response in clinical trials [8,9]. In this paper we report on analyses of the effects of suvorexant on the ISI using pooled data from Phase 3 trials.

* Corresponding author. Merck & Co., Inc., UG 4C-13, PO Box 1000, North Wales, PA 19454-1099, USA. Fax: +11 267 305 6390.
E-mail address: william_herring@merck.com (W.J. Herring).

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2. Material and methods

2.1. Overview

Full details of trial methods are in the primary publication [6]. The following sections summarize key information relevant to understanding the present analyses.

The ISI analyses included pooled data from two phase-3 randomized, double-blind, placebo-controlled, parallel-group, three-month clinical trials in non-elderly (18–64 years) and elderly (≥65 years) patients with primary insomnia [6]. Suvorexant doses of 40/30 mg (non-elderly/elderly) and 20/15 mg (non-elderly/elderly) were evaluated, with fewer patients randomized to 20/15 mg than 40/30 mg or placebo. Doses differed by age to adjust for previously-observed plasma exposure differences (<65: 40 mg or 20 mg; ≥65: 30 mg or 15 mg).

2.2. Patients

Non-elderly (18–64) and elderly (≥65) women and men who met DSM-IV-TR criteria for primary insomnia [10] and were otherwise in good physical and mental health were enrolled. All patients in the two pivotal efficacy studies provided subjective sleep estimates using an electronic sleep diary/questionnaire and completed the ISI. A subgroup of approximately 75% of those patients also underwent polysomnography (PSG). Patients who completed only self-report assessments are referred to as the questionnaire (Q)-cohort; those who completed both self-report and PSG assessments are referred to as the PSG + questionnaire (PQ)-cohort. To enter the Q-cohort, patients had to report a total sleep time <6.5 h and time to sleep onset ≥30 min, both on ≥4 of seven-nights during the last week of a two-week placebo run-in before randomization. For the PQ-cohort, patients had to meet the following PSG criteria for screening and baseline PSG nights: latency to onset of persistent sleep >20 min, and mean (across screening and baseline) wakefulness after persistent sleep onset ≥60 min with neither night ≤45 min. PQ-cohort patients were not required to also meet the Q-cohort diary entry criteria. All patients (PQ + Q cohorts) also had to report ≥1 h of wakefulness after sleep on ≥3 of seven nights each week during the four weeks prior to the initial screening visit.

2.3. Design and procedure

Patients were discontinued from hypnotic medications prior to entering the trials. During the trials, patients were asked to limit alcohol consumption (≤2 drinks per day and ≥3 h before bedtime, or ≥24 h before on PSG nights), caffeine consumption (≤5 cups per day and none after 4 pm, or after 1 pm on PSG nights), and smoking (≤15 cigarettes per day and none during the night).

Patients were randomized to treatment with suvorexant 40/30 mg, suvorexant 20/15 mg, or placebo, with fewer patients randomized to treatment with 20/15 mg than 40/30 mg or placebo. Randomization was stratified by age-category (non-elderly vs. elderly) in all trials and also by cohort (Q vs. PQ). Patients were assigned to treatment groups using an allocation-schedule system that provided a computer-generated randomization schedule based upon input from a statistician from Merck & Co., Inc., from whom treatment allocation was masked. Treatment assignment was implemented through an interactive voice response system. Study investigators, site staff, patients, and monitoring staff from Merck & Co., Inc. remained blinded to treatment allocation throughout the study.

The trials were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies for each site. Informed consent was obtained from all patients. The trials were registered at ClinicalTrials.gov (NCT01097616, NCT01097629).

2.4. ISI

The ISI is a 7-item self-rated questionnaire including items related to perceived severity of nocturnal insomnia symptoms (sleep onset, sleep maintenance, or early morning awakenings), sleep dissatisfaction, impact of sleep disturbance on daytime functioning, noticeability of sleep problems in terms of impairing quality of life, and degree of distress [7,8]. Each item is rated on 0–4 scale, with a higher score corresponding to increasing severity. The ISI has excellent psychometric properties (Cronbach alpha >0.90), with good sensitivity/specificity, and principal components analysis suggests three factors: (1) impact of insomnia, (2) severity of insomnia, and (3) sleep satisfaction/dissatisfaction [8,9,11,12]. Patients completed the ISI at baseline and at Months one and three, and were instructed to base their ratings on severity during the preceding month.

2.5. Statistical analysis

The pooled efficacy analysis was pre-specified to allow a more robust evaluation than in each individual trial, and included all patients in the two trials who took ≥1 dose of treatment, had baseline data, and had ≥1 post-treatment efficacy measure (the full-analysis-set). The following change-from-baseline ISI measures were pre-specified for analysis: (1) change-from-baseline in mean ISI total score; (2) change-from-baseline in mean score on each ISI item; and (3) the percentage of responders, defined as those with a ≥6 point improvement from baseline in ISI total score [13]. In addition, the following measures were analyzed on a post hoc basis: (1) change from baseline in mean score on the impact of insomnia factor (last three items) [8]; (2) the percentages of responders, using alternate definitions of a ≥8 point, ≥9 point, and ≥10 point improvement from baseline in ISI total score [9]; (3) the percentage of patients in remission/with an insomnia complaint below a clinical threshold, defined as an ISI total score <10 and < baseline (to exclude patients who had a score <10 at baseline and who then worsened or showed no improvement) [8,9,14]; and (4) the distribution of patients by ISI total score category: 0–7 = no or minimal insomnia, 8–14 = sub-threshold insomnia, 15–21 = moderate insomnia, 22–28 = severe insomnia [8].

Efficacy endpoints (ie, change-from-baseline in ISI scores) were assessed using a longitudinal data analysis model with terms for study, baseline value, age category (<65, ≥65), region (North America, European Union, other), cohort (PQ, Q), sex, treatment, time point, and treatment-by-time point interaction. Analysis of responders was based on a generalized linear mixed model using the same terms. The primary comparisons of interest were differences between the suvorexant groups versus placebo.

No formal multiplicity strategy was employed for these pooled analyses since the primary purpose was to provide improved precision in the estimates of the treatment group comparisons; nominal *p*-values for these treatment differences were computed as a measure of strength of evidence for the effect rather than a formal test of hypothesis. Furthermore, in interpreting *p*-values for treatment differences it should be noted that the sample size for the suvorexant 20/15 mg group was smaller than for the 40/30 mg group.

Results for suvorexant 20/15 mg in the pooled dataset on the change-from- baseline in mean total ISI score and percentage of responders using the ≥6 point improvement definition have been previously reported [5].

2.6. Power

No power calculations were made for the ISI analyses.

3. Results

3.1. Patients

Patient baseline characteristics were generally similar among treatment groups and are summarized in Table 1. At baseline, patients reported a mean time to sleep onset of over 1 h and a mean total sleep time of approximately 5 h.

3.2. ISI

At baseline patients in all treatment groups had a mean ISI total score of 16, which corresponds to "moderate insomnia" (Table 1). Of the individual ISI items, "dissatisfied with current sleep pattern" was scored highest at baseline.

Mean changes from baseline are shown in Table 2. ISI total scores and impact scores improved from Month one to Month three in both suvorexant groups and the placebo group relative to baseline but the improvements were greater ($p < 0.01$) in the suvorexant groups (Table 2). Mean change scores on most of the individual ISI items were also improved to a greater extent in the suvorexant groups than the placebo group, with the strongest effects tending to be seen on the "dissatisfied with current sleep pattern" item.

The number and percentage of responders according to the four definitions are shown in Table 3. While the proportion of responders in all groups, including placebo, decreased as the response criteria became more stringent, the odds ratios for response for suvorexant versus placebo were generally similar across all definitions, and were consistently greater for both doses of suvorexant compared to placebo.

The number and percentage of patients who met remission criteria are shown in Table 3. While 23% of patients on placebo were in remission by Month one and 40% by Month three, patients on suvorexant were approximately 1.5–2.5 times more likely to be in remission than those on placebo.

The pre- and post-treatment distributions of ISI severity categories are shown in Fig. 1. Numerically, a greater percentage of patients treated with suvorexant were in the ISI <8/"no or minimal insomnia" category at Months one and three versus placebo, although formal statistical testing was not performed. The increase in "no or minimal insomnia" was mostly due to a reduction in the percentages of patients in the "severe insomnia" and "moderate insomnia" categories relative to baseline.

Table 1
Baseline characteristics of treated patients for pooled phase 3 data.

	Suvorexant 20/15 mg	Suvorexant 40/30 mg	Placebo
Demographics			
N	493	770	767
Sex, n (%)			
Female	319 (64.7)	497 (64.5)	492 (64.1)
Male	174 (35.3)	273 (35.5)	275 (35.9)
Age			
Mean (SD), years	55 (16)	56 (15)	56 (15)
<65 years, n (%)	291 (59.0)	451 (58.6)	449 (58.5)
≥65 years, n (%)	202 (41.0)	319 (41.4)	318 (41.5)
Body mass index			
Mean (SD), kg/m^2	25.4 (4.1)	25.7 (4.3)	25.6 (4.2)
Underweight <18.5, n (%)	11 (2.2)	18 (2.3)	16 (2.1)
Normal 18.5-<25, n (%)	232 (47.1)	323 (41.9)	351 (45.8)
Overweight 25–30, n (%)	194 (39.4)	317 (41.2)	289 (37.7)
Obese >30, n (%)	56 (11.4)	111 (14.4)	110 (14.3)
Race, n (%)			
White	358 (72.6)	563 (73.1)	553 (72.1)
Asian	93 (18.9)	124 (16.1)	124 (16.2)
Black	19 (3.9)	38 (4.9)	46 (6.0)
Other	23 (4.7)	45 (5.8)	44 (5.7)
Mean (SD) baseline diary sleep measures[a]			
N	479	752	740
Subjective total sleep time, min	311 (71)	315 (73)	311 (71)
Subjective time to sleep onset, min	75 (62)	72 (57)	75 (62)
Mean (SD) baseline ISI total and item scores[a]			
N	440	699	685
Total score	16.1 (3.8)	15.9 (4.0)	15.9 (4.1)
1. Difficulty falling asleep	2.4 (0.8)	2.4 (0.7)	2.4 (0.7)
2. Difficulty staying asleep	2.5 (0.8)	2.5 (0.7)	2.5 (0.7)
3. Waking too early	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)
4. Dissatisfied with sleep	3.0 (0.7)	3.0 (0.7)	3.0 (0.6)
5. Sleep problem interferes with daily function	2.1 (1.0)	2.1 (0.9)	2.1 (1.0)
6. Sleep problem impairs quality of life	1.6 (1.0)	1.6 (1.0)	1.5 (1.0)
7. Worried/distressed about sleep problem	2.3 (0.9)	2.3 (0.9)	2.2 (1.0)
Impact factor (items 5 + 6+7)	6.0 (2.4)	5.9 (2.4)	5.8 (2.5)

[a] Based on the full-analysis-set population.

4. Discussion

We found that suvorexant improved ISI total scores at Months one and three to a greater extent than placebo. Suvorexant also improved mean change scores on most of the individual ISI items more than placebo. The individual item showing the largest improvement was the "dissatisfied with current sleep pattern" item which was also the item scored highest at baseline. *A priori* we might have expected to see the greatest improvements on those ISI items directly related to sleep maintenance (items two and three) given that in previous analyses of PSG and subjective sleep diary measures suvorexant appeared to have strongest effects on measures of sleep maintenance. The findings suggest that suvorexant's effects translate into an overall increased patient satisfaction with sleep. Furthermore, suvorexant improved patients' scores on the "impact" factor, suggesting that suvorexant effects on improving sleep result in measurable next day and quality of life benefits.

In addition to looking at mean change from baseline scores we also looked at the percentage of responders who met various response criteria for improvement from baseline. Since various different response definitions have been proposed in the literature we looked at cut-points ranging from a ≥6-point improvement to a ≥10-point improvement [9,13]. While the percentage of responders in all groups decreased as the response criteria became more stringent, the odds ratios for response for suvorexant versus placebo were generally similar across all definitions, and were consistently greater for both doses of suvorexant compared to placebo, by approximately 1.5–2 times for the 20/15 mg dose and two to three times for the 40/30 mg dose. Our findings suggests that if one is concerned purely with assessing treatment effects (difference versus placebo) then the precise definition of a responder does not matter.

We also looked at the percentage of patients in remission/with an insomnia complaint below a clinical threshold, defined as an ISI total score <10 and < baseline (to exclude patients who had a score <10 at baseline and who then worsened or showed no improvement). Based on this definition, patients on suvorexant were approximately 1.5 (20/15 mg dose) to 2.5 (40/30 mg dose) times

Table 2
Change from baseline in least squares mean ISI scores by treatment group, and difference (95% CI) for suvorexant versus placebo.

ISI score	Month 1					Month 3				
	20/15 mg (N = 440)	40/30 mg (N = 699)	Placebo (N = 685)	20/15 mg vs. placebo	40/30 mg vs. placebo	20/15 mg (N = 411)	40/30 mg (N = 656)	Placebo (N = 638)	20/15 mg vs. placebo	40/30 mg vs. placebo
Total	−4.4	−4.8	−3.0	−1.4 (−1.9, −0.9)***	−1.8 (−2.2, −1.3)***	−6.2	−6.7	−4.9	−1.3 (−1.8, −0.7)***	−1.8 (−2.3, −1.3)***
Item 1	−0.7	−0.8	−0.4	−0.2 (−0.3, −0.1)***	−0.4 (−0.4, −0.3)***	−0.9	−1.1	−0.8	−0.2 (−0.3, −0.1)**	−0.3 (−0.4, −0.2)***
Item 2	−0.6	−0.7	−0.4	−0.3 (−0.4, −0.2)***	−0.3 (−0.4, −0.2)***	−0.9	−0.9	−0.7	−0.2 (−0.3, −0.1)***	−0.3 (−0.4, −0.2)***
Item 3	−0.5	−0.6	−0.3	−0.1 (−0.2, −0.0)**	−0.2 (−0.3, −0.1)***	−0.7	−0.9	−0.6	−0.1 (−0.2, 0.0)	−0.2 (−0.3, −0.1)***
Item 4	−0.8	−0.9	−0.5	−0.4 (−0.5, −0.3)***	−0.4 (−0.5, −0.3)***	−1.1	−1.2	−0.8	−0.3 (−0.4, −0.2)***	−0.4 (−0.5, −0.2)***
Item 5	−0.6	−0.7	−0.5	−0.1 (−0.2, −0.0)*	−0.1 (−0.2, −0.0)**	−0.9	−0.9	−0.8	−0.1 (−0.2, 0.0)	−0.2 (−0.3, −0.1)**
Item 6	−0.5	−0.5	−0.4	−0.1 (−0.2, 0.0)	−0.1 (−0.2, −0.0)**	−0.7	−0.8	−0.6	−0.2 (−0.3,−0.1)***	−0.2 (−0.3, −0.1)***
Item 7	−0.7	−0.7	−0.5	−0.2 (−0.3, −0.1)***	−0.2 (−0.3, −0.1)***	−1.0	−1.0	−0.8	−0.3 (−0.4, −0.1)***	−0.3 (−0.4, −0.2)***
Impact	−1.8	−1.9	−1.4	−0.4 (−0.7, −0.2)**	−0.5 (−0.7, −0.3)***	−2.6	−2.8	−2.1	−0.5 (−0.8, −0.2)***	−0.7 (−0.9, −0.4)***

Results based on a mixed effects model with terms for study, baseline value, age category (<65, ≥65), region (North America, European Union, other), cohort (PQ, Q), sex, treatment, time point, and treatment-by-time point interaction as covariates. See Table 1 for description of ISI items and the Impact factor.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

Table 3
Number and percentage of responders and remitters based on ISI total score by treatment group, and odds ratio (95% CI) for suvorexant versus placebo.

Responder definition	Month 1					Month 3				
	20/15 mg (N = 440)	40/30 mg (N = 699)	Placebo (N = 685)	20/15 mg vs. placebo	40/30 mg vs. placebo	20/15 mg (N = 411)	40/30 mg (N = 656)	Placebo (N = 638)	20/15 mg vs. placebo	40/30 mg vs. placebo
≥6 point improvement	149 (33.9%)	279 (39.9%)	157 (22.9%)	1.8 (1.4, 2.4)***	2.4 (1.9, 3.1)***	228 (55.5%)	360 (54.9%)	269 (42.2%)	1.8 (1.4, 2.3)***	1.8 (1.4, 2.2)***
≥8 point improvement	102 (23.2%)	183 (26.2%)	92 (13.4%)	2.0 (1.5, 2.8)***	2.5 (1.9, 3.3)***	155 (37.7%)	272 (41.5%)	180 (28.2%)	1.6 (1.2, 2.1)**	1.9 (1.5, 2.5)***
≥9 point improvement	83 (18.9%)	149 (21.3%)	66 (9.6%)	2.3 (1.6, 3.3)***	2.8 (2.1, 3.9)***	121 (29.4%)	232 (35.4%)	142 (22.3%)	1.4 (1.1, 1.9)*	2.1 (1.6, 2.7)***
≥10 point improvement	68 (15.5%)	119 (17.0%)	57 (8.3%)	2.1 (1.4, 3.1)***	2.5 (1.8, 3.5)***	102 (24.8%)	191 (29.1%)	117 (18.3%)	1.4 (1.1, 2.0)*	2.0 (1.5, 2.6)***
Remission										
<10 and < baseline	132 (30.0%)	248 (35.5%)	159 (23.2%)	1.5 (1.2, 2.0)**	1.9 (1.5, 2.4)***	197 (47.9%)	367 (55.9%)	256 (40.1%)	1.5 (1.2, 2.0)**	2.0 (1.6, 2.5)***

Results based on a mixed effects model with terms for study, baseline value, age category (<65, ≥65), region (North America, European Union, other), cohort (PQ, Q), sex, treatment, time point, and treatment-by-time point interaction as covariates.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

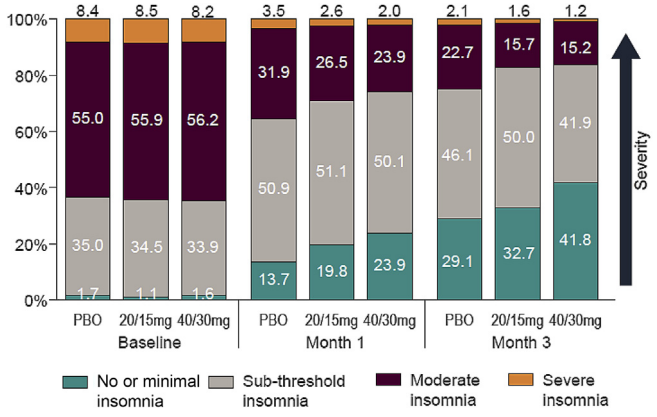

Fig. 1. Pre- and post-treatment ISI severity distribution. 0–7 = no or minimal insomnia, 8–14 = sub-threshold insomnia, 15–21 = moderate insomnia, 22–28 = severe insomnia.

more likely to be in remission than patients on placebo. It should be noted that 23% of patients in the placebo group were in remission by Month one and this increased to 40% by Month three, confirming the large placebo effect typically seen in sleep studies.

Our analysis has a number of strengths: data came from randomized, blinded, placebo-controlled trials and the numbers of patients evaluated were relatively large (although smaller for the 20/15 dose than the 40/30 mg dose). However, several limitations should be acknowledged. First, some of the analyses were *post hoc* in nature. Secondly, patients did not have to meet a prespecified ISI cut score to qualify for inclusion and patients were not randomized according to ISI score. Nevertheless, Fig. 1 shows that at baseline the treatment groups had similar distributions according to ISI severity categories. Notably, a small percentage of patients in each group fell into the "no insomnia" ISI category at baseline, which is surprising given that all patients had to meet established diagnostic criteria for insomnia [10] as well as additional research criteria. Finally, although we did not include a formal dose-response analysis, suvorexant effects tended to be greatest for the 40/30 mg dose. While results for 40/30 mg are informative for the orexin receptor

antagonist mechanism, the findings with the 20/15 mg dose are the most clinically relevant. given that the maximum approved dose is 20 mg The trials used for the analysis did not include active comparators so we were unable to compare the efficacy of suvorexant to other sleep medications, but improvements on the ISI have been reported for other treatments [14,15].

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Conflicts of interest

WJH, KMC, ES, DBS, CL, and DM are employees of, and own stock/stock options in, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

CMM has served as consultant on advisory boards for Cereve, Phillips, Esai, and Merck & Co., Inc., and received honorarium as speaker for Merck & Co., Inc.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.010.

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