Lemborexant for the Treatment of Insomnia: Direct and Indirect Comparisons With Other Hypnotics Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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ABSTRACT

Objective: To describe lemborexant for the treatment of insomnia (*DSM-5*) in adults using number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods: Lemborexant data were obtained from two Phase 3 trials conducted 2016–2018. Efficacy was assessed using different categorical definitions for response, and tolerability was assessed by evaluating rates of adverse events (AEs). Direct comparisons were made with zolpidem extended release (ER), and indirect comparisons were made with other hypnotic agents, including suvorexant, doxepin, ramelteon, zolpidem immediate release, eszopiclone, zaleplon, and selected benzodiazepines, using data from published reports and regulatory documents.

Results: Lemborexant had a clinically relevant magnitude of therapeutic effect, as evidenced by NNT values versus placebo as robust as 3 (95% CI, 2–3). In general, NNH values for lemborexant versus placebo were ≥ 10, suggesting that lemborexant is relatively tolerable. Somnolence was the most common AE, with NNH estimates of 28 (95% CI, 18–61) and 15 (95% CI, 11–22) for lemborexant 5 mg and 10 mg, respectively. Rates of discontinuation of lemborexant because of an AE were low, and for lemborexant 5 mg the rate was lower than that for placebo. LHH contrasting the statistically significant endpoint efficacy measures versus discontinuation because of an AE ranged from 13 to 54. NNT values for lemborexant were generally more robust than for zolpidem ER for the polysomnography and sleep diary outcomes. In indirect comparisons, NNT data for the other hypnotics demonstrated effect sizes that were generally similar to those for lemborexant.

Conclusions: In Phase 3 trials, the benefit-risk ratio for lemborexant is favorable as measured by NNT, NNH, and LHH.

Trial Registration: ClinicalTrials.gov identifiers: NCT02783729, NCT02952820

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Problems with sleep are commonly encountered in routine clinical practice in both primary and specialty care, and current diagnostic guidance encourages the identification of insomnia disorder whether it occurs as an independent condition or is comorbid with another psychiatric or medical condition.[1] Left untreated, insomnia can be associated with marked impairment in function and quality of life as well as psychiatric and physical morbidity.[2] Several considerations are involved in the management of insomnia; these considerations include whether insomnia symptoms persist despite good sleep hygiene and/or treatment of any underlying conditions, as well as a patient's suitability for targeted interventions such as cognitive-behavioral therapy or pharmacotherapy.[3]

It can be challenging to select among the different hypnotics available, especially for new agents that may be unfamiliar to clinicians and patients. When evaluating potential treatments using data from registrational trials, testing for statistical significance for drug versus placebo is insufficient. Consideration must also be made of the size of the treatment effect. Effect size can describe the potential importance of an intervention's efficacy and tolerability profile. Clinically intuitive measures of effect size include number needed to treat (NNT) to describe benefit (therapeutic response) and number needed to harm (NNH) to describe untoward events such as an adverse event (AE) or discontinuation due to an AE[4,5] (see also Supplementary Box 1). The ratio of NNH to NNT can further describe the benefit-risk ratio and is called "likelihood to be helped or harmed" (LHH).[5] This approach can be especially valuable when assessing new treatments and when head-to-head comparisons with other agents are generally not available. A recent example of using NNT, NNH, and LHH is the evaluation of a novel treatment for treatment-resistant major depressive disorder.[6]

Lemborexant, a dual orexin receptor antagonist (DORA), has been approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with insomnia (as characterized by difficulties with sleep onset and/or sleep maintenance)[7] and is also available in Japan and Canada. The mechanism of action of DORAs, which attenuate excessive wakefulness/arousal signaling, differs from that of hypnotic agents such as γ-aminobutyric acid (GABA)-A receptor agonists (for example, the benzodiazepine temazepam and the non-benzodiazepine zolpidem) and others (for example, the melatonin receptor agonist ramelteon) that augment sleep signaling.[8]

This study reviews the evidence base for lemborexant for the treatment of insomnia in adults using the metrics of NNT, NNH, and LHH to help place this intervention into clinical perspective. In

Clinical Points

- Insomnia is common, and there are many pharmacologic treatment options available to choose from.
- Using number needed to treat and number needed to harm can help place new hypnotics, such as lemborexant, into clinical perspective.

addition to comparisons with placebo, which in turn permit indirect comparisons with other hypnotics for which studies with placebo controls are available, direct comparisons are made with zolpidem extended release (ER), which served as an active treatment arm in one of the two Phase 3 trials that were conducted with lemborexant.

METHODS

Overview

Data were taken from the two Phase 3 randomized placebo-controlled trials of lemborexant for the treatment of insomnia (*DSM-5*) in adults: SUNRISE 1 (NCT02783729, E2006-G000-304) and SUNRISE 2 (NCT02952820, E2006-G000-303), conducted 2016–2018. The study protocols were reviewed and approved by the relevant Institutional Review Board or Independent Ethics Committee at each study site, and informed consent was obtained from all participants. Outcome measures examined were different categorical definitions for response using several rating thresholds, and several categorical tolerability outcomes including AEs of interest, similar to what has been reported with suvorexant.[9,10] Direct comparisons were made with an active control/comparator (zolpidem ER). Indirect comparisons were made with other hypnotics for which similar data are available; to that end, supplementing the data collected in the lemborexant clinical trial program are data as reported in the Drug Approval Packages made available by the FDA (for a description of a drug approval package, see Citrome[11]). Specifically, the FDA drug approval packages for suvorexant, doxepin, ramelteon, eszopiclone, zaleplon, zolpidem immediate release (IR), and zolpidem ER[12–18] were screened for the existence of responder analyses to help inform the selection of additional efficacy outcomes to be extracted from the lemborexant clinical trial database. Relevant drug approval packages are not available for the commonly used benzodiazepine hypnotics triazolam, temazepam, and flurazepam. AE rates for the hypnotics are as extracted from their respective product labels when such data are provided, including those for triazolam, temazepam, and flurazepam,[9,19–27] and refined when additional information was available from the relevant drug approval package. Some of the many parallel-group, placebo-controlled, registrational studies that were used to support approval of lemborexant and the other hypnotics as reported in the published literature and in briefing documents[28–42] provided additional data. Limited categorical data (see also Table 1) are available on subjective outcomes (including, depending on the agent, at least one of the following measures: subjective total sleep time [sTST], subjective sleep onset latency [sSOL], subjective wake after sleep onset [sWASO], scores on the Insomnia Severity Index [ISI], scores on the Patient Global Impression–Insomnia [PGI-I], or scores on Clinical Global Impression items that are consistent with the PGI-I) for suvorexant,[10] doxepin,[28,29] eszopiclone,[30,31] zolpidem ER,[32,33,42] and zolpidem IR[34] and on objective outcomes (latency to persistent sleep [LPS]) for ramelteon.[14,35] Less information is available for the agents approved decades ago but still in use, namely triazolam (approved in 1982) and temazepam (approved in 1981), and no specific AE rates are available for flurazepam (approved in 1970) (approval years from https://www.accessdata.fda.gov/, accessed April 19, 2020).

Description of Studies SUNRISE 1 and SUNRISE 2

SUNRISE 1 was a 1-month, global, randomized, double-blind, parallel-group, placebo-controlled, active-comparator study conducted at 67 sites in North America and Europe.[37] Participants were aged 55 years or older and had insomnia disorder characterized by reported sleep maintenance difficulties and confirmed by sleep history, sleep diary, and polysomnography (PSG). Participants could also have had sleep onset difficulties, but this was not required. Participants received placebo, zolpidem ER 6.25 mg, lemborexant 5 mg, or lemborexant 10 mg for 1 month at bedtime. All patients received instructions consistent with principles of good sleep hygiene. Paired polysomnograms were collected at baseline during a single blind placebo run-in period, the first 2 nights or treatment, and the last 2 nights of treatment. Among 1,006 participants randomized (placebo, n = 208; zolpidem ER 6.25 mg, n = 263; lemborexant 5 mg, n = 266; and lemborexant 10 mg, n = 269), 869 (86.4%) were women, 256 (24.4%) were Black or African American, and the median age was 63 years (range, 55–88 years). Both lemborexant 5 mg and lemborexant 10 mg demonstrated statistically significant greater changes on the primary outcome measure of change from baseline in objective sleep onset as assessed by LPS as measured by PSG at the end of 1 month compared with placebo. The key secondary endpoints of change from baseline in sleep efficiency and wake after sleep onset (WASO) also demonstrated superiority of lemborexant over placebo.

SUNRISE 2 was a 12-month, global, randomized, double-blind (first 6 months), parallel-group, placebo-controlled study conducted at 119 sites in North America, Europe, Asia, and Oceania.[38] Participants were aged 18 years or older and had insomnia disorder, with complaints of sleep onset difficulties, sleep maintenance difficulties, or both. Participants received placebo, lemborexant 5 mg, or lemborexant 10 mg for 6 months at bedtime (Period 1), followed by lemborexant 5 mg and lemborexant 10 mg for an additional 6 months (Period 2); subjects randomized to placebo for the first 6 months in Period 1 were re-randomized to receive either lemborexant 5 mg or lemborexant 10 mg in Period 2. All patients received instructions consistent with principles of good sleep hygiene. An Electronic Sleep Diary was completed. Among 971 participants randomized (placebo,

Table 1. Categorical Efficacy Outcomes Assessed in SUNRISE 1 and SUNRISE 2

Outcome	Definition of Responder	Comments
Sleep Diary		
Subjective sleep onset latency (sSOL)	sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes	Prespecified outcome
Subjective wake after sleep onset (sWASO)	sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline	Prespecified outcome
Subjective total sleep time (sTST)	≥ 15% improvement in mean sTST	This outcome is available for suvorexant[10]
sSOL (alternate responder definition)	≥ 15% improvement in mean sSOL	This outcome is available for suvorexant[10]
sWASO (alternate responder definition)	≥ 15% improvement in mean sWASO	This outcome is available for suvorexant[10]
Polysomnography (SUNRISE 1 only)		
Latency to persistent sleep (LPS)	LPS at study baseline > 30 minutes and mean LPS at time point in question ≤ 20 minutes	Prespecified outcome
Wake after sleep onset (WASO)	WASO at study baseline > 60 minutes and mean WASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline	Prespecified outcome
LPS (alternate responder definition)	LPS decrease of ≥ 50% from baseline	This outcome is available for ramelteon in a published article[35]
LPS (alternate responder definition)	LPS ≤ 30 minutes	This outcome is available for ramelteon in the FDA drug approval package[14]
Subjective Rating Scale Outcomes		
Patient Global Impression–Insomnia (PGI-I)	PGI-I score = 1 for helped sleep PGI-I score = 1 for increased total sleep time PGI-I score = 1 for decreased time to fall asleep PGI-I score = 2 medication strength "just right"	PGI-I was not assessed at week 1, but data are available for the other time points of interest; PGI-I categorical outcomes are available for doxepin,[28,29] zolpidem extended release,[32,33,42] and zolpidem immediate release[34]
Insomnia Severity Index (ISI)	≥ 6-point improvement (clinically relevant improvement) ≤ 7 (no insomnia) ≤ 14 (no or subthreshold insomnia)	ISI outcome of clinically relevant improvement is available for suvorexant[10]; outcomes of no insomnia or subthreshold insomnia are available for eszopiclone[30,31]

Abbreviation: FDA = US Food and Drug Administration.

n = 325; lemborexant 5 mg, n = 323; and lemborexant 10 mg, n = 323), 643 (66.2%) were women, 76 (8.0%) were Black or African American, and the median age was 55 years (range, 18–88 years). Decreases from baseline in sSOL (the primary endpoint) were significantly greater with lemborexant 5 mg and lemborexant 10 mg versus placebo at month 6. The key secondary endpoints of change from baseline in subjective sleep efficiency and sWASO also demonstrated superiority of lemborexant over placebo.

Efficacy Outcomes

Examined were categorical efficacy outcomes of clinical interest, occurring during the double-blind period, as listed in Table 1; in addition to prespecified protocol-determined definitions of response, additional responder categories were assessed based on available data for the other hypnotics. The denominator was the number of randomized subjects who received at least one dose of study drug and had a post-baseline assessment on the efficacy outcome of interest. Data were extracted by study arm. Time points examined for both studies for non-PSG measures included week 1 and month 1. For SUNRISE 2, additional time points were month 3 and month 6. For SUNRISE 1, the time points examined for the PSG outcomes were day 1, day 2, day 29, and day 30.

Tolerability Outcomes

Examined were discontinuation from the clinical trial because of an AE and treatment emergent AEs occurring at any time during the double-blind period. The denominator was the number of all randomized subjects who had received at least one dose of study drug. Data were extracted by study arm for each study. Threshold for reporting AEs was a rate of ≥ 1% for any individual active arm of SUNRISE 1 or SUNRISE 2. When pooling the AE data for SUNRISE 1 and SUNRISE 2, only events occurring in the first month of SUNRISE 2 were included; threshold for reporting was a rate of ≥ 1% for any dose of lemborexant, with reporting of the following AEs regardless of rate: sleep paralysis, dizziness, and fall.

Data Analysis

NNT and NNH, with their respective 95% CIs, were calculated for lemborexant 5/10 mg versus placebo, individually for each study and pooled as appropriate. If there was an active control, analogous analyses were done comparing the active control versus placebo and lemborexant was directly compared with the active control. LHH was calculated to illustrate potential trade-offs for efficacy and tolerability outcomes, specifically response versus the most encountered AE and for discontinuation because of an AE. In all instances, if the 95% CI included "infinity," the result was considered not statistically significant at the $P < .05$ threshold. The terms *statistically significant* and *not statistically significant* are used descriptively and not inferentially. The notation *NS* is used rather than showing the non-continuous 95% CIs generated when statistical

significance was not achieved. If the AE rates were the same or lower for drug versus placebo, the notation *no difference* was made. Formulae used are listed in Supplementary Box 2.

RESULTS

Results are provided as follows and in Tables 2–3, Supplementary Tables 1–21, Figures 1–2, and Supplementary Figure 1. Discussed first are the efficacy and tolerability outcomes from SUNRISE 1 and SUNRISE 2, followed by indirect comparisons with other agents using data from other clinical trials.

Direct Comparisons of Efficacy

In SUNRISE 1, effect sizes for the subjective efficacy outcomes for lemborexant 5/10 mg versus placebo were similar between week 1 and week 4 (prespecified sSOL and sWASO response at week 4 is illustrated in Figure 1), indicating that there is little or no lag time between start of therapy and onset of efficacy (see Supplementary Table 1). In general, sTST/sWASO/sSOL outcomes based on 15% improvement thresholds had more robust NNT values than the prespecified sSOL/sWASO outcomes based on absolute time thresholds. Most NNT values versus placebo were < 10, and some were as low as 4, suggesting that lemborexant 5/10 mg had a clinically relevant magnitude of therapeutic effect. Results for zolpidem ER 6.25 mg versus placebo in this study showed a similar pattern, but with generally weaker effect sizes except for the PGI-I and ISI outcomes. When directly comparing lemborexant 5/10 mg with zolpidem ER 6.25 mg (Supplementary Table 2), NNT values < 10 were observed at week 4 for sSOL response defined by ≥ 15% improvement for lemborexant 10 mg and pooled lemborexant 5 mg/lemborexant 10 mg, demonstrating a small advantage for lemborexant on this outcome.

The PSG prespecified categorical outcomes of LPS and WASO response at month 1 from the SUNRISE 1 study are shown in Figure 1. PSG outcomes at days 1, 2, 29, and 30 are listed in Supplementary Tables 1 and 2, the latter including direct comparisons of lemborexant 5/10 mg versus zolpidem ER 6.25 mg. LPS response, defined in the study protocol as LPS at study baseline > 30 minutes and mean LPS at time point in question ≤ 20 minutes, demonstrated statistically significantly superiority of lemborexant 10 mg to placebo only at day 29 (NNT = 13; 95% CI, 7–625). Of note, subjects did not need to report sleep onset difficulties for inclusion in SUNRISE 1. WASO response, defined in the study protocol as WASO at study baseline > 60 minutes and mean WASO at time point in question ≤ 60 minutes and showing a reduction of > 10 minutes compared to study baseline, consistently demonstrated statistically significant superiority of lemborexant 5/10 mg to placebo, with robust effect sizes as low as a NNT of 3. When subjects with missing information due to early withdrawal or other reasons were considered as nonresponders, effect sizes for WASO response remained robust for both lemborexant 5/10 mg and zolpidem ER 6.25 mg (Supplementary Table 3). For lemborexant 5/10 mg and zolpidem ER 6.25 mg, the effect sizes for WASO response were stronger at day 1/2 versus day 29/30. Zolpidem ER 6.25 mg in SUNRISE 1 performed poorly on the LPS measures (Supplementary Table 1), with "negative" NNT values versus placebo that were statistically significant at day 30 (ie, placebo superior to zolpidem ER release 6.25 mg on this outcome). Although not a prespecified outcome in the original statistical analysis plan as such, when directly comparing lemborexant 5/10 mg with zolpidem ER 6.25 mg, NNT values were < 10 in favor of lemborexant 5/10 mg for all listed PSG outcomes at day 30 (LPS and WASO response) and for many of the outcomes at the earlier time points of day 1, 2, and 29 (Supplementary Table 2).

In SUNRISE 2 (Figure 1, Supplementary Table 4), the pattern of results for lemborexant 5/10 mg versus placebo was similar to that for SUNRISE 1 but with more robust effect sizes (ie, smaller NNT values) for the prespecified outcome measures of sSOL and sWASO. When subjects with missing information due to early withdrawal or other reasons were considered as nonresponders in the analysis, effect sizes for sWASO response did not become consistently statistically significant until toward the end of the study, and more so for lemborexant 5 mg than for lemborexant 10 mg (Supplementary Table 5). The most robust effect sizes were noted at months 4 and 6.

Pooled subjective efficacy results for lemborexant 5/10 mg from both SUNRISE 1 and SUNRISE 2 for the first 4 weeks are shown in Supplementary Table 6. The pattern of results remains the same, with NNT values versus placebo < 10 for the majority of the outcomes for lemborexant 5/10 mg.

Indirect Comparisons of Efficacy

Table 2 describes indirect comparisons of the NNTs versus placebo for lemborexant 5/10 mg and zolpidem ER 6.25 mg from SUNRISE 1 and SUNRISE 2 and for other hypnotics with similar reported outcomes at similar time points (Supplementary Tables 1, 4, 6, 11–14, and 17). In general, effect sizes versus placebo for lemborexant 5/10 mg were larger (NNT values smaller) than those for the other available DORA, suvorexant, at week 1, week 4, and month 3 (the time points for which data are available for both agents) for sTST/sWASO/sSOL outcomes based on based on 15% improvement thresholds and for ISI response as defined by a ≥ 6-point improvement (clinically relevant improvement).[10,12,36] Regarding hypnotics with fundamentally different mechanisms of action, doxepin 3 mg at month 3 and 6 mg at week 4 demonstrated effect sizes versus placebo similar to that for lemborexant 5/10 mg on PGI-I outcomes.[28,29] Data for eszopiclone were limited to ISI outcomes at month 6 (nonelderly adults) and week 12 (elderly adults), and NNT values for the 2-mg dose were similar to those for lemborexant 5/10 mg; an apparent dose-response is observed for eszopiclone, with more robust NNT values observed at the higher dose (and more robust than seen with lemborexant 5/10 mg).[30,31] Zolpidem IR ≤ 10 mg outcomes (Supplementary Table 16)[34] mirrored the effect sizes observed in the SUNRISE 1 study for zolpidem ER 6.25 mg,

Table 2. Indirect Comparisons of NNTs vs Placebo (With 95% CIs) for Lemborexant and Zolpidem ER From SUNRISE 1 and SUNRISE 2, and for Other Hypnotics With Similar Reported Outcomes at Similar Time Points[a]

Outcome	Lemborexant 5 or 10 mg[b]	Zolpidem ER 6.25 mg[b]	Suvorexant 15 or 20 mg	Doxepin 3 or 6 mg		Ramelteon 8 mg[c]	Eszopiclone		Zolpidem ER[d]	
				3 mg	6 mg		2 mg	3 mg	6.25 mg	12.5 mg
Week 1										
sTST responder, defined as ≥15% improvement in mean sTST	**7 (5 to 10)**	**5 (4 to 7)**	**9 (6 to 15)**							
sSOL responder, defined as ≥15% improvement in mean sSOL	**5 (4 to 6)**	**6 (5 to 11)**	**8 (6 to 14)**							
sWASO responder, defined as ≥15% improvement in mean sWASO	**6 (5 to 9)**	**4 (3 to 5)**	**12 (8 to 39)**							
Week 4										
sTST responder, defined as ≥15% improvement in mean sTST	**7 (5 to 11)**	**5 (4 to 7)**	**8 (6 to 14)**							
sWASO responder, defined as ≥15% improvement in mean sWASO	**8 (6 to 14)**	**5 (4 to 7)**	**12 (8 to 37)**							
sSOL responder, defined as ≥15% improvement in mean sSOL	**5 (4 to 6)**	**8 (5 to 17)**	**12 (7 to 34)**							
PSG LPS responder, defined as a decrease of ≥50% from baseline (day 29 and day 30 PSG, SUNRISE 1)	**8 (5 to 18),** 14 (NS)	–115 (NS), **-8 (–5 to –20)**				**6 (4 to 19)**				
PSG LPS responder, defined as LPS ≤30 minutes	**7 (5 to 13),** **9 (6 to 26)**	31 (NS), **-9 (–5 to –39)**				**8 (5 to 115)** to 31 (NS)				
PGI-I score=1 for helped sleep	**5 (4 to 6)**	**3 (3 to 4)**			**6 (4 to 19)**				**7 (4 to 51)**	**3 (2 to 4),** **3 (2 to 3)**
PGI-I score=1 for decreased time to fall asleep	**5 (4 to 6)**	**5 (4 to 7)**			**8 (4 to 106)**				**7 (4 to 84)**	**3 (2 to 5),** **3 (3 to 4)**
PGI-I score=1 for increased total sleep time	**6 (4 to 7)**	**4 (3 to 4)**			11 (NS)				**5 (3 to 11)**	**4 (3 to 6),** **3 (2 to 3)**
PGI-I score=2 medication strength "just right"	**7 (5 to 10)**	**6 (4 to 9)**			**7 (4 to 33)**				**7 (4 to 142)**	**3 (3 to 4)**
ISI score with a ≥6-point improvement (clinically relevant improvement)	**7 (5 to 11)**	**5 (4 to 6)**	**10 (7 to 19)**							
Month 3										
sTST responder, defined as ≥15% improvement in mean sTST	**7 (5 to 14)**		**13 (7 to 46)**							
sSOL responder, defined as ≥15% improvement in mean sSOL	**6 (4 to 8)**		26 (NS)							
sWASO responder, defined as ≥15% improvement in mean sWASO	**10 (6 to 26)**		**16 (9 to 102)**							
PGI-I score=1 for helped sleep	**4 (4 to 6)**			**3 (3 to 6)**						**3 (3 to 4)**
PGI-I score=1 for decreased time to fall asleep	**4 (3 to 5)**			**4 (3 to 8)**						**4 (3 to 5)**
PGI-I score=1 for increased total sleep time	**6 (4 to 9)**			**4 (3 to 6)**						**3 (3 to 4)**
PGI-I score=2 medication strength "just right"	**7 (5 to 11)**			**4 (3 to 10)**						**4 (3 to 5)**
ISI score with ≥6-point improvement (clinically relevant improvement)	**5 (4 to 8)**		**8 (6 to 14)**							
ISI score≤7 (no insomnia)	**8 (6 to 14)**						**9 (5 to 31)**			
ISI score≤14 (no or subthreshold insomnia)	**7 (5 to 12)**						**6 (4 to 13)**			
Month 6										
PGI-I score=1 for helped sleep	**5 (4 to 7)**									**4 (3 to 4)**
PGI-I score=1 for decreased time to fall asleep	**4 (3 to 5)**									**4 (3 to 5)**
PGI-I score=1 for increased total sleep time	**5 (4 to 8)**									**4 (3 to 4)**
PGI-I score=2 medication strength "just right"	**6 (4 to 10)**									**5 (4 to 6)**
ISI score≤7 (no insomnia)	**7 (5 to 11)**							**4 (3 to 4)**		
ISI score≤14 (no or subthreshold insomnia)	**9 (6 to 18)**							**5 (4 to 7)**		

[a]See Supplementary Tables 1, 4, 6, 11–14, and 17. Excludes outcomes unavailable outside of SUNRISE 1 or SUNRISE 2 (for example, see Figure 1 and Supplementary Table 1 for PSG WASO response for SUNRISE 1). Results for the NNT are bolded when statistical significance is achieved at the $P<.05$ threshold. A negative NNT means that the rate for medication was lower than that for placebo.

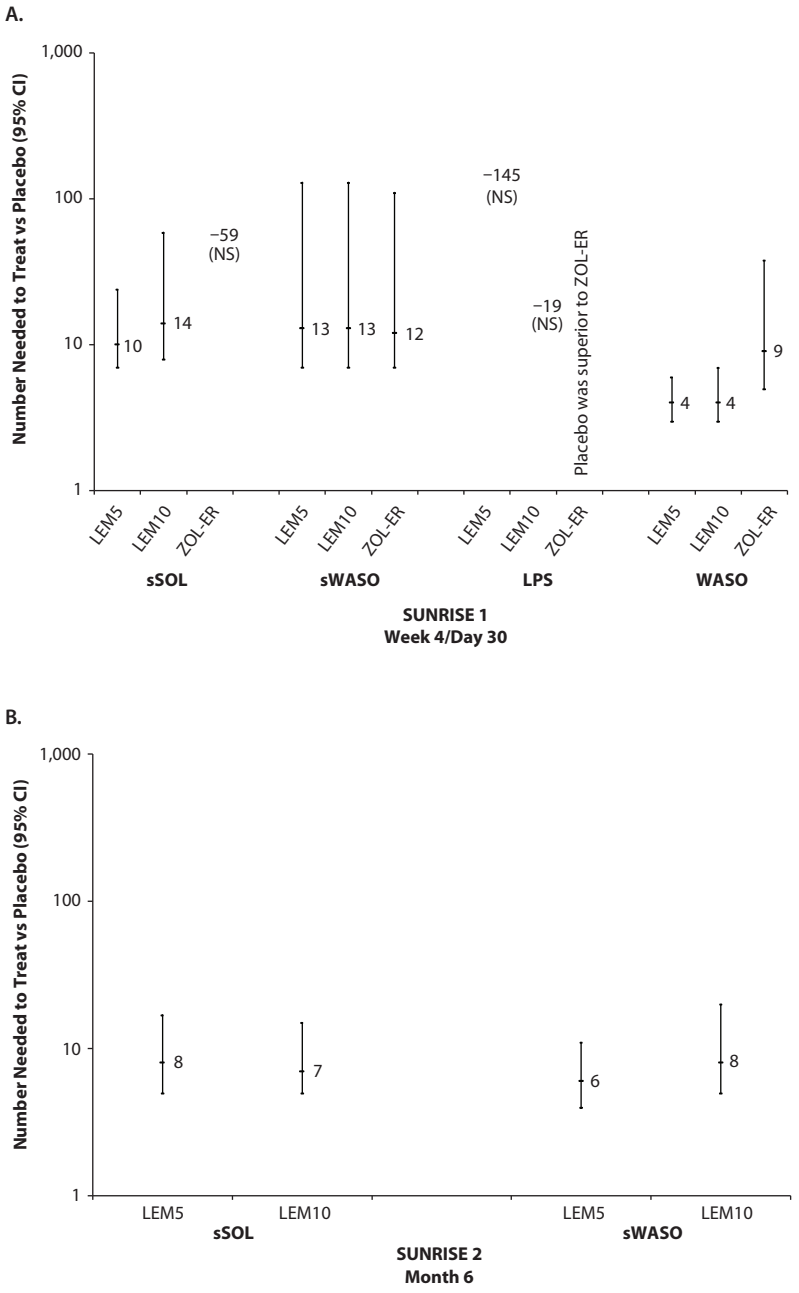
[b]Lemborexant data for months 3 and 6 are from SUNRISE 2 (Supplementary Table 4); otherwise, data are pooled from SUNRISE 1 and SUNRISE 2 (Supplementary Table 6). PSG outcomes are from SUNRISE 1 only (Supplementary Table 1).

[c]At 5 weeks. Range reported from different studies and/or different analytic approaches (see Supplementary Table 13).

[d]Week 4 data are from week 3 or week 4 (see Supplementary Table 17).

Abbreviations: ER=extended release, ISI=Insomnia Severity Index, LPS=latency to persistent sleep, NNT=number needed to treat, NS=not significant, PGI-I=Patient Global Impression–Insomnia, PSG=polysomnography, sSOL=subjective sleep onset latency, sTST=subjective total sleep time, sWASO=subjective wake after sleep onset.

Figure 1. Prespecified Categorical Outcome Measures From (A) SUNRISE 1 and (B) SUNRISE 2: sSOL, sWASO, LPS, and WASO Responders[a] at Study Endpoint[b,c]



[a]sSOL responder defined as sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes; sWASO responder defined as sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; LPS responder defined as LPS at study baseline > 30 minutes and mean LPS at time point in question ≤ 20 minutes; WASO responder defined as WASO at study baseline > 60 minutes and mean WASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline.
[b]Results are similar for the earlier time points.
[c]Study subjects in SUNRISE 1 were only required to have sleep maintenance issues; therefore, SUNRISE 1 study participants may not have reported LPS > 30 minutes at screening.
Abbreviations: LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LPS = latency to persistent sleep, NS = not significant, sSOL = subjective sleep onset latency, sWASO = subjective wake after sleep onset, WASO = wake after sleep onset, ZOL-ER = zolpidem extended release 6.25 mg.

as did outcomes for the registrational studies for zolpidem ER that examined zolpidem ER 12.5 mg (Supplementary Table 17).[32,33] However, although taken from different studies, week 3 data on the PGI-I outcomes for zolpidem ER 6.25 mg from the zolpidem ER registrational studies were somewhat weaker than the corresponding data for the 12.5 mg dose.[32,33,42]

Only one other hypnotic—ramelteon—had available PSG categorical outcome results allowing for indirect comparison, which evidenced effect sizes similar to those for lemborexant 5/10 mg with NNT versus placebo < 10 on LPS response (defined as LPS decrease of ≥ 50% from baseline or LPS ≤ 30 minutes) at 1 month (Table 2, Supplementary Table 13).[14,35]

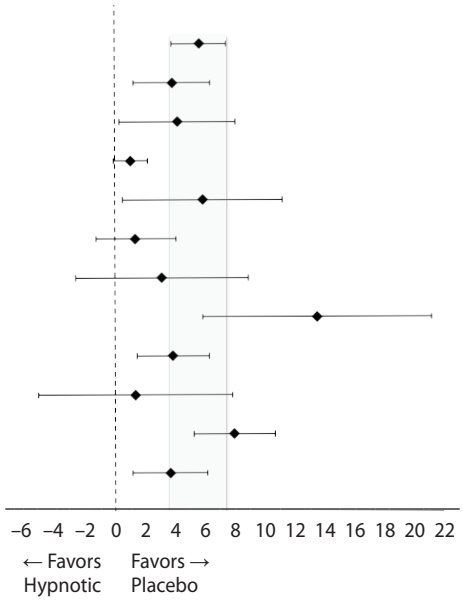
Direct Comparisons of Tolerability

Table 3 provides the pooled lemborexant tolerability outcomes from SUNRISE 1 and SUNRISE 2 (through week 4/day 30). Supplementary Tables 7–9 provide the data from the individual studies, including direct comparisons of lemborexant 5/10 mg versus zolpidem ER 6.25 mg from SUNRISE 1. From pooled data through week 4/day 30, the rates of discontinuation because of an AE were similar for lemborexant 5 mg and placebo (1.4% vs 1.5%), but about double for lemborexant 10 mg (2.6%), with resultant NNH estimates versus placebo of no difference, 95 (NS), and 216 (NS) for lemborexant 5 mg, 10 mg, and pooled doses, respectively. The most common reason for discontinuation of lemborexant was somnolence, with rates of 0.7% for lemborexant 5 mg, 1.0% for lemborexant 10 mg, and 0.4% for placebo, with resultant NNH estimates versus placebo of 322 (NS), 154 (NS), and 208 (NS) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Somnolence was the most common AE, with statistically significant NNH estimates versus placebo of 28 (95% CI, 18–61), 15 (95% CI, 11–22), and 19 (95% CI, 14–28) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Supplementary Figure 1 illustrates the risk of somnolence across SUNRISE 1 and SUNRISE 2 treatment arms. Other AEs had lower incidence rates, smaller differences from placebo, and thus very small effect sizes (ie, high NNH values).

For SUNRISE 1, discontinuation rates because of an AE were low overall for both doses of lemborexant, 0.8% and 1.1% for

Figure 2. Adverse Event of Somnolence: Absolute Risk Increase (ARI) and Number Needed to Harm (NNH) vs Placebo, Indirect Comparisons[a]

Hypnotic	Rate With Hypnotic n/N (%)[b]	Rate With Placebo n/N (%)[b]	ARI (95% CI)	NNH (95% CI)
LEM5 + LEM10, pooled, 1 mo	78/1,162 (6.7)	7/528 (1.3)		19 (14 to 28)
Suvorexant 15/20 mg, 3 mo	33/493 (6.7)	31/1,025 (3.0)		28 (17 to 82)
Doxepin 3/6 mg, 1–3 mo	30/360 (8.3)	12/278 (4.3)		25 (13 to 341)
Ramelteon 8 mg, duration not specified	42/1,405 (3)	29/1,456 (2)		100 (NS)
Eszopiclone 2/3 mg, 6 wk	18/209 (8.6)	3/99 (3.0)		18 (10 to 202)
Zaleplon 5/10/20 mg, 4/5 wk	46/866 (5.3)	14/344 (4)		75 (NS)
Zolpidem IR ≤ 10 mg, 4/5 wk	12/152 (8)	18/161 (5)		34 (NS)
Zolpidem ER 12.5 mg, 3 wk	15/102 (14.7)	2/110 (1.8)		8 (5 to 18)
Zolpidem ER 12.5 mg, 6 mo	38/669 (5.7)	7/349 (2.0)		28 (17 to 73)
Zolpidem ER 6.25 mg, 3 wk	6/99 (6)	5/106 (5)		75 (NS)
Triazolam all doses, 1–42 d	140/1,003 (14.0)	64/997 (6.4)		14 (10 to 21)
Temazepam all doses, duration not specified	98/1,076 (9.1)	44/783 (5.6)		29 (18 to 88)



[a]The shaded area of the plot illustrates the overlap between the 95% CIs for the pooled lemborexant dose group and that for the other hypnotics on the outcome of somnolence.
[b]Numerators are estimates unless exact values are available (see tables and text); for doxepin, the combined term *somnolence or sedation* was used; for zolpidem IR ≤ 10 mg, triazolam, and temazepam, the term *drowsiness* was used.
Abbreviations: ER = extended release, IR = immediate release, LEM5 + LEM10 = lemborexant 5 mg and 10 mg pooled, NS = not significant.

Table 3. Lemborexant Tolerability Outcomes, SUNRISE 1, SUNRISE 2, Pooled, Through Week 4/Day 30[a]

Outcome	Lemborexant 5 mg n	Lemborexant 5 mg N	Lemborexant 5 mg %	Lemborexant 10 mg n	Lemborexant 10 mg N	Lemborexant 10 mg %	Placebo n	Placebo N	Placebo %	Lemborexant 5 mg vs Placebo, NNH (95% CI)	Lemborexant 10 mg vs Placebo, NNH (95% CI)	Pooled Lemborexant vs Placebo, NNH (95% CI)
Discontinuation because of an AE	8	580	1.4	15	582	2.6	8	528	1.5	ND	95 (NS)	216 (NS)
Discontinuation due to somnolence	4	580	0.7	6	582	1.0	2	528	0.4	322 (NS)	154 (NS)	208 (NS)
Specific AE												
Somnolence[b]	29	580	5.0	49	582	8.4	7	528	1.3	**28 (18 to 61)**	**15 (11 to 22)**	**19 (14 to 28)**
Headache[c]	35	580	6.0	27	582	4.6	21	528	4.0	49 (NS)	152 (NS)	74 (NS)
Urinary tract infection	4	580	0.7	12	582	2.1	6	528	1.1	ND	109 (NS)	416 (NS)
Nasopharyngitis	16	580	2.8	10	582	1.7	5	528	0.9	**56 (30 to 411)**	130 (NS)	**78 (41 to 953)**
Fatigue	12	580	2.1	9	582	1.5	0	528	0	**49 (31 to 110)**	**65 (40 to 184)**	**56 (39 to 96)**
Back pain	4	580	0.7	6	582	1.0	3	528	0.6	824 (NS)	217 (NS)	342 (NS)
Nightmare[d]	3	580	0.5	6	582	1.0	2	528	0.4	723 (NS)	154 (NS)	253 (NS)
Abnormal dreams[d]	2	580	0.3	6	582	1.0	4	528	0.8	ND	366 (NS)	ND
Sleep paralysis	1	580	0.2	5	582	0.9	0	528	0	580 (NS)	**117 (63 to 915)**	**194 (108 to 960)**
Nausea	8	580	1.4	4	582	0.7	1	528	0.2	**84 (46 to 586)**	201 (NS)	**119 (66 to 651)**
Upper respiratory tract infection	7	580	1.2	4	582	0.7	5	528	0.9	385 (NS)	ND	ND
Dizziness	5	580	0.9	4	582	0.7	7	528	1.3	ND	ND	ND
Fall	4	580	0.7	0	582	0	3	528	0.6	824 (NS)	ND	ND

[a]Results for the NNH are bolded when statistical significance is achieved at the $P < .05$ threshold.
[b]Rates for the AE of somnolence at 1 month as reported in the product label combined the AE terms *somnolence*, *lethargy*, *fatigue*, and *sluggishness* for the pooled SUNRISE 1 and SUNRISE 2 (first 30 days) data and were 6.9%, 9.6%, and 1.3%, for lemborexant 5 mg, lemborexant 10 mg, and placebo, respectively, yielding NNH estimates vs placebo of 18 (95% CI, 13–31), 13 (95% CI, 10–18), and 15 (95% CI, 12–20), for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively.
[c]Numerators used for the AE of headache as reported in the product label differ and were 5.9%, 4.5%, and 3.4% for lemborexant 5 mg, lemborexant 10 mg, and placebo, respectively, yielding NNH estimates vs placebo of 41 (NS), 95 (NS), and 57 (NS), respectively.
[d]The AE of nightmare or abnormal dreams at 1 month was also reported in the product label using combined terms, and the rates were 0.9%, 2.2%, and 0.9% for lemborexant 5 mg, lemborexant 10 mg, and placebo, respectively, yielding NNH estimates vs placebo of no difference, 78 (NS), and 167 (NS), respectively.
Abbreviations: AE = adverse event, ND = no difference, NNH = number needed to harm, NS = not significant.

lemborexant 5 mg and lemborexant 10 mg, respectively, and were like that observed for placebo (1.0%). The discontinuation rate because of an AE was higher for zolpidem ER 6.25 mg (2.7%); however, the NNH versus placebo of 59 for that agent was not statistically significant. In the SUNRISE 1 study, no discontinuation rates because of any specific AE met the threshold of 1% in any study arm. Discontinuation rates because of somnolence were low (0.4%, 0%, 0.4%, and 0.5%, for lemborexant 5 mg, lemborexant 10 mg, zolpidem ER 6.25 mg, and placebo, respectively) and did not demonstrate a dose-response. Regarding the specific AE of somnolence, although the NNH versus placebo for somnolence for lemborexant 5 mg was not statistically significant, it was statistically significant for lemborexant 10 mg (NNH = 20; 95% CI, 12–64) and for the two doses pooled (NNH = 27; 95% CI, 16–100); thus, somnolence appears dose-related. Although rates of somnolence were lower for zolpidem ER 6.25 mg than for placebo, zolpidem ER 6.25 mg evidenced a statistically significant NNH versus placebo for fatigue (NNH = 66; 95% CI, 34–2,393). Further details about other AEs can be found in Supplementary Tables 7 and 8. In direct comparisons of lemborexant 5/10 mg with zolpidem ER 6.25 mg (Supplementary Table 8), NNH for somnolence for lemborexant 5 mg versus zolpidem ER 6.25 mg was 39 (NS) but for lemborexant 10 mg versus zolpidem ER 6.25 mg was 18 (95% CI, 12–47). Differences regarding other AEs were smaller in magnitude.

The time interval for reporting AEs in SUNRISE 2 was 6 months, allowing for more events of different types to be enumerated than for the 1-month duration of SUNRISE 1. Rates of discontinuation because of an AE were similar for lemborexant 5 mg and placebo (4.1% vs 3.8%), but about double for lemborexant 10 mg (8.3%), yielding a statistically significant NNH for lemborexant 10 mg versus placebo of 23 (95% CI, 13–122). Rates of discontinuation because of somnolence were 1.0% for lemborexant 5 mg, 2.9% for lemborexant 10 mg, and 0.6% for placebo, with a NNH versus placebo for discontinuation because of somnolence of 305 (NS), 45 (95% CI, 24–499), and 78 (NS) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Rates of discontinuation because of nightmare were 0.3% for lemborexant 5 mg, 1.3% for lemborexant 10 mg, and 0% for placebo, with a NNH versus placebo for discontinuation because of nightmare of 314 (NS), 79 (95% CI, 40–2,990), and 126 (95% CI, 68–990) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Preexisting history of nightmares was not known. Somnolence was the most common AE and, consistent with SUNRISE 1, was dose-related. NNH for somnolence for lemborexant 5/10 mg versus placebo was statistically significant, and for lemborexant 10 mg (but not lemborexant 5 mg) the NNH was < 10; NNH for both doses pooled was 11 (95% CI, 9–16). At the 3-month time point (of interest because of data available for other hypnotics), somnolence rates were 26/323 (8.0%), 38/323 (11.8%), and 4/325 (1.2%) for lemborexant 5 mg, lemborexant 10 mg, and placebo, respectively, resulting in NNH values versus placebo of 15 (95% CI, 10–28), 10 (95% CI, 7–15), and 12 (95% CI, 9–17) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Fatigue was the other AE that achieved statistical significance for NNH versus placebo for lemborexant 5/10 mg, with estimates of 29 (95% CI, 18–77), 32 (95% CI, 19–94), and 30 (95% CI, 21–57) for lemborexant 5 mg, lemborexant 10 mg, and pooled doses, respectively. Other AEs evidenced less important effect sizes and were more commonly encountered with lemborexant 10 mg than with lemborexant 5 mg. Overall, lemborexant 5 mg appears to have been better tolerated than lemborexant 10 mg.

Indirect Comparisons of Tolerability

Figure 2 shows a forest plot of the absolute risk increase versus placebo for the AE of somnolence for the pooled doses of lemborexant from SUNRISE 1 and SUNRISE 2 (30 days) and the AE of somnolence for hypnotics from other studies. For doxepin, the combined AE terms *somnolence* and *sedation* were reported; for zolpidem IR ≤ 10 mg, triazolam, and temazepam, the AE term *drowsiness* was reported. Except for ramelteon, there was overlap of the 95% CIs with lemborexant and all of the other included hypnotics.

NNH estimates for somnolence for eszopiclone for non-elderly adults were like those for lemborexant (Supplementary Tables 10 and 14A). Somnolence with zolpidem IR appeared dose dependent and could also be clinically relevant (Supplementary Table 16). In one study of zolpidem ER 12.5 mg, the NNH versus placebo for somnolence at 3 weeks was 8 (95% CI, 5–18); however, in another study at the lower dose of 6.25 mg, the NNH versus placebo at 3 weeks was 75 (NS) (Supplementary Table 17). In a longer study of zolpidem ER 12.5 mg, the NNH versus placebo at 6 months was 28 (95% CI, 17–73) (Supplementary Table 17). NNH estimates for suvorexant and doxepin versus placebo for somnolence were statistically significant and were also similar to the NNH for lemborexant 5 mg for the single AE term for somnolence but were generally more favorable than that for lemborexant for the combined terms as reported in product labeling (see notes in Table 3). Both ramelteon and zaleplon did not appear to carry significant risk for somnolence, with NNH values versus placebo of 100 (NS) and 75 (NS), respectively (Supplementary Tables 13 and 15).

Overall, in general, when examining the rates of AEs for other hypnotics (as per Supplementary Tables 11–19), NNH values < 10 were seldomly encountered. However, they could be found for unpleasant taste with eszopiclone (Supplementary Tables 14A and 14B) and "nervous system disorders" and somnolence with zolpidem ER 12.5 mg (Supplementary Table 17). Supplementary Table 10 provides a "heat map" for indirect comparisons of NNHs versus placebo (with 95% CIs) for lemborexant 5/10 mg (Table 3) and zolpidem ER 6.25 mg (Supplementary Table 7) from SUNRISE 1 and SUNRISE 2 (see text for month 3 data) and for other hypnotics (Supplementary Tables 11–19) and

when statistical significance was achieved. Risk for an AE is considered higher for NNH < 10, intermediate for NNH between 10 and 19, and low for NNH ≥ 20. These levels of risk are represented in Supplementary Table 10 by red, yellow, and green highlighting, respectively. Note that dosing may mitigate some of the AE risk for somnolence and related events.

Likelihood to Be Helped or Harmed

Pooling the data from SUNRISE 1 and SUNRISE 2, the rates of discontinuation because of an AE were low, and for lemborexant 5 mg the rate was lower than that for placebo. Pooling both doses provided a NNH estimate of 216 (NS) versus placebo on this outcome. After dividing this figure by any of the NNT estimates for the statistically significant endpoint efficacy measures, the resultant LHH ranged from 13 to 43 for the subjective outcomes and from 24 to 54 for the PSG outcomes. Thus, in the clinical trials, lemborexant was much more likely to result in a therapeutic response than a discontinuation because of an AE. The effect sizes for endpoint therapeutic benefit were most pronounced for the day 30 PSG outcome of WASO response in the SUNRISE 1 study (Supplementary Table 1) and the month 6 subjective outcome of PGI-I score = 1 for decreased time to fall asleep for the SUNRISE 2 study (Supplementary Table 4), with both having NNT estimates of 4. Taking the NNH for the most common AE associated with lemborexant 5/10 mg, somnolence, with a NNH of 19 (Table 3) and dividing by the NNT of 4 gives a LHH of 4.8; thus, lemborexant was about 5 times likelier to result in a PSG outcome of WASO response, or patient reported decreased time to fall asleep, than an AE of somnolence. When assuming that subjects with missing information due to early withdrawal or other reasons were nonresponders, the NNT for WASO response for lemborexant 5/10 mg at day 1/2 was 3 and at day 29/30 was 5 (Supplementary Table 3), resulting in LHH values (therapeutic response vs AE somnolence) of 6.3 and 3.8 for day 1/2 and day 29/30, respectively.

Supplementary Table 20 provides the LHH for hypnotics for which statistically significant values for a NNT versus placebo for any efficacy measure and a statistically significant NNH versus placebo for somnolence were available. The most robust (smallest) NNT values for efficacy available for each medication were used to calculate LHH. All LHH values were > 1; thus, for each medication (lemborexant, suvorexant, doxepin, eszopiclone, and zolpidem ER), it is more likely to encounter therapeutic response than somnolence. A limitation is that the actual efficacy outcome measure and the length of observation differed among the listed hypnotics. When comparing the two DORA hypnotics currently available, lemborexant 5/10 mg and suvorexant 15/20 mg, 3-month data are available for sTST, sSOL, or sWASO response defined by ≥ 15% improvement and ISI response defined as a mean improvement of ≥ 6 points. Pairing the NNT versus placebo for these outcomes versus NNH of somnolence at 3 months, LHH values are comparable and range from 1.2 to 2.4 for lemborexant and 1.1 to 3.5 for suvorexant (Supplementary Table 21).

DISCUSSION

NNT values versus placebo that are < 10, and NNH values versus placebo that are ≥ 10, are desirable.[5] Most NNT values for lemborexant 5/10 mg versus placebo were < 10, and some were as low as 3, suggesting that lemborexant has a clinically relevant magnitude of therapeutic effect.[4,5] The most robust NNT values were generally for patient-reported outcomes and WASO response. All NNH values versus placebo for lemborexant from the pooled AE data were ≥ 10, evidencing that lemborexant is relatively tolerable. Rates of discontinuation because of an AE were low, and for lemborexant 5 mg these rates were similar to those for placebo (1.4% and 1.5%, respectively). Moreover, the NNH versus placebo for discontinuation because of an AE for pooled doses of lemborexant through day 30 was 216, and the 95% CI includes infinity, and thus was not statistically significant. LHH contrasting the statistically significant endpoint efficacy measures versus discontinuation because of an AE ranged from 13 to 54.

In SUNRISE 1, NNT values for lemborexant 5/10 mg were generally more robust than for zolpidem ER 6.25 mg for PSG and sleep diary outcomes, but generally not for the PGI-I or ISI categorical outcomes. The degree of overlap in effect sizes across all measures was considerable except for some of the PSG outcomes, particularly at day 30 when placebo was superior to zolpidem ER 6.25 mg on LPS categorical outcomes.

In indirect comparisons, lemborexant 5/10 mg demonstrated a numerically larger effect size (lower NNT) versus placebo than suvorexant on sleep measures at week 1, week 4, and month 3 (the time points for which data were available for both agents); however, the 95% CIs generally overlapped, and an appropriately designed head-to-head study would be required to properly compare these two medications. Except for the limited categorical PSG data available for ramelteon (with results similar to that for lemborexant 5/10 mg), NNT data for the other hypnotics for which comparison is possible are restricted to PGI-I and ISI outcomes with effect sizes that are similar to or more robust than that for lemborexant and with 95% CIs that are also generally overlapping.

Although somnolence was the most common AE observed with lemborexant 5/10 mg, with a NNH versus placebo between 15 and 28 for the first 30 days when pooling SUNRISE 1 and SUNRISE 2 data, this did not usually result in discontinuation of treatment within the first 30 days (SUNRISE 1 and SUNRISE 2), or within the first 6 months (SUNRISE 2). Moreover, having an AE of somnolence does not equal having impairment. Nonetheless, given the similar efficacy for lemborexant 5 mg and lemborexant 10 mg, the optimal starting dose for lemborexant appears to be 5 mg, which is consistent with approved prescribing information. Compared to starting at the 10 mg dose, initiating

lemborexant at 5 mg carries a lower risk for somnolence as well as a lower risk for discontinuation because of an AE.

It is not surprising that somnolence would be reported as a common adverse effect with many hypnotic medications. Although more or better quality of sleep is the expected benefit of the treatment, next-day somnolence may need to be managed for some patients. This can include an adjustment of the time to retire to bed, or in the case of somnolence being dose-related, then dose reduction could be considered.

Although there may have been instances in which NNH values versus placebo were < 10, for example in SUNRISE 2 for somnolence with lemborexant 10 mg, unpleasant taste with eszopiclone, and "nervous system disorders" and somnolence with zolpidem ER 12.5 mg, a single-digit NNH may be acceptable if the adverse event is mild or moderate, does not lead to discontinuation, is temporary or causes little distress, and does not pose a serious health risk or if a treatment has good (single-digit NNT) efficacy and there is a compelling need for efficacy that mitigates the low NNH tolerability limitation.[5] A NNH in the range of 10–100 may be acceptable for adverse events that may lead to discontinuation, but are not associated with serious immediate health risks, or when alternatives do not have a better profile.[5] LHH values can help better understand these tradeoffs, and although a LHH >> 1 on its face is desirable, there is sometimes the need to accept a LHH that approximates 1 or is < 1.[43–45]

Limitations

The data analyzed in this study are limited to dichotomous outcomes from trials in which medications were taken daily (and not "as needed"). The results may not be generalizable to patients outside the confines of a clinical trial; this is always a concern for results of registrational trials because of the strict inclusion/exclusion criteria that these studies require. Definitions of insomnia also may vary from trial to trial and reflect diagnostic criteria that have evolved over time, including the inclusion or exclusion of patients with somatic and/or psychiatric comorbidities. Exposure to lemborexant has been systematically studied up through 12 months in SUNRISE 2, although the double-blind period was 6 months in duration; the optimal length of medication treatment necessary to address insomnia was not examined. Although the two lemborexant studies that were pooled for the 30-day outcomes were similar, there were important differences in design (SUNRISE 1 employed PSG and recruited only older patients, although median age remained high in SUNRISE 2 at 55 years, versus 63 years in the SUNRISE 1; in addition, SUNRISE 1 required the presence of sleep maintenance difficulties [participants could also have had sleep-onset difficulties, but this was not required], and SUNRISE 2 enrolled patients with sleep onset and/or sleep maintenance difficulties). In the lemborexant trials but not necessarily in other studies of other agents, all patients received instructions consistent with principles of good sleep hygiene, which may have contributed to the improvement in sleep, especially among patients randomized to placebo. The metrics of NNT and NNH are not appropriate for continuous outcomes, such as WASO, and such outcomes require dichotomization for NNT to be directly calculated. Reasons for clinical trial discontinuation can be complex, so that the NNH for discontinuation due to AEs in a study may not always generalize to overall tolerability in clinical practice. We did not calculate discontinuation rates per month or time to discontinuation; such data would be of interest and should be considered when planning any future head-to-head comparisons of hypnotics and their acceptability to patients with insomnia. Some patients may be more sensitive to somnolence or other AEs than other patients, and thus all prescribing decisions should be individualized. The brief durations of the available controlled studies of lemborexant limit the sensitivity of calculating NNH for delayed adverse outcomes, and the relatively small sample sizes of the studies limit sensitivity of calculating NNH for uncommon adverse outcomes and subpopulation effects. Indirect comparisons of NNT, NNH, and LHH with other hypnotics as calculated in other studies of these agents versus placebo must be approached with caution because of heterogeneity in study design, including age of participants, dosing, and duration, as well as differences in available study outcome measures. The less commonly used benzodiazepine hypnotics estazolam and quazepam were not included in this report.

CONCLUSION

The data support the use of lemborexant as a potentially beneficial hypnotic for adults with insomnia, but no definitive conclusions can be drawn regarding whether its efficacy is substantially better or worse than that of other choices. Evidence for efficacy was demonstrable as early as day 1 based on PSG outcomes. Except for ramelteon, the occurrence of somnolence as a side effect is similar to other choices. However, orexin receptor antagonists such as lemborexant and suvorexant serve as an alternative to the older hypnotics, and because of the different mechanism of action, DORAs largely avoid the obstacles of physiologic tolerance, rebound, and withdrawal.[7,9] Head-to-head trials among DORAs versus other hypnotics, as well as between lemborexant and suvorexant, are desirable to better understand their similarities and differences in clinically relevant populations.

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(NEI), Vindico, and Universities and professional organizations/societies; owns stocks (small number of shares of common stock) in Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer (purchased > 10 years ago); and has received royalties from Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end of 2019), UpToDate (reviewer), Springer Healthcare (book), and Elsevier (Topic Editor: Psychiatry, Clinical Therapeutics). **Drs Juday**, **Frech**, and **Atkins** are employees of Eisai Inc.

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Supplementary Material

Article Title: Lemborexant for the Treatment of Insomnia: Direct and Indirect Comparisons With Other Hypnotics Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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24. **Table 21** Likelihood to be helped or harmed (LHH) for lemborexant 5 and 10 mg and suvorexant 15 and 20 mg based on number needed to treat (NNT) vs. placebo for response measured by sTST, sSOL, sWASO or ISI and number needed to harm (NNH) vs. placebo for somnolence, at Month 3

25. **Figure 1** Adverse event of somnolence: absolute risk increase (ARI) and number needed to harm (NNH) vs placebo, SUNRISE 1, SUNRISE 2, pooled.

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Supplementary Box 1. What are number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH) (4, 5)?

- What are NNT and NNH? NNT and NNH are measures of effect size and indicate how many patients would need to be treated with one intervention (such as a medication) instead of the comparator (such as another medication or placebo) to encounter one additional outcome of interest.
- What is the importance of a low vs. high value for NNT or NNH? Lower NNTs are evidenced when there are large differences between the interventions in question. For example, a NNT of 2 would be a very large effect size, as a difference is encountered after treating just 2 patients with one of the interventions versus the other. A NNT of 50 would mean little difference between the two interventions, as it would take treating 50 patients to encounter a difference in outcome. NNH is used when referring to undesirable events. A useful medication is one with a low NNT and a high NNH when comparing it with another intervention; a low NNT and a high NNH would mean one is more likely to encounter a benefit than a harm.
- What is the difference between a NNT of 10, 20 or 100? A rule of thumb is that single digit NNTs for efficacy measures suggest that the intervention has potentially useful benefits, and that double digit or higher NNHs for adverse events (AEs) indicate that the intervention is potentially well tolerated. A NNH < 10 means that the ARI (absolute risk increase, i.e., difference of event rate between the two interventions) is > 10%, and thus important to consider in day-to-day practice. A NNH ≥ 10 but < 20 means that the ARI is between 5 and 10%, and thus possibly still worth thinking about depending on the individual patient but this difference in outcome will be less commonly encountered. A NNH ≥ 20 means that the ARI is equal to or smaller than 5%, and of less clinical concern, unless the safety event has significant health consequences. A NNH > 100 means that the ARI is less than 1%, and not a concern under most circumstances.
- How is NNT or NNH different from a '*P*-Value'? It is generally understood that a result is statistically significant when the '*P*-Value' is lower than a pre-specified threshold, such as < 0.05. However, a statistically significant result may not be clinically relevant if the size of the treatment effect is small. It is best to calculate NNT or NNH values from statistically significant results if possible. The precision of the NNT or NNH estimate can be described using a Confidence Interval (CI), and it is common to calculate a 95% CI. If the CI includes "infinity" the NNT or NNH estimate is not statistically significant.
- What does this mean for individual patients? It is important to note that individual patients may have higher propensities for specific AEs and the treating clinician must be guided by the overall presentation of the patient, including past experiences with that patient and/or patient report. If a patient is particularly sensitive to a specific AE and wants to avoid it above all other considerations, then the occurrence of that AE may lead to discontinuation of the medication.
- What is the importance of the ratio of NNH to NNT? NNT and NNH can be used to quantify benefit versus risk by calculating the ratio of NNH to NNT (likelihood to be helped or harmed [LHH]). In general, a LHH greater than 1 would mean the likelihood to be helped is greater than the likelihood to be harmed. For a LHH less than 1, the reverse is true. For a LHH to be meaningful, the efficacy outcome and adverse outcome must be clinically relevant for the patient being treated.

Supplementary Box 2. Formulae used for number needed to treat (NNT), number needed to harm (NNH), 95% confidence interval (95% CI), and likelihood to be helped or harmed (LHH)

- Absolute Risk Increase (ARI) = (incidence on intervention of interest) – (incidence on comparator) = $f_1 - f_2$
- The 95% CI was calculated by
  - Lower bound of the CI = ARI - $z\sqrt{\frac{f_1(1-f_1)}{n_1}+\frac{f_2(1-f_2)}{n_2}}$, where z=1.96 for a 95% CI
  - Upper bound of the CI = ARI + $z\sqrt{\frac{f_1(1-f_1)}{n_1}+\frac{f_2(1-f_2)}{n_2}}$, where z=1.96 for a 95% CI
- NNT (or NNH) = 1/ARI, and rounded up to the next highest whole number
- The CI for the NNT (or NNH) was calculated by taking the reciprocal of the lower and upper bounds of the CI for the ARI
- LHH = NNH/NNT

Supplementary Table 1. Lemborexant efficacy outcomes, SUNRISE 1. WEEK 1, WEEK 4, PSG DAY 1, PSG DAY 2, PSG DAY 29, PSG DAY 30. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold. A negative NNT means that the rate for medication was lower than that for placebo.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Placebo			Lemborexant 5 mg vs. placebo NNT (95% CI)	Lemborexant 10 mg vs. placebo NNT (95% CI)	Pooled lemborexant vs. placebo NNT (95% CI)	Zolpidem extended release 6.25 mg vs. placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%	n	N	%				
WEEK 1																
sSOL responder[a]	26	259	10.0	28	266	10.5	20	251	8.0	6	202	3.0	15 (9-37)	14 (9-32)	14 (10-27)	20 (11-110)
sWASO responder[b]	45	261	17.2	55	262	21.0	44	253	17.4	20	202	9.9	14 (8-85)	9 (6-22)	11 (7-26)	14 (8-80)
sTST responder[c]	127	251	50.6	155	254	61.0	131	240	54.6	79	197	40.1	10 (6-79)	5 (4-9)	7 (5-14)	7 (5-20)
sSOL responder, alternate definition[d]	177	258	68.6	172	266	64.7	145	251	57.8	88	201	43.8	4 (3-7)	5 (4-9)	5 (4-7)	8 (5-21)
sWASO responder, alternate definition[e]	162	261	62.1	186	262	71.0	177	253	70.0	105	202	52.0	10 (6-98)	6 (4-10)	7 (5-16)	6 (4-11)
WEEK 4																
sSOL responder[a]	45	252	17.9	39	258	15.1	23	246	9.3	15	196	7.7	10 (7-24)	14 (8-59)	12 (8-26)	59 (ns)
sWASO responder[b]	62	253	24.5	62	253	24.5	61	247	24.7	32	196	16.3	13 (7-130)	13 (7-130)	13 (7-56)	12 (7-111)
sTST responder[c]	138	245	56.3	159	244	65.2	144	235	61.3	83	190	43.7	8 (5-31)	5 (4-9)	6 (4-12)	6 (4-13)
sSOL responder, alternate definition[d]	182	251	72.5	190	258	73.6	152	246	61.8	90	195	46.2	4 (3-6)	4 (3-6)	4 (3-6)	7 (4-16)
sWASO responder, alternate definition[e]	166	253	65.6	179	253	70.8	178	247	72.1	109	196	55.6	10 (6-110)	7 (5-17)	8 (5-23)	7 (4-14)
PGI-I = 1 for helped sleep[f]	165	257	64.2	161	253	63.6	176	244	72.1	84	198	42.4	5 (4-8)	5 (4-9)	5 (4-8)	4 (3-5)
PGI-I = 1 for decreased time to fall asleep[f]	154	257	59.9	165	253	65.2	154	244	63.1	85	198	42.9	6 (4-13)	5 (4-8)	6 (4-9)	5 (4-10)
PGI-I = 1 for increased total sleep time[f]	159	257	61.9	157	253	62.1	173	244	70.9	88	198	44.4	6 (4-12)	6 (4-12)	6 (4-11)	4 (3-6)
PGI-I = 2 medication strength "just right"[f]	133	257	51.8	141	253	55.7	127	244	52.0	78	198	39.4	9 (5-32)	7 (4-14)	7 (5-16)	8 (5-30)
ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	162	257	63.0	153	253	60.5	166	244	68.0	99	198	50.0	8 (5-26)	10 (6-79)	9 (5-28)	6 (4-12)
ISI ≤ 7 (no insomnia)[h]	71	257	27.6	70	253	27.7	68	244	27.9	29	198	14.6	8 (5-18)	8 (5-18)	8 (6-15)	8 (5-18)

ISI ≤ 14 (no or subthreshold insomnia)[h]	186	257	72.4	184	253	72.7	182	244	74.6	116	198	58.6	8 (5-20)	8 (5-19)	8 (5-17)	7 (4-14)
DAY 1 PSG																
LPS responder[i]	46	266	17.3	50	268	18.7	39	261	14.9	41	208	19.7	-42 (ns)	-95 (ns)	-58 (ns)	-21 (ns)
WASO responder[j]	152	266	57.1	176	268	65.7	129	261	49.4	48	208	23.1	3 (3-4)	3 (2-3)	3 (3-4)	4 (3-6)
LPS responder, alternate definition[k]	104	266	39.1	97	268	36.2	89	261	34.1	65	208	31.3	13 (ns)	21 (ns)	16 (ns)	36 (ns)
LPS responder, alternate definition[l]	191	266	71.8	182	268	67.9	162	262	61.8	121	208	58.2	8 (5-20)	11 (6-100)	9 (6-26)	28 (ns)
DAY 2 PSG																
LPS responder[i]	47	263	17.9	68	262	26.0	38	258	14.7	43	203	21.2	-31 (ns)	21 (ns)	139 (ns)	-16 (ns)
WASO responder[j]	137	263	52.1	173	262	66.0	113	258	43.8	52	203	25.6	4 (3-6)	3 (3-4)	3 (3-4)	6 (4-11)
LPS responder, alternate definition[k]	112	263	42.6	124	262	47.3	84	258	32.6	77	203	37.9	22 (ns)	11 (6-256)	15 (ns)	-19 (ns)
LPS responder, alternate definition[l]	194	263	73.8	194	262	74.0	156	259	60.2	126	203	62.1	9 (5-32)	9 (5-29)	9 (6-24)	-55 (ns)
DAY 29 PSG																
LPS responder[i]	58	260	22.3	68	259	26.3	42	249	16.9	37	200	18.5	27 (ns)	13 (7-625)	18 (ns)	-62 (ns)
WASO responder[j]	121	260	46.5	131	259	50.6	113	249	45.4	59	200	29.5	6 (4-13)	5 (4-9)	6 (4-9)	7 (4-15)
LPS responder, alternate definition[k]	114	260	43.8	128	259	49.4	80	249	32.1	66	200	33.0	10 (6-51)	7 (4-14)	8 (5-18)	-115 (ns)
LPS responder, alternate definition[l]	189	260	72.7	191	259	73.7	152	250	60.8	115	200	57.5	7 (5-16)	7 (4-14)	7 (5-13)	31 (ns)
DAY 30 PSG																
LPS responder[i]	59	260	22.7	71	260	27.3	28	248	11.3	44	200	22.0	145 (ns)	19 (ns)	34 (ns)	-10 (-6 to -27) (NNT in favor of placebo)
WASO responder[j]	144	260	55.4	135	260	51.9	95	248	38.3	54	200	27.0	4 (3-6)	4 (3-7)	4 (3-6)	9 (5-38)
LPS responder, alternate definition[k]	118	260	45.4	134	260	51.5	67	248	27.0	82	200	41.0	23 (ns)	10 (6-71)	14 (ns)	-8 (-5 to -20) (NNT in favor of placebo)
LPS responder, alternate definition[l]	194	260	74.6	201	260	77.3	131	248	52.8	129	200	64.5	10 (6-62)	8 (5-23)	9 (6-26)	-9 (-5 to –39) (NNT in favor of placebo)

[a]sSOL responder defined as sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes; this was a pre-specified outcome.

[b]sWASO responder defined as sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.

[c]sTST responder defined as ≥ 15% improvement in mean sTST; this outcome is available for suvorexant (10).

[d]sSOL responder, alternate definition, defined as ≥ 15% improvement in mean sSOL; this outcome is available for suvorexant (10).

[e]sWASO responder, alternate definition defined as ≥ 15% improvement in mean sWASO; this outcome is available for suvorexant (10).

[f]PGI-I was not assessed at Week 1, but data are available for the other time points of interest; PGI-I categorical outcomes are available for doxepin (28, 29) and zolpidem extended release (32, 33, 42) and zolpidem immediate release (34).

[g]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for suvorexant (10).

[h]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for eszopiclone (30, 31).

[i]LPS responder defined as LPS at study baseline > 30 minutes and mean LPS at time point in question ≤ 20 minutes; this was a pre-specified outcome.

[j]WASO responder defined as WASO at study baseline > 60 minutes and mean WASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.

[k]LPS responder, alternate definition, defined as a decrease of ≥ 50% from baseline; this outcome is available for ramelteon in a published paper (35).

[l]LPS responder, alternate definition, defined as LPS ≤ 30 minutes; this outcome is available for ramelteon in the FDA drug approval package (14).

Abbreviations

CI: confidence interval; ISI: Insomnia Severity Index; LPS: latency to persistent sleep; NNT: number needed to treat; ns: not significant; PGI-I: Patient Global Impression – Insomnia; PSG: polysomnography; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset; WASO: wake after sleep onset

Supplementary Table 2. Lemborexant vs. zolpidem ER efficacy outcomes, SUNRISE 1. WEEK 1, WEEK 4, PSG DAY 1, PSG DAY 2, PSG DAY 29, PSG DAY 30. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold. A negative NNT means that the rate for lemborexant was lower than that for zolpidem ER.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Lemborexant 5 mg vs. zolpidem extended release 6.25 mg NNT (95% CI)	Lemborexant 10 mg vs. zolpidem extended release 6.25 mg NNT (95% CI)	Pooled lemborexant vs. zolpidem extended release 6.25 mg NNT (95% CI)
	n	N	%	n	N	%	n	N	%			
WEEK 1												
sSOL responder[a]	26	259	10.0	28	266	10.5	20	251	8.0	49 (ns)	40 (ns)	44 (ns)
sWASO responder[b]	45	261	17.2	55	262	21.0	44	253	17.4	-667 (ns)	28 (ns)	58 (ns)
sTST responder[c]	127	251	50.6	155	254	61.0	131	240	54.6	-26 (ns)	16 (ns)	80 (ns)
sSOL responder, alternate definition[d]	177	258	68.6	172	266	64.7	145	251	57.8	10 (6-40)	15 (ns)	12 (7-67)
sWASO responder, alternate definition[e]	162	261	62.1	186	262	71.0	177	253	70.0	-13 (ns)	97 (ns)	-30 (ns)
WEEK 4												
sSOL responder[a]	45	252	17.9	39	258	15.1	23	246	9.3	12 (7-40)	18 (9-1254)	14 (9-45)
sWASO responder[b]	62	253	24.5	62	253	24.5	61	247	24.7	-526 (ns)	-526 (ns)	-526 (ns)
sTST responder[c]	138	245	56.3	159	244	65.2	144	235	61.3	-21 (ns)	26 (ns)	-185 (ns)
sSOL responder, alternate definition[d]	182	251	72.5	190	258	73.6	152	246	61.8	10 (6-40)	9 (5-27)	9 (6-25)
sWASO responder, alternate definition[e]	166	253	65.6	179	253	70.8	178	247	72.1	-16 (ns)	-77 (ns)	-26 (ns)
PGI-I = 1 for helped sleep[f]	165	257	64.2	161	253	63.6	176	244	72.1	-13 (ns)	-12 (-6 to -311)	-13 (-7 to -83)
PGI-I = 1 for decreased time to fall asleep[f]	154	257	59.9	165	253	65.2	154	244	63.1	-32 (ns)	48 (ns)	-177 (ns)
PGI-I = 1 for increased total sleep time[f]	159	257	61.9	157	253	62.1	173	244	70.9	-12 (-6 to -125)	-12 (-6 to -171)	-12 (-7 to -54)
PGI-I = 2 medication strength "just right"[f]	133	257	51.8	141	253	55.7	127	244	52.0	-336 (ns)	28 (ns)	60 (ns)
ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	162	257	63.0	153	253	60.5	166	244	68.0	-20 (ns)	-14 (ns)	-16 (ns)
ISI ≤ 7 (no insomnia)[h]	71	257	27.6	70	253	27.7	68	244	27.9	-413 (ns)	-498 (ns)	-451 (ns)
ISI ≤ 14 (no or subthreshold insomnia)[h]	186	257	72.4	184	253	72.7	182	244	74.6	-46 (ns)	-54 (ns)	-49 (ns)
DAY 1 PSG												
LPS responder[i]	46	266	17.3	50	268	18.7	39	261	14.9	43 (ns)	27 (ns)	33 (ns)
WASO responder[j]	152	266	57.1	176	268	65.7	129	261	49.4	13 (ns)	7 (5-13)	9 (6-22)
LPS responder, alternate definition[k]	104	266	39.1	97	268	36.2	89	261	34.1	20 (ns)	48 (ns)	29 (ns)
LPS responder, alternate definition[l]	191	266	71.8	182	268	67.9	162	262	61.8	10 (6-51)	17 (ns)	13 (7-104)
DAY 2 PSG												
LPS responder[i]	47	263	17.9	68	262	26.0	38	258	14.7	32 (ns)	9 (6-23)	14 (8-63)
WASO responder[j]	137	263	52.1	173	262	66.0	113	258	43.8	13 (ns)	5 (4-8)	7 (5-13)

LPS responder, alternate definition[k]	112	263	42.6	124	262	47.3	84	258	32.6	10 (6-57)	7 (5-16)	9 (6-19)
LPS responder, alternate definition[l]	194	263	73.8	194	262	74.0	156	259	60.2	8 (5-18)	8 (5-18)	8 (5-16)
DAY 29 PSG												
LPS responder[i]	58	260	22.3	68	259	26.3	42	249	16.9	19 (ns)	11 (7-44)	14 (8-68)
WASO responder[j]	121	260	46.5	131	259	50.6	113	249	45.4	87 (ns)	20 (ns)	32 (ns)
LPS responder, alternate definition[k]	114	260	43.8	128	259	49.4	80	249	32.1	9 (5-30)	6 (4-12)	7 (5-14)
LPS responder, alternate definition[l]	189	260	72.7	191	259	73.7	152	250	60.8	9 (5-27)	8 (5-21)	9 (6-19)
DAY 30 PSG												
LPS responder[i]	59	260	22.7	71	260	27.3	28	248	11.3	9 (6-21)	7 (5-11)	8 (6-13)
WASO responder[j]	144	260	55.4	135	260	51.9	95	248	38.3	6 (4-12)	8 (5-20)	7 (5-13)
LPS responder, alternate definition[k]	118	260	45.4	134	260	51.5	67	248	27.0	6 (4-10)	5 (4-7)	5 (4-7)
LPS responder, alternate definition[l]	194	260	74.6	201	260	77.3	131	248	52.8	5 (4-8)	5 (4-7)	5 (4-7)

[a]sSOL responder defined as sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes; this was a pre-specified outcome.

[b]sWASO responder defined as sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.

[c]sTST responder defined as ≥ 15% improvement in mean sTST.

[d]sSOL responder, alternate definition, defined as ≥ 15% improvement in mean sSOL.

[e]sWASO responder, alternate definition defined as ≥ 15% improvement in mean sWASO.

[f]PGI-I was not assessed at Week 1, but data are available for the other time points of interest.

[g]ISI was not assessed at Week 1, but data are available for the other time points of interest.

[h]ISI was not assessed at Week 1, but data are available for the other time points of interest.

[i]LPS responder defined as LPS at study baseline > 30 minutes and mean LPS at time point in question ≤ 20 minutes; this was a pre-specified outcome.

[j]WASO responder defined as WASO at study baseline > 60 minutes and mean WASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.

[k]LPS responder, alternate definition, defined as a decrease of ≥ 50% from baseline.

[l]LPS responder, alternate definition, defined as LPS ≤ 30 minutes.

Abbreviations

CI: confidence interval; ISI: Insomnia Severity Index; LPS: latency to persistent sleep; NNT: number needed to treat; ns: not significant; PGI-I: Patient Global Impression – Insomnia; PSG: polysomnography; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset; WASO: wake after sleep onset

Supplementary Table 3. Lemborexant objective sleep maintenance responders (WASO ≤ 60 minutes and a reduction from baseline by > 10 minutes, provided baseline WASO > 60 minutes), SUNRISE 1. Subjects with missing information due to early withdrawal or other reasons are considered as non-responders in the analysis. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Placebo			Lemborexant 5 mg vs. placebo NNT (95% CI)	Lemborexant 10 mg vs. placebo NNT (95% CI)	Pooled lemborexant vs. placebo NNT (95% CI)	Zolpidem extended release 6.25 mg vs. placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%	n	N	%				
Responder, Day 1/2	136	266	51.1	173	266	65.0	121	261	46.4	35	205	17.1	3 (3-4)	3 (2-3)	3 (3-3)	4 (3-5)
Responder Day 29/30	118	266	44.4	124	266	46.6	91	261	34.9	46	205	22.4	5 (4-8)	5 (4-7)	5 (4-7)	8 (5-24)

Abbreviations
CI: confidence interval; NNT: number needed to treat; WASO: wake after sleep onset

Supplementary Table 4. Lemborexant efficacy outcomes, SUNRISE 2. WEEK 1, WEEK 4, MONTH 3, MONTH 6. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Placebo			Lemborexant 5 mg vs. placebo NNT (95% CI)	Lemborexant 10 mg vs. placebo NNT (95% CI)	Pooled lemborexant vs. placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%			
WEEK 1												
sSOL responder[a]	31	310	10.0	28	310	9.0	13	315	4.1	17 (11-54)	21 (12-97)	19 (12-46)
sWASO responder[b]	46	308	14.9	45	309	14.6	31	313	9.9	20 (ns)	22 (ns)	21 (11-196)
sTST responder[c]	107	294	36.4	130	296	43.9	83	304	27.3	11 (6-61)	6 (5-11)	8 (6-16)
sSOL responder, alternate definition[d]	185	310	59.7	189	310	61.0	124	315	39.4	5 (4-8)	5 (4-8)	5 (4-7)
sWASO responder, alternate definition[e]	158	306	51.6	167	309	54.0	114	313	36.4	7 (5-14)	6 (4-11)	7 (5-11)
WEEK 4												
sSOL responder[a]	40	298	13.4	54	297	18.2	26	299	8.7	22 (ns)	11 (7-25)	15 (9-37)
sWASO responder[b]	59	297	19.9	60	293	20.5	47	297	15.8	25 (ns)	22 (ns)	23 (ns)
sTST responder[c]	113	284	39.8	145	282	51.4	99	291	34.0	18 (ns)	6 (4-11)	9 (6-22)
sSOL responder, alternate definition[d]	194	298	65.1	210	297	70.7	148	299	49.5	7 (5-13)	5 (4-8)	6 (4-9)
sWASO responder, alternate definition[e]	170	295	57.6	170	293	58.0	136	297	45.8	9 (5-26)	9 (5-24)	9 (6-20)
PGI-I = 1 for helped sleep[f]	180	301	59.8	179	291	61.5	103	299	34.4	4 (3-6)	4 (3-6)	4 (3-6)
PGI-I = 1 for decreased time to fall asleep[f]	185	301	61.5	193	291	66.3	119	299	39.8	5 (4-8)	4 (3-6)	5 (4-6)
PGI-I = 1 for increased total sleep time[f]	160	301	53.2	170	291	58.4	106	299	35.5	6 (4-11)	5 (4-7)	5 (4-8)
PGI-I = 2 medication strength "just right"[f]	132	301	43.9	126	291	43.3	86	299	28.8	7 (5-14)	7 (5-15)	7 (5-12)
ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	164	301	54.5	160	287	55.7	116	296	39.2	7 (5-14)	6 (5-12)	7 (5-11)
ISI ≤ 7 (no insomnia)[h]	69	301	22.9	70	287	24.4	36	296	12.2	10 (6-22)	9 (6-17)	9 (6-16)
ISI ≤ 14 (no or subthreshold insomnia)[h]	192	301	63.8	185	287	64.5	160	296	54.1	11 (6-54)	10 (6-41)	10 (6-32)
MONTH 3												
sSOL responder[a]	69	270	25.6	74	263	28.1	45	279	16.1	11 (7-38)	9 (6-20)	10 (7-21)
sWASO responder[b]	84	269	31.2	69	261	26.4	50	278	18.0	8 (5-17)	12 (7-69)	10 (6-21)
sTST responder[c]	143	258	55.4	152	250	60.8	116	269	43.1	9 (5-27)	6 (4-11)	7 (5-14)
sSOL responder, alternate definition[d]	205	270	75.9	200	263	76.0	158	279	56.6	6 (4-9)	6 (4-9)	6 (4-8)
sWASO responder, alternate definition[e]	182	268	67.9	173	261	66.3	156	278	56.1	9 (5-27)	10 (6-51)	10 (6-26)
PGI-I = 1 for helped sleep[f]	179	275	65.1	172	262	65.6	115	283	40.6	5 (4-7)	4 (3-6)	4 (4-6)
PGI-I = 1 for decreased time to fall asleep[f]	188	275	68.4	183	262	69.8	119	283	42.0	4 (3-6)	4 (3-6)	4 (3-5)
PGI-I = 1 for increased total sleep time[f]	152	275	55.3	156	262	59.5	111	283	39.2	7 (5-13)	5 (4-9)	6 (4-9)
PGI-I = 2 medication strength "just right"[f]	137	275	49.8	135	262	51.5	97	283	34.3	7 (5-14)	6 (4-11)	7 (5-11)

ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	187	274	68.2	176	259	68.0	135	283	47.7	5 (4-8)	5 (4-9)	5 (4-8)
ISI ≤ 7 (no insomnia)[h]	82	274	29.9	92	259	35.5	54	283	19.1	10 (6-27)	7 (5-12)	8 (6-14)
ISI ≤ 14 (no or subthreshold insomnia)[h]	197	274	71.9	200	259	77.2	166	283	58.7	8 (5-19)	6 (4-10)	7 (5-12)
MONTH 6												
sSOL responder[a]	78	245	31.8	75	228	32.9	45	249	18.1	8 (5-17)	7 (5-15)	7 (5-13)
sWASO responder[b]	92	244	37.7	76	226	33.6	51	248	20.6	6 (4-11)	8 (5-20)	7 (5-12)
sTST responder[c]	139	235	59.1	135	219	61.6	117	242	48.3	10 (6-53)	8 (5-24)	9 (6-24)
sSOL responder, alternate definition[d]	209	245	85.3	185	228	81.1	151	249	60.6	5 (4-6)	5 (4-8)	5 (4-7)
sWASO responder, alternate definition[e]	179	243	73.7	163	226	72.1	142	248	57.3	7 (5-13)	7 (5-16)	7 (5-12)
PGI-I = 1 for helped sleep[f]	171	254	67.3	158	231	68.4	115	255	45.1	5 (4-8)	5 (4-7)	5 (4-7)
PGI-I = 1 for decreased time to fall asleep[f]	185	254	72.8	168	231	72.7	116	255	45.5	4 (3-6)	4 (3-6)	4 (3-5)
PGI-I = 1 for increased total sleep time[f]	148	254	58.3	144	231	62.3	102	255	40.0	6 (4-11)	5 (4-8)	5 (4-8)
PGI-I = 2 medication strength "just right" [f]	142	254	55.9	123	231	53.2	93	255	36.5	6 (4-10)	6 (4-13)	6 (4-10)
ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	195	257	75.9	173	234	73.9	148	258	57.4	6 (4-10)	6 (4-12)	6 (4-10)
ISI ≤ 7 (no insomnia)[h]	106	257	41.2	99	234	42.3	66	258	25.6	7 (5-14)	6 (4-12)	7 (5-11)
ISI ≤ 14 (no or subthreshold insomnia)[h]	207	257	80.5	187	234	79.9	175	258	67.8	8 (5-20)	9 (6-23)	9 (6-18)

[a]sSOL responder defined as sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes; this was a pre-specified outcome.
[b]sWASO responder defined as sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.
[c]sTST responder defined as ≥ 15% improvement in mean sTST; this outcome is available for suvorexant (10).
[d]sSOL responder, alternate definition, defined as ≥ 15% improvement in mean sSOL; this outcome is available for suvorexant (10).
[e]sWASO responder, alternate definition defined as ≥ 15% improvement in mean sWASO; this outcome is available for suvorexant (10).
[f]PGI-I was not assessed at Week 1, but data are available for the other time points of interest; PGI-I categorical outcomes are available for doxepin (28, 29) and zolpidem extended release (32, 33, 42) and zolpidem immediate release (34).
[g]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for suvorexant (10).
[h]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for eszopiclone (30, 31).

Abbreviations
CI: confidence interval; ISI: Insomnia Severity Index; NNT: number needed to treat; ns: not significant; PGI-I: Patient Global Impression – Insomnia; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset

Supplementary Table 5. Lemborexant subjective sleep maintenance responders (sWASO ≤ 60 minutes and a reduction from baseline by > 10 minutes, provided baseline sWASO > 60 minutes), SUNRISE 2. Subjects with missing information due to early withdrawal or other reasons are considered as non-responders in the analysis. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Placebo			Lemborexant 5 mg vs. placebo NNT (95% CI)	Lemborexant 10 mg vs. placebo NNT (95% CI)	Pooled lemborexant vs. placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%			
Responder, Day 7	46	263	17.5	45	257	17.5	31	250	12.4	20 (ns)	20 (ns)	20 (ns)
Responder, Month 1	59	263	22.4	60	257	23.3	47	250	18.8	28 (ns)	22 (ns)	25 (ns)
Responder, Month 2	69	263	26.2	71	257	27.6	50	250	20.0	16 (ns)	14 (7-407)	15 (8-150)
Responder, Month 3	84	263	31.9	70	257	27.2	50	250	20.0	9 (6-23)	14 (ns)	11 (7-31)
Responder, Month 4	84	263	31.9	85	257	33.1	50	250	20.0	9 (6-23)	8 (5-19)	8 (6-17)
Responder, Month 5	87	263	33.1	78	257	30.4	57	250	22.8	10 (6-39)	14 (ns)	12 (7-43)
Responder, Month 6	92	263	35.0	77	257	30.0	51	250	20.4	7 (5-15)	11 (6-49)	9 (6-18)

Abbreviations
CI: confidence interval; NNT: number needed to treat; ns: not significant; sWASO: subjective wake after sleep onset

Supplementary Table 6. Lemborexant efficacy outcomes (subjective), SUNRISE 1, SUNRISE 2, pooled, through Week 4. Results for the NNT are bolded when statistical significance is achieved at the P < .05 threshold. Results for placebo are pooled across both studies. zolpidem extended release 6.25 mg was not included in SUNRISE 2 and thus omitted from this table – see Table 2.

	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Placebo			Lemborexant 5 mg vs. placebo NNT (95% CI)	Lemborexant 10 mg vs. placebo NNT (95% CI)	Pooled lemborexant vs. placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%	n	N	%			
WEEK 1															
sSOL responder[a]	57	569	10.0	56	576	9.7	20	251	8.0	19	517	3.7	16 (11-30)	17 (12-32)	17 (12-27)
sWASO responder[b]	91	569	16.0	100	571	17.5	44	253	17.4	51	515	9.9	17 (10-48)	14 (9-29)	15 (10-29)
sTST responder[c]	234	545	42.9	285	550	51.8	131	240	54.6	162	501	32.3	10 (7-21)	6 (4-8)	7 (5-10)
sWASO responder, alternate definition[d]	320	567	56.4	353	571	61.8	177	253	70.0	219	515	42.5	8 (5-13)	6 (4-8)	6 (5-9)
sSOL responder, alternate definition[e]	362	568	63.7	361	576	62.7	145	251	57.8	212	516	41.1	5 (4-6)	5 (4-7)	5 (4-6)
WEEK 4															
sSOL responder[a]	85	550	15.5	93	555	16.8	23	246	9.3	41	41	8.3	14 (10-31)	12 (9-23)	13 (9-22)
sWASO responder[b]	121	550	22.0	122	546	22.3	61	247	24.7	79	79	16.0	17 (10-81)	16 (9-65)	17 (10-49)
sTST responder[c]	251	529	47.4	304	526	57.8	144	235	61.3	182	481	37.8	11 (7-29)	5 (4-8)	7 (5-11)
sWASO responder, alternate definition[d]	336	548	61.3	349	546	63.9	178	247	72.1	245	493	49.7	9 (6-18)	7 (5-13)	8 (6-14)
sSOL responder, alternate definition[e]	376	549	68.5	400	555	72.1	152	246	61.8	238	494	48.2	5 (4-7)	5 (4-6)	5 (4-6)
PGI-I = 1 for helped sleep[f]	345	558	61.8	340	544	62.5	176	244	72.1	187	187	37.6	5 (4-6)	4 (4-6)	5 (4-6)
PGI-I = 1 for decreased time to fall asleep[f]	339	558	60.8	358	544	65.8	154	244	63.1	204	204	41.0	6 (4-8)	4 (4-6)	5 (4-6)
PGI-I = 1 for increased total sleep time[f]	319	558	57.	327	544	60.1	173	244	70.9	194	194	39.0	6 (5-9)	5 (4-7)	6 (4-7)
PGI-I = 2 medication strength "just right" [f]	265	558	47.5	267	544	49.1	127	244	52.0	164	164	33.0	7 (5-12)	7 (5-10)	7 (5-10)
ISI with a ≥ 6-point improvement (clinically relevant improvement)[g]	326	558	58.4	313	540	58.0	166	244	68.0	215	215	43.5	7 (5-12)	7 (5-12)	7 (5-11)
ISI ≤ 7 (no insomnia)[h]	140	558	25.1	140	540	25.9	68	244	27.9	65	65	13.2	9 (6-14)	8 (6-13)	9 (7-12)
ISI ≤ 14 (no or subthreshold insomnia)[h]	378	558	67.7	369	540	68.3	182	244	74.6	276	494	55.9	9 (6-17)	8 (6-16)	9 (6-15)

[a]sSOL responder defined as sSOL at study baseline > 30 minutes and mean sSOL at time point in question ≤ 20 minutes; this was a pre-specified outcome.

[b]sWASO responder defined as sWASO at study baseline > 60 minutes and mean sWASO at time point in question ≤ 60 minutes and showed a reduction of > 10 minutes compared to study baseline; this was a pre-specified outcome.

[c]sTST responder defined as ≥ 15% improvement in mean sTST; this outcome is available for suvorexant (10).

[d]sWASO responder, alternate definition, defined as ≥ 15% improvement in mean sWASO; this outcome is available for suvorexant (10).

[e]sSOL responder, alternate definition, defined as ≥ 15% improvement in mean sSOL; this outcome is available for suvorexant (10).

[f]PGI-I was not assessed at Week 1, but data are available for the other time points of interest; PGI-I categorical outcomes are available for doxepin (28, 29) and zolpidem extended release (32, 33, 42) and zolpidem immediate release (34).

[g]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for suvorexant (10).
[h]ISI was not assessed at Week 1, but data are available for the other time points of interest; this outcome is available for eszopiclone (30, 31).

Abbreviations
CI: confidence interval; ISI: Insomnia Severity Index; NNT: number needed to treat; ns: not significant; PGI-I: Patient Global Impression – Insomnia; PSG: polysomnography; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset

Supplementary Table 7. Lemborexant tolerability outcomes, SUNRISE 1. Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Placebo			Lemborexant 5 mg vs. placebo NNH (95% CI)	Lemborexant 10 mg vs. placebo NNH (95% CI)	Pooled lemborexant vs. placebo NNH (95% CI)	Zolpidem extended release 6.25 mg vs. placebo NNH (95% CI)
	n	N	%	n	N	%	n	N	%	n	N	%				
Discontinuation because of an AE	2	266	0.8	3	268	1.1	7	263	2.7	2	209	1.0	ND	616 (ns)	ND	59 (ns)
AE headache	17	266	6.4	13	268	4.9	14	263	5.3	13	209	6.2	586 (ns)	ND	ND	ND
AE somnolence	11	266	4.1	19	268	7.1	4	263	1.5	4	209	1.9	45 (ns)	**20 (12-64)**	**27 (16-100)**	ND
AE urinary tract infection	3	266	1.1	9	268	3.4	2	263	0.8	2	209	1.0	586 (ns)	42 (ns)	78 (ns)	ND
AE nasopharyngitis	7	266	2.6	1	268	0.4	1	263	0.4	3	209	1.4	84 (ns)	ND	1595 (ns)	ND
AE upper respiratory tract infection	6	266	2.3	1	268	0.4	2	263	0.8	4	209	1.9	293 (ns)	ND	ND	ND
AE dizziness	3	266	1.1	2	268	0.7	8	263	3.0	4	209	1.9	ND	ND	ND	89 (ns)
AE nausea	3	266	1.1	2	268	0.7	5	263	1.9	1	209	0.5	154 (ns)	374 (ns)	219 (ns)	71 (ns)
AE abnormal dreams	0	266	0	4	268	1.5	3	263	1.1	1	209	0.5	ND	99 (ns)	370 (ns)	151 (ns)
AE diarrhea	1	266	0.4	3	268	1.1	5	263	1.9	5	209	2.4	ND	ND	ND	ND
AE fall	4	266	1.5	0	268	0	0	263	0	0	209	0	**67 (34-2428)**	ND	**134 (68-5639)**	ND
AE pyuria	1	266	0.4	3	268	1.1	0	263	0	0	209	0	266 (ns)	90 (ns)	**134 (68-5639)**	ND
AE sleep paralysis	1	266	0.4	3	268	1.1	0	263	0	0	209	0	266 (ns)	90 (ns)	**134 (68-5639)**	ND
AE ventricular extrasystoles	1	266	0.4	3	268	1.1	1	263	0.4	0	209	0	266 (ns)	90 (ns)	**134 (68-5639)**	263 (ns)
AE fatigue	2	266	0.8	1	268	0.4	4	263	1.5	0	209	0	133 (ns)	288 (ns)	178 (ns)	**66 (34-2393)**
AE muscle spasms	3	266	1.1	0	268	0	1	263	0.4	1	209	0.5	154 (ns)	ND	1201 (ns)	ND
AE myalgia	3	266	1.1	0	268	0	1	263	0.4	1	209	0.5	154 (ns)	ND	1201 (ns)	ND
AE anxiety	2	266	0.8	0	268	0	5	263	1.9	0	209	0	133 (ns)	ND	267 (ns)	**53 (29-399)**
AE cough	1	266	0.4	1	268	0.4	4	263	1.5	2	209	1.0	ND	ND	ND	178 (ns)
AE aspartate aminotransferase increase	0	266	0	1	268	0.4	3	263	1.1	1	209	0.5	ND	ND	ND	151 (ns)
AE constipation	0	266	0	1	268	0.4	4	263	1.5	1	209	0.5	ND	ND	ND	96 (ns)
AE hypertriglyceridemia	0	266	0	1	268	0.4	4	263	1.5	0	209	0	ND	268 (ns)	534 (ns)	**66 (34-2393)**
AE decrease appetite	0	266	0	0	268	0	3	263	1.1	0	209	0	ND	ND	ND	88 (ns)
AE depression	0	266	0	0	268	0	3	263	1.1	0	209	0	ND	ND	ND	88 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; ND: no difference; NNH: number needed to harm; ns: not significant

Supplementary Table 8. Lemborexant vs. zolpidem ER tolerability outcomes, SUNRISE 1. Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold. A negative NNH means that the rate for lemborexant was lower than that for zolpidem ER.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem extended release 6.25 mg			Lemborexant 5 mg vs. zolpidem extended release 6.25 mg NNH (95% CI)	Lemborexant 10 mg vs. zolpidem extended release 6.25 mg NNH (95% CI)	Pooled lemborexant vs. zolpidem extended release 6.25 mg NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Discontinuation because of an AE	2	266	0.8	3	268	1.1	7	263	2.7	-53 (ns)	-65 (ns)	-58 (ns)
AE headache	17	266	6.4	13	268	4.9	14	263	5.3	94 (ns)	-212 (ns)	340 (ns)
AE somnolence	11	266	4.1	19	268	7.1	4	263	1.5	39 (ns)	**18 (12-47)**	**25 (16-61)**
AE urinary tract infection	3	266	1.1	9	268	3.4	2	263	0.8	273 (ns)	**39 (20-503)**	68 (ns)
AE nasopharyngitis	7	266	2.6	1	268	0.4	1	263	0.4	**45 (24-530)**	-14097 (ns)	90 m(ns)
AE upper respiratory tract infection	6	266	2.3	1	268	0.4	2	263	0.8	67 (ns)	-259 (ns)	182 (ns)
AE dizziness	3	266	1.1	2	268	0.7	8	263	3.0	-53 (ns)	-44 (ns)	-48 (ns)
AE nausea	3	266	1.1	2	268	0.7	5	263	1.9	-130 (ns)	-87 (ns)	-104 (ns)
AE abnormal dreams	0	266	0	4	268	1.5	3	263	1.1	-88 (ns)	285 (ns)	-256 (ns)
AE diarrhea	1	266	0.4	3	268	1.1	5	263	1.9	-66 (ns)	-128 (ns)	-87 (ns)
AE fall	4	266	1.5	0	268	0	0	263	0	**67 (34-2428)**	ND	**134 (68-5639)**
AE pyuria	1	266	0.4	3	268	1.1	0	263	0	266 (ns)	90 (ns)	**134 (68-5639)**
AE sleep paralysis	1	266	0.4	3	268	1.1	0	263	0	266 (ns)	90 (ns)	**134 (68-5639)**
AE ventricular extrasystoles	1	266	0.4	3	268	1.1	1	263	0.4	-2330 (ns)	136 (ns)	272 (ns)
AE fatigue	2	266	0.8	1	268	0.4	4	263	1.5	-131 (ns)	-88 (ns)	-105 (ns)
AE muscle spasms	3	266	1.1	0	268	0	1	263	0.4	134 (ns)	-263 (ns)	551 (ns)
AE myalgia	3	266	1.1	0	268	0	1	263	0.4	134 (ns)	-263 (ns)	551 (ns)
AE anxiety	2	266	0.8	0	268	0	5	263	1.9	-87 (ns)	**-53 (-29 to -399)**	-66 (ns)
AE cough	1	266	0.4	1	268	0.4	4	263	1.5	-88 (ns)	-88 (ns)	-88 (ns)
AE aspartate aminotransferase increase	0	266	0	1	268	0.4	3	263	1.1	-88 (ns)	-131 (ns)	-105 (ns)
AE constipation	0	266	0	1	268	0.4	4	263	1.5	**-66 (-34 to -2393)**	-88 (ns)	-75 (ns)
AE hypertriglyceridemia	0	266	0	1	268	0.4	4	263	1.5	**-66 (-34 to -2393)**	-88 (ns)	-75 (ns)
AE decrease appetite	0	266	0	0	268	0	3	263	1.1	-88 (ns)	-88 (ns)	-88 (ns)
AE depression	0	266	0	0	268	0	3	263	1.1	-88 (ns)	-88 (ns)	-88 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; ND: no difference; NNH: number needed to harm; ns: not significant

Supplementary Table 9. Lemborexant tolerability outcomes, SUNRISE 2. Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Placebo			Lemborexant 5 mg vs. placebo NNH (95% CI)	Lemborexant 10 mg vs. placebo NNH (95% CI)	Pooled lemborexant vs. placebo NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Discontinuation because of an AE	13	314	4.1	26	314	8.3	12	319	3.8	265 (ns)	23 (13-122)	41 (ns)
Discontinuation because of AE somnolence	3	314	1.0	9	314	2.9	2	319	0.6	305 (ns)	45 (24-499)	78 (ns)
Discontinuation because of AE nightmare	1	314	0.3	4	314	1.3	0	319	0	314 (ns)	79 (40-2990)	126 (68-990)
AE somnolence	27	314	8.6	41	314	13.1	5	319	1.6	15 (10-28)	9 (7-14)	11 (9-16)
AE nasopharyngitis	30	314	9.6	29	314	9.2	40	319	12.5	ND	ND	ND
AE headache	28	314	8.9	21	314	6.7	21	319	6.6	43 (ns)	954 (ns)	82 (ns)
AE influenza	15	314	4.8	16	314	5.1	15	319	4.7	1336 (ns)	255 (ns)	428 (ns)
AE upper respiratory tract infection	13	314	4.1	11	314	3.5	10	319	3.1	100 (ns)	272 (ns)	146 (ns)
AE fatigue	12	314	3.8	11	314	3.5	1	319	0.3	29 (18-77)	32 (19-94)	30 (21-57)
AE back pain	12	314	3.8	9	314	2.9	8	319	2.5	77 (ns)	279 (ns)	120 (ns)
AE arthralgia	14	314	4.5	3	314	1.0	9	319	2.8	62 (ns)	ND	ND
AE urinary tract infection	4	314	1.3	9	314	2.9	7	319	2.2	ND	149 (ns)	ND
AE gastroenteritis	5	314	1.6	7	314	2.2	4	319	1.3	296 (ns)	103 (ns)	153 (ns)
AE nausea	8	314	2.5	4	314	1.3	3	319	0.9	63 (ns)	300 (ns)	104 (ns)
AE abnormal dreams	7	314	2.2	4	314	1.3	6	319	1.9	287 (ns)	ND	ND
AE nightmare	4	314	1.3	7	314	2.2	1	319	0.3	105 (ns)	53 (28-584)	70 (38-413)
AE fall	5	314	1.6	5	314	1.6	10	319	3.1	ND	ND	ND
AE dizziness	5	314	1.6	4	314	1.3	6	319	1.9	ND	ND	ND
AE weight increased	3	314	1.0	6	314	1.9	4	319	1.3	ND	153 (ns)	558 (ns)
AE oropharyngeal pain	5	314	1.6	3	314	1.0	1	319	0.3	79 (ns)	156 (ns)	105 (ns)
AE bronchitis	6	314	1.9	1	314	0.3	4	319	1.3	153 (ns)	ND	ND
AE diarrhea	2	314	0.6	5	314	1.6	5	319	1.6	ND	4007 (ns)	ND
AE osteoarthritis	5	314	1.6	2	314	0.6	3	319	0.9	154 (ns)	ND	574 (ns)
AE sinusitis	4	314	1.3	3	314	1.0	8	319	2.5	ND	ND	ND
AE viral upper respiratory tract infection	2	314	0.6	5	314	1.6	5	319	1.6	ND	4007 (ns)	ND
AE cough	4	314	1.3	2	314	0.6	0	319	0	79 (40-2990)	157 (ns)	105 (59-514)
AE hypertension	3	314	1.0	3	314	1.0	4	319	1.3	ND	ND	ND
AE increased appetite	3	314	1.0	3	314	1.0	1	319	0.3	156 (ns)	156 (ns)	156 (ns)
AE abdominal pain upper	2	314	0.6	3	314	1.0	2	319	0.6	10017 (ns)	305 (ns)	591 (ns)
AE alanine aminotransferase increased	3	314	1.0	2	314	0.6	1	319	0.3	156 (ns)	310 (ns)	208 (ns)
AE anxiety	4	314	1.3	1	314	0.3	3	319	0.9	300 (ns)	ND	ND

AE contusion	2	314	0.6	3	314	1.0	4	319	1.3	ND	ND	ND
AE dry mouth	2	314	0.6	3	314	1.0	1	319	0.3	310 (ns)	156 (ns)	208 (ns)
AE hyperhidrosis	3	314	1.0	2	314	0.6	1	319	0.3	156 (ns)	310 (ns)	208 (ns)
AE muscle spasms	4	314	1.3	1	314	0.3	1	319	0.3	105 (ns)	20034 (ns)	208 (ns)
AE musculoskeletal pain	1	314	0.3	4	314	1.3	0	319	0	314 (ns)	79 (40-2990)	126 (68-990)
AE neck pain	4	314	1.3	1	314	0.3	1	319	0.3	105 (ns)	20034 (ns)	208 (ns)
AE edema peripheral	5	314	1.6	0	314	0	2	319	0.6	104 (ns)	ND	591 (ns)
AE palpitations	2	314	0.6	3	314	1.0	1	319	0.3	310 (ns)	156 (ns)	208 (ns)
AE sleep paralysis	0	314	0	5	314	1.6	0	319	0	ND	63 (34-482)	126 (68-990)
AE vertigo	2	314	0.6	3	314	1.0	3	319	0.9	ND	6678 (ns)	ND
AE vomiting	1	314	0.3	4	314	1.3	0	319	0	314 (ns)	79 (40-2990)	126 (68-990)
AE abdominal pain	1	314	0.3	3	314	1.0	0	319	0	314 (ns)	105 (ns)	157 (80-6789)
AE pharyngitis	3	314	1.0	1	314	0.3	3	319	0.9	6678 (ns)	ND	ND
AE tachycardia	4	314	1.3	0	314	0	0	319	0	79 (40-2990)	ND	157 (80-6789)
AE blood triglyceride increased	3	314	1.0	0	314	0	2	319	0.6	305 (ns)	ND	ND
AE confusional state	0	314	0	3	314	1.0	0	319	0	ND	105 (ns)	210 (ns)
AE feeling abnormal	3	314	1.0	0	314	0	0	319	0	105 (ns)	ND	210 (ns)
AE head discomfort	0	314	0	3	314	1.0	0	319	0	ND	105 (ns)	210 (ns)
AE ligament sprain	0	314	0	3	314	1.0	1	319	0.3	ND	156 (ns)	609 (ns)
AE paresthesia	0	314	0	3	314	1.0	1	319	0.3	ND	156 (ns)	609 (ns)
AE tinnitus	0	314	0	3	314	1.0	0	319	0	ND	105 (ns)	210 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; ND: no difference; NNH: number needed to harm; ns: not significant

Supplementary Table 10. Indirect comparisons of NNHs vs. placebo (with 95% CIs) for lemborexant (Table 3) and zolpidem ER (Supplementary Table 7) from SUNRISE 1 and SUNRISE 2 (see also text), and for other hypnotics (Supplementary Tables 11-19), and where statistical significance was achieved. When NNH < 10, risk for the adverse event is considered higher, for NNH between 10-19 intermediate, and for ≥ 20 low. This is represented by red, yellow, and green highlighting, respectively. Note that dosing may mitigate some of the adverse event risk for somnolence and related events. Clinical interpretation is required when assessing the relevance of these adverse effects for an individual patient.

Agent	Outcome and dose	Corresponding NNH (95% CI)
Lemborexant	AE somnolence, 1 month, dose 5 mg, 10 mg, and pooled	28 (18-61), 15 (11-22), 19 (14-28)
	AE terms somnolence, lethargy, fatigue, sluggishness, 1 month, as reported in product label, dose 5 mg, 10 mg, and pooled	18 (13-31), 13 (10-18), 15 (12-20)
	AE nasopharyngitis, 1 month, dose 5 mg and pooled (ns for 10 mg)	56 (30-411), 78 (41-953)
	AE fatigue, 1 month, dose 5 mg, 10 mg, and pooled	49 (31-110), 65 (40-184), 56 (39-96)
	AE sleep paralysis, 1 month, dose 10 mg and pooled (ns for 5 mg)	117 (63-915), 194 (108-960)
	AE nausea, 1 month, 5 mg and pooled (ns for 10 mg)	84 (46-586), 119 (66-651)
	AE somnolence, 3 months, 1 month, 5 mg, 10 mg, and pooled	15 (10-28), 10 (7-15), 12 (9-17)
Suvorexant	AE somnolence, 3 months	28 (17-82)
Doxepin	AE somnolence or sedation, 4 or 12 weeks, 6 mg or when doses pooled (ns for 3 mg)	19 (10-127), 25 (13-341)
	AE hypertension, 4 or 12 weeks, 3 mg or when doses pooled (ns for 6 mg)	34 (18-302), 63 (35-339)
Ramelteon	All NNH outcomes ns	
Eszopiclone	*6 weeks, non-elderly*	
	AE anxiety, pooled 2 mg and 3 mg (ns for the individual doses)	53 (27-1776)
	AE depression, 2 mg or when doses pooled (ns for 3 mg)	26 (14-667), 42 (23-312)
	AE hallucinations, pooled 2 mg and 3 mg (ns for the individual doses)	53 (27-1776)
	AE somnolence, pooled 2 mg and 3 mg (ns for the individual doses)	18 (10-202)
	AE infection (respiratory system), 3 mg (ns for 2 mg or when doses pooled)	14 (7-147)
	AE unpleasant taste, 2 mg, 3 mg, or when doses pooled	7 (5-16), 4 (3-5), 5 (4-7)
	6 months, non-elderly, 3 mg only	
	Discontinuation because of an AE	31 (16-333)
	AE unpleasant taste	5 (5-6)
	AE infection	16 (11-35)
	AE somnolence	17 (13-27)
	AE pharyngitis	28 (17-83)
	2 weeks, elderly	
	AE dry mouth, 2 mg or when doses pooled (ns for 1 mg)	22 (12-126), 28 (15-246)
	AE unpleasant taste, 1 mg, 2 mg, or when doses pooled	13 (7-72), 9 (7-14), 10 (7-15)
	12 weeks, elderly, 2 mg only	
	AE unpleasant taste	10 (7-17)

Zaleplon	AE abdominal pain, 4 or 5 weeks, 5 or 10 mg, or when doses pooled (ns for 20 mg)	34 (18-292), 34 (19-167)
	AE amnesia, 4 or 5 weeks, 20 mg, or when doses pooled (ns for 5 or 10 mg mg)	34 (19-187), 60 (32-553)
	AE paresthesia, 4 or 5 weeks, 5 or 10 mg, or when doses pooled (ns for 20 mg)	50 (27-404), 50 (29-222)
	AE ear pain, 4 or 5 weeks, when doses pooled (ns for 5 or 10 mg, or 20 mg)	149 (83-785)
Zolpidem IR ≤ 10 mg	*Up to 10 nights*	
	AE drowsiness	50 (33-106)
	AE dizziness	50 (33-106)
	AE diarrhea	100 (58-393)
	4 or 5 weeks	
	AE dizziness	25 (13-478)
	AE drugged feeling	34 (18-348)
Zolpidem ER	*30 days, 6.25 mg (from SUNRISE 1)*	
	AE fatigue	66 (34-2393)
	AE anxiety	53 (29-399)
	AE hypertriglyceridemia	66 (34-2393)
	3 weeks, 12.5 mg (all ns for 6.25 mg)	
	AE nervous system disorders	6 (4-17)
	AE eye disorders	17 (9-416)
	AE somnolence	8 (5-18)
	6 months, 12.5 mg	
	Discontinuation because of an AE	28 (15-164)
	AE anxiety	27 (17-82)
	AE somnolence	28 (17-73)
	AE dizziness	36 (21-170)
	AE disturbance in attention	39 (22-180)
	AE sinusitis	42 (25-131)
Triazolam	AE drowsiness	14 (10-21)
	AE dizziness	22 (15-37)
	AE light-headedness	25 (19-40)
	AE coordination disorders/ataxia	27 (20-42)
Temazepam	AE drowsiness	29 (18-88)
	AE hangover	72 (39-465)
	AE euphoria	91 (52-401)

Abbreviations
AE: adverse event; CI: confidence interval; ER: extended release; IR: immediate release; NNH: number needed to harm; ns: not significant

Supplementary Table 11. Suvorexant 15 or 20 mg efficacy (NNT) and tolerability (NNH) outcomes. Data taken from (9, 10, 12, 36). Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Suvorexant			Placebo			NNT or NNH (95%CI)
	n	N	%	n	N	%	
Efficacy							
Week 1							
sTST responder, defined as ≥ 15% improvement in mean sTST	150	479	31.3	145	740	19.6	9 (6-15)
sSOL responder, defined as ≥ 15% improvement in mean sSOL	267	479	55.7	316	740	42.7	8 (6-14)
sWASO responder, defined as ≥ 15% improvement in mean sWASO	267	474	56.3	350	729	48.0	12 (8-39)
Month 1							
sTST responder, defined as ≥ 15% improvement in mean sTST	197	463	42.5	210	715	29.4	8 (6-14)
sSOL responder, defined as ≥ 15% improvement in mean sSOL	289	463	62.4	384	715	53.7	12 (7-34)
sWASO responder, defined as ≥ 15% improvement in mean sWASO	307	457	67.2	414	704	58.8	12 (8-37)
ISI with a ≥ 6-point improvement (clinically relevant improvement)	149	440	33.9	157	685	22.9	10 (7-19)
Month 3							
sTST responder, defined as ≥ 15% improvement in mean sTST	213	425	50.1	278	664	41.9	13 (7-46)
sSOL responder, defined as ≥ 15% improvement in mean sSOL	297	425	69.9	438	664	66.0	26 (ns)
sWASO responder, defined as ≥ 15% improvement in mean sWASO	322	425	75.8	458	660	69.4	16 (9-102)
ISI with a ≥ 6-point improvement (clinically relevant improvement)	228	411	55.5	269	638	42.2	8 (6-14)
Tolerability (3 months)							
Discontinuation because of an AE	15	493	3.0	50	1025	4.9	ND
AE somnolence	33	493	6.7	31	1025	3.0	28 (17-82)
AE headache	36	493	7.3	61	1025	6.0	74 (ns)
AE diarrhea	12	493	2.4	15	1025	1.5	103 (ns)
AE dry mouth	9	493	1.8	14	1025	1.4	218 (ns)
AE upper respiratory tract infection	8	493	1.6	12	1025	1.2	222 (ns)
AE dizziness	15	493	3.0	29	1025	2.8	469 (ns)
AE abnormal dreams	9	493	1.8	10	1025	1.0	118 (ns)
AE cough	10	493	2.0	8	767	1.0	102 (ns)
Suicidal ideation as assessed by scale	1	493	0.2	1	767	0.1	1320 (ns)
AE excessive daytime sleepiness	3	493	0.6	1	767	0.1	208 (ns)
AE falls	5	493	1.0	7	767	0.9	802 (ns)

AE complex sleep-related behaviors	0	493	0	0	767	0	ND
AE hypnagogic or hypnopompic hallucinations	2	493	0.4	0	767	0	247 (ns)
AE cataplexy	0	493	0	0	767	0	ND
AE sleep paralysis	1	493	0.2	0	767	0	493 (ns)
AE sleep onset paralysis (adjudicated)	0	493	0	0	767	0	ND
AEs with potential for abuse liability (depersonalization, derealization, dissociation, euphoric mood, hallucination, mania, and potential trial medication misuse)	20	493	4.1	19	767	2.5	61 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; ISI: Insomnia Severity Index; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; NNT: number needed to treat; ns: not significant; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset

Supplementary Table 12. Doxepin 3 mg and 6 mg efficacy (NNT) and tolerability (NNH) outcomes. Data taken from (13, 19, 28, 29, 39). Patient Global Impression items data estimated from the provided graph in the relevant published papers where these data were available (28, 29). Numerators were calculated using the percentages displayed on the graphs and using study population randomized as the denominator. Discontinuation because of an adverse event was calculated from the study reports of three randomized parallel group long-term studies (28, 29, 39), estimating the numerators when only the percentages are provided, and pooled. Sedation/somnolence numerators available from the drug approval package (13). Remainder of adverse events are from product labeling (19) and numerators were estimated with the percentages provided. Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold.

Outcome	Doxepin 3 mg			Doxepin 6 mg			Placebo			Doxepin 3 mg vs. placebo NNT or NNH (95% CI)	Doxepin 6 mg vs. placebo NNT or NNH (95% CI)	Pooled doxepin vs. placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Efficacy - Study (28), 3 months												
PGI helped sleep, Week 12	~61	82	74	NA	NA	NA	~33	81	40	**3 (3-6)**	NA	NA
PGI shortened onset, Week 12	~53	82	64	NA	NA	NA	~30	81	37	**4 (3-8)**	NA	NA
PGI increased duration, Week 12	~56	82	68	NA	NA	NA	~29	81	36	**4 (3-6)**	NA	NA
PGI got better sleep, Week 12	~61	82	74	NA	NA	NA	~33	81	40	**3 (3-6)**	NA	NA
PGI drug strength just right, Week 12	~44	82	54	NA	NA	NA	~23	81	29	**4 (3-10)**	NA	NA
Efficacy - Study (29), 1 month												
PGI helped sleep, Week 4	NA	NA	NA	~72	130	55	~47	124	38	NA	**6 (4-19)**	NA
PGI shortened onset, Week 4	NA	NA	NA	~63	130	48	~44	124	35	NA	**8 (4-106)**	NA
PGI increased duration, Week 4	NA	NA	NA	~59	130	46	~45	124	36	NA	11 (ns)	NA
PGI got better sleep, Week 4	NA	NA	NA	~70	130	54	~53	124	43	NA	9 (ns)	NA
PGI drug strength just right, Week 4	NA	NA	NA	~58	130	45	~37	124	30	NA	**7 (4-33)**	NA
Tolerability for the longer-term studies combined (28 to 85 days)												
Discontinuation because of an AE	~6	159	3.5	~4	206	2.0	~5	281	1.9	61 (ns)	1038 (ns)	130 (ns)
AE somnolence or sedation	10	157	6.4	20	203	9.9	12	278	4.3	49 (ns)	**19 (10-127)**	**25 (13-341)**
AE upper respiratory tract infection/nasopharyngitis	~6	157	4	~4	203	2	~6	278	2	50 (ns)	ND	115 (ns)
AE gastroenteritis	~3	157	2	0	203	0	0	278	0	50 (ns)	ND	115 (ns)
AE nausea	~3	157	2	~4	203	2	~3	278	1	100 (ns)	100 (ns)	100 (ns)
AE hypertension	~5	157	3	1	203	<1	0	278	0	**34 (18-302)**	203 (ns)	**63 (35-339)**

Abbreviations
AE: adverse event; CI: confidence interval; NA: not applicable; ND: no difference; NNH: number needed to harm; NNT: number needed to treat; ns: not significant; PGI-I: Patient Global Impression

Supplementary Table 13. Ramelteon 8 mg efficacy (NNT) and tolerability (NNH) outcomes. Data taken from (14, 20, 35). Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold. Efficacy data from report of a post hoc analysis for decrease ≥ 50% on LPS (35) and from the drug approval package for LPS ≤ 30 minutes (14); in the latter, the FDA re-analyzed the categorical data to include all drop-outs as a non-responder. Discontinuation rates because of an adverse event from the drug approval package (14) describing pooled results from 5 placebo-controlled chronic insomnia studies; data for ramelteon 8 mg shown. Adverse events are from product labeling (20) and numerators were estimated with the percentages provided.

Outcome	Ramelteon 8 mg			Placebo			Ramelteon 8 mg vs. placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	
Efficacy, 5 weeks							
LPS responder, defined as a decrease of ≥ 50% from baseline, Week 5	91	138	65.9	64	131	48.9	6 (4-19)
LPS responder, defined as LPS ≤ 30 minutes, Week 5, Study TL-021	90	138	65.2	69	131	52.7	8 (5-115)
LPS responder, defined as LPS ≤ 30 minutes, Week 5, Study TL-021, FDA re-analysis	82	139	59.0	66	131	50.4	12 (ns)
LPS responder, defined as LPS ≤ 30 minutes, Week 5, Study TL-025	81	273	29.7	71	274	25.9	27 (ns)
LPS responder, defined as LPS ≤ 30 minutes, Week 5, Study TL-025, FDA re-analysis	69	274	25.2	60	274	21.9	31 (ns)
LPS responder, defined as LPS ≤ 30 minutes, Week 5, Study TL-023	91	98	92.9	83	97	85.6	14 (ns)
Tolerability (duration not specified)							
Discontinuation because of an AE	18	741	2.4	17	750	2.3	616 (ns)
AE somnolence	~42	1405	3	~29	1456	2	100 (ns)
AE fatigue	~42	1405	3	~29	1456	2	100 (ns)
AE dizziness	~56	1405	4	~44	1456	3	100 (ns)
AE nausea	~42	1405	3	~29	1456	2	100 (ns)
AE insomnia exacerbated	~42	1405	3	~29	1456	2	100 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; FDA: Food and Drug Administration; LPS: latency to persistent sleep; NNH: number needed to harm; NNT: number needed to treat; ns: not significant

Supplementary Table 14. Eszopiclone efficacy (NNT) and tolerability (NNH) outcomes.

Table 14a. Nonelderly adults. Data taken from (15, 21, 30, 31, 40, 41). Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold. Efficacy data from (30), with numerators calculated from the percentages provided; this study is not described in the product label. The product label (21) provides adverse events from the 6-week trial (40) and the numerators can be found in the drug approval package (15); the published paper provided the discontinuation rates due to an adverse event. Data for 6-month tolerability is pooled from 2 study reports where frequency for an AE was > 5% in both studies (30, 41).

Outcome	Eszopiclone 2 mg			Eszopiclone 3 mg			Placebo			Eszopiclone 2 mg vs. placebo NNT or NNH (95% CI)	Eszopiclone 3 mg vs. placebo NNT or NNH (95% CI)	Pooled eszopiclone vs. placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Efficacy, 6 months												
ISI ≤ 7 (no insomnia), 6 months	NA	NA	NA	~272	548	49.7	~52	280	18.7	NA	4 (3-4)	NA
ISI ≤ 14 (no or subthreshold insomnia), 6 months	NA	NA	NA	~456	548	83.3	~172	280	61.3	NA	5 (4-7)	NA
Tolerability, 6 Weeks												
Discontinuation because of an AE	3	104	2.9	0	105	0	0	99	0	35 (ns)	ND	70 (ns)
AE headache	22	104	21.2	18	105	17.1	13	99	13.1	13 (ns)	25 (ns)	17 (ns)
AE viral infection	3	104	2.9	3	105	2.9	1	99	1.0	54 (ns)	55 (ns)	54 (ns)
AE dry mouth	5	104	4.8	7	105	6.7	3	99	3.0	57 (ns)	28 (ns)	37 (ns)
AE dyspepsia	4	104	3.8	5	105	4.8	4	99	4.0	ND	139 (ns)	377 (ns)
AE nausea	5	104	4.8	4	105	3.8	4	99	4.0	131 (ns)	ND	377 (ns)
AE vomiting	3	104	2.9	0	105	0	1	99	1.0	54 (ns)	ND	236 (ns)
AE anxiety	3	104	2.9	1	105	1.0	0	99	0	35 (ns)	105 (ns)	53 (27-1776)
AE confusion	0	104	0	3	105	2.9	0	99	0	ND	35 (ns)	70 (ns)
AE depression	4	104	3.8	1	105	1.0	0	99	0	26 (14-667)	105 (ns)	42 (23-312)
AE dizziness	5	104	4.8	7	105	6.7	4	99	4.0	131 (ns)	39 (ns)	59 (ns)
AE hallucinations	1	104	1.0	3	105	2.9	0	99	0	104 (ns)	35 (ns)	53 (27-1776)
AE libido decreased	0	104	0	3	105	2.9	0	99	0	ND	35 (ns)	70 (ns)
AE nervousness	5	104	4.8	0	105	0	3	99	3.0	57 (ns)	ND	ND
AE somnolence	10	104	9.6	8	105	7.8	3	99	3.0	16 (ns)	22 (ns)	18 (10-202)
AE infection (respiratory system)	5	104	4.8	11	105	10.5	3	99	3.0	57 (ns)	14 (7-147)	22 (ns)
AE rash	3	104	2.9	4	105	3.8	1	99	1.0	54 (ns)	36 (ns)	43 (ns)
AE unpleasant taste	18	104	17.3	36	105	34.3	3	99	3.0	7 (5-16)	4 (3-5)	5 (4-7)
AE dysmenorrhea (women)	2	77	2.6	0	66	0	0	56	0	39 (ns)	ND	72 (ns)
AE gynecomastia (men)	1	38	2.6	0	28	0	0	43	0	38 (ns)	ND	66 (ns)
Tolerability, 6 Months												

Discontinuation because of an AE	NA	NA	NA	124	1141	10.9	36	475	7.6	NA	31 (16-333)	NA
AE unpleasant taste	NA	NA	NA	263	1141	23.0	14	475	2.9	NA	5 (5-6)	NA
AE infection	NA	NA	NA	185	1141	16.2	47	475	9.9	NA	16 (11-35)	NA
AE headache	NA	NA	NA	199	1141	17.4	79	475	16.6	NA	124 (ns)	NA
AE pain	NA	NA	NA	115	1141	10.1	41	475	8.6	NA	70 (ns)	NA
AE somnolence	NA	NA	NA	102	1141	8.9	14	475	2.9	NA	17 (13-27)	NA
AE pharyngitis	NA	NA	NA	92	1141	8.1	21	475	4.4	NA	28 (17-83)	NA
AE dyspepsia	NA	NA	NA	75	1141	6.6	28	475	5.9	NA	148 (ns)	NA
AE back pain	NA	NA	NA	74	1141	6.5	26	475	5.5	NA	99 (ns)	NA
AE accidental injury	NA	NA	NA	70	1141	6.1	28	475	5.9	NA	417 (ns)	NA

Abbreviations
AE: adverse event; CI: confidence interval; ISI: Insomnia Severity Index; NA: not applicable; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; NNT: number needed to treat; ns: not significant

Table 14b. Elderly adults. Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold. Efficacy data from (31), with numerators calculated from the percentages provided; this study is not described in the product label. The product label (21) provides adverse events from the 2 week studies and the numerators can be found in the drug approval package (15) except for headache for the 2 mg and placebo groups (for these, numerators were calculated from the percentages provided). Data for 12-week tolerability is from the published report (31) and the numerators were calculated from the percentages provided.

Outcome	Eszopiclone 1 mg			Eszopiclone 2 mg			Placebo			Eszopiclone 1 mg vs. placebo NNT or NNH (95% CI)	Eszopiclone 2 mg vs. placebo NNT or NNH (95% CI)	Pooled eszopiclone vs. placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Efficacy, 12 weeks												
ISI ≤ 7 (no insomnia), 12 weeks	NA	NA	NA	~71	194	36.8	~47	194	24.4	NA	9 (5-31)	NA
ISI ≤ 14 (no or subthreshold insomnia), 12 weeks	NA	NA	NA	~151	194	78.0	~119	194	61.1	NA	6 (4-13)	NA
Tolerability, 2 Weeks												
Discontinuation because of an AE	1	72	1.4	5	215	2.3	8	208	3.8	ND	ND	ND
AE accidental injury	0	72	0	6	215	2.8	2	208	1.0	ND	55 (ns)	89 (ns)
AE headache	11	72	15.3	~28	215	13	~29	208	14	79 (ns)	ND	ND
AE pain	3	72	4.2	10	215	4.7	4	208	1.9	45 (ns)	37 (ns)	39 (ns)
AE diarrhea	3	72	4.2	5	215	2.3	5	208	2.4	57 (ns)	ND	261 (ns)
AE dry mouth	2	72	2.8	14	215	6.5	4	208	1.9	117 (ns)	22 (12-126)	28 (15-246)
AE dyspepsia	4	72	5.6	4	215	1.9	5	208	2.4	32 (ns)	ND	261 (ns)
AE abnormal dreams	2	72	2.8	2	215	0.9	1	208	0.5	44 (ns)	223 (ns)	110 (ns)
AE dizziness	1	72	1.4	12	215	5.6	5	208	2.4	ND	32 (ns)	47 (ns)
AE nervousness	0	72	0	5	215	2.3	3	208	1.4	ND	114 (ns)	334 (ns)
AE neuralgia	2	72	2.8	0	215	0	0	208	0	36 (ns)	ND	144 (ns)
AE pruritis	3	72	4.2	3	215	1.4	3	208	1.4	37 (ns)	ND	155 (ns)
AE unpleasant taste	6	72	8.3	26	215	12.1	1	208	0.5	13 (7-72)	9 (7-14)	10 (7-15)
AE urinary tract infection	2	72	2.8	0	215	0	1	208	0.5	44 (ns)	ND	463 (ns)
Tolerability, 12 weeks												
Discontinuation because of an AE	NA	NA	NA	14	194	7.2	9	194	4.6	NA	39 (ns)	NA
AE headache	NA	NA	NA	27	194	13.9	24	194	12.4	NA	65 (ns)	NA
AE unpleasant taste	NA	NA	NA	24	194	12.4	3	194	1.5	NA	10 (7-17)	NA
AE nasopharyngitis	NA	NA	NA	11	194	5.7	12	194	6.2	NA	ND	NA
AE dizziness	NA	NA	NA	8	194	4.1	3	194	1.5	NA	39 (ns)	NA
AE falls	NA	NA	NA	2	194	1.0	1	194	0.5	NA	194 (ns)	NA
AE hallucinations	NA	NA	NA	1	194	0.5	0	194	0	NA	194 (ns)	NA
AE memory impairment	NA	NA	NA	2	194	1.0	0	194	0	NA	97 (ns)	NA

AE attention disturbance	NA	NA	NA	1	194	0.5	0	194	0	NA	194 (ns)	NA
AE nervousness	NA	NA	NA	3	194	1.5	0	194	0	NA	65 (ns)	NA
AE anxiety	NA	NA	NA	4	194	2.1	2	194	1.0	NA	97 (ns)	NA

Abbreviations
AE: adverse event; CI: confidence interval; ISI: Insomnia Severity Index; NA: not applicable; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; NNT: number needed to treat; ns: not significant

Supplementary Table 15. Zaleplon tolerability (NNH) outcomes. Data taken from (22). Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold. The product label (22) provides adverse events from long-term (28 and 35 days) placebo-controlled clinical trials studies and the numerators were calculated from the percentages provided. When occurrence is < 1%, an estimate of 0.5% was used.

Outcome	Zaleplon 5 or 10 mg			Zaleplon 20 mg			Placebo			Zaleplon 5 or 10 mg vs. placebo NNH (95% CI)	Zaleplon 20 mg vs. placebo NNH (95% CI)	Pooled zaleplon vs. placebo NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Tolerability, 4 or 5 weeks												
Discontinuation because of an AE	3.1% of 744 patients who received placebo and 3.7% of 2,149 patients who received zaleplon (any dose) discontinued treatment because of an AE, NNH=167 (ns)											
AE abdominal pain	~34	569	6	~18	297	6	~10	344	3	**34 (18-292)**	34 (ns)	**34 (19-167)**
AE asthenia	~28	569	5	~21	297	7	~17	344	5	ND	50 (ns)	146 (ns)
AE headache	~171	569	30	~125	297	42	~120	344	35	ND	15 (ns)	ND
AE malaise	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE photosensitivity reaction	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE anorexia	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE colitis	0	569	0	~3	297	1	0	344	0	ND	100 (ns)	292 (ns)
AE nausea	~34	569	6	~24	297	8	~24	344	7	ND	100 (ns)	ND
AE peripheral edema	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE amnesia	~11	569	2	~12	297	4	~3	344	1	100 (ns)	**34 (19-187)**	**60 (32-553)**
AE confusion	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE depersonalization	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE dizziness	~40	569	7	~27	297	9	~24	344	7	ND	50 (ns)	146 (ns)
AE hallucinations	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE hypertonia	~6	569	1	~3	297	1	~2	344	<1	200 (ns)	200 (ns)	200 (ns)
AE hyperesthesia	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE paresthesia	~17	569	3	~9	297	3	~3	344	1	**50 (27-404)**	50 (ns)	**50 (29-222)**
AE somnolence	~28	569	5	~18	297	6	~14	344	4	100 (ns)	50 (ns)	75 (ns)
AE tremor	~11	569	2	~6	297	2	~3	344	1	100 (ns)	100 (ns)	100 (ns)
AE vertigo	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE epistaxis	~3	569	<1	~3	297	1	~2	344	<1	ND	200 (ns)	584 (ns)
AE abnormal vision	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE ear pain	~3	569	<1	~3	297	1	0	344	0	200 (ns)	100 (ns)	**149 (83-785)**
AE eye pain	~23	569	4	~9	297	3	~7	344	2	50 (ns)	100 (ns)	61 (ns)
AE hyperacusis	~6	569	1	~6	297	2	~2	344	<1	200 (ns)	67 (ns)	119 (ns)
AE parosmia	~3	569	<1	~6	297	2	~2	344	<1	ND	67 (ns)	195 (ns)
AE dysmenorrhea	NC	NA	3	NC	NA	4	NC	NA	2	100 (NC)	50 (NC)	NC

Abbreviations
AE: adverse event; CI: confidence interval; NA: not available; NC: 95% CI not calculable as no denominator provided; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; ns: not significant

Supplementary Table 16. Zolpidem immediate release (IR) efficacy (NNT) and tolerability (NNH) outcomes. Data taken from (23, 34). Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold. Efficacy outcomes come from a 7 to 10-night study (34); numerators were calculated using the percentages provided. The product label (23) includes adverse events from placebo-controlled clinical trials lasting up to 10 nights and up to 35 days; the numerators were calculated from the percentages provided.

Outcome	Zolpidem IR **≤ 10 mg**			Placebo			Zolpidem IR **≤ 10 mg vs.** placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	
Efficacy (7-10 days)							
CGI excellent or good quality of sleep, 7-10 days	53	68	78	28	67	42	3 (2-5)
CGI sleep improved a lot or somewhat, 7-10 days	57	68	84	32	67	48	3 (2-5)
CGI shorter time to fall asleep, 7-10 days	55	68	81	28	67	42	3 (2-5)
CGI increase in amount of sleep, 7-10 days	54	68	79	29	67	43	3 (2-5)
CGI medication strength just right, 7-10 days	42	68	62	19	67	28	3 (2-6)
CGI posttreatment sleep much or somewhat better, 7-10 days	51	68	75	27	67	40	3 (2-6)
Tolerability							
Clinical trials lasting up to 10 nights							
Discontinuation because of an AE	NA	NA	NA	NA	NA	NA	NA
AE headache	~48	685	7	~28	473	6	100 (ns)
AE drowsiness	~14	685	2	0	473	0	**50 (33-106)**
AE dizziness	~14	685	2	0	473	0	**50 (33-106)**
AE diarrhea	~7	685	1	0	473	0	100 (58-393)
Clinical trials lasting 28 to 35 nights							
Discontinuation because of an AE	NA	NA	NA	NA	NA	NA	NA
AE dry mouth	~5	152	3	~2	161	1	50 (ns)
AE allergy	~6	152	4	~2	161	1	34 (ns)
AE back pain	~5	152	3	~3	161	2	100 (ns)
AE influenza-like symptoms	~3	152	2	0	161	0	50 (ns)
AE chest pain	~2	152	1	0	161	0	100 (ns)
AE palpitation	~3	152	2	0	161	0	50 (ns)
AE drowsiness	~12	152	8	~8	161	5	34 (ns)
AE dizziness	~8	152	5	~2	161	1	**25 (13-478)**
AE lethargy	~5	152	3	~2	161	1	50 (ns)
AE drugged feeling	~5	152	3	0	161	0	**34 (18-348)**
AE lightheadedness	~3	152	2	~2	161	1	100 (ns)
AE depression	~3	152	2	~2	161	1	100 (ns)
AE abnormal dreams	~2	152	1	~0	161	0	100 (ns)

AE amnesia	~2	152	1	0	161	0	100 (ns)
AE sleep disorder	~2	152	1	0	161	0	100 (ns)
AE diarrhea	~5	152	3	~3	161	2	100 (ns)
AE abdominal pain	~3	152	2	~3	161	2	ND
AE constipation	~3	152	2	~2	161	1	100 (ns)
AE sinusitis	~6	152	4	~3	161	2	50 (ns)
AE pharyngitis	~5	152	3	~2	161	1	50 (ns)
AE rash	~3	152	2	~2	161	1	100 (ns)

Abbreviations
AE: adverse event; CGI: Clinical Global Impression rated by the patient (thus similar to a Patient Global Impression); CI: confidence interval; NA: not available; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; ns: not significant

Supplementary Table 17. Zolpidem extended release (ER) efficacy (NNT) and tolerability (NNH) outcomes. Data taken from (24, 32, 33, 42). Results for the NNT or NNH are bolded when statistical significance is achieved at the P < .05 threshold. Efficacy outcomes come from (32, 33, 42) and numerators are calculated using the percentages reported and using study population randomized as the denominator. For (42) numerators were calculated using the percentages displayed on the graphs The product label (24) includes adverse events from two 3-week placebo-controlled clinical trials, both of which have been published (33, 42) and for one of the studies (33) the AEs reported contain both numerators and denominators and although limited to AEs with an incidence of ≥ 5% in the zolpidem ER group, these data were more precise than the rounded percentages provided in the label for all AEs with an incidence ≥ 1% in the zolpidem ER group and greater than that seen with placebo. For the second study (42), percentages are reported in the paper but are a subset of what is contained in the product label; threshold of ≥ 2% is used for this table and the numerators are estimated using the percentages provided. 6-month AE data are from (32).

Outcome	Zolpidem ER 6.25 mg			Zolpidem ER 12.5 mg			Placebo			Zolpidem ER 6.25 mg vs. placebo NNT or NNH (95% CI)	Zolpidem ER 12.5 mg vs. placebo NNT or NNH (95% CI)
	n	N	%	n	N	%	n	N	%		
Efficacy - Study (33)											
PGI helped sleep, Week 3	NA	NA	NA	~80	102	78.7	~43	110	39.4	NA	3 (2-4)
PGI shortened onset, Week 3	NA	NA	NA	~73	102	71.3	~38	110	34.3	NA	3 (2-5)
PGI increased duration, Week 3	NA	NA	NA	~72	102	70.2	~43	110	39.4	NA	4 (3-6)
Efficacy - Study (42)											
PGI helped sleep, Week 3	~67	99	68.1	NA	NA	NA	~56	106	52.9	7 (4-51)	NA
PGI shortened onset, Week 3	~53	99	53.2	NA	NA	NA	~41	106	38.5	7 (4-84)	NA
PGI increased duration, Week 3	~62	99	62.8	NA	NA	NA	~43	106	40.4	5 (3-11)	NA
PGI drug strength just right, Week 3	~52	99	52.1	NA	NA	NA	~40	106	37.9	7 (4-142)	NA
Efficacy - Study (32)											
PGI helped sleep, Month 1	NA	NA	NA	~572	669	85.5	~130	349	37	NA	3 (2-3)
PGI shortened onset, Month 1	NA	NA	NA	~461	669	69	~106	349	30	NA	3 (3-4)
PGI increased duration, Month 1	NA	NA	NA	~536	669	80	~126	349	36	NA	3 (2-3)
PGI drug strength just right, Month 1	NA	NA	NA	~437	669	65	~99	349	28	NA	3 (3-4)
CGI much or very much improved, Month 1	NA	NA	NA	~444	669	66	~84	349	24	NA	3 (3-3)
PGI helped sleep, Month 3	NA	NA	NA	~605	669	90.5	~191	349	55	NA	3 (3-4)
PGI shortened onset, Month 3	NA	NA	NA	~477	669	71	~150	349	43	NA	4 (3-5)
PGI increased duration, Month 3	NA	NA	NA	~561	669	84	~169	349	48	NA	3 (3-4)
PGI drug strength just right, Month 3	NA	NA	NA	~477	669	71	~151	349	43	NA	4 (3-5)
CGI much or very much improved, Month 3	NA	NA	NA	~523	669	78	~139	349	40	NA	3 (3-4)
PGI helped sleep, Month 6	NA	NA	NA	~616	669	92	~209	349	60	NA	4 (3-4)
PGI shortened onset, Month 6	NA	NA	NA	~521	669	78	~172	349	49	NA	4 (3-5)
PGI increased duration, Month 6	NA	NA	NA	~578	669	86	~192	349	55	NA	4 (3-4)

PGI drug strength just right, Month 6	NA	NA	NA	~500	669	75	~179	349	51	NA	5 (4-6)
CGI much or very much improved, Month 6	NA	NA	NA	~561	669	84	~168	349	48	NA	3 (3-4)
Tolerability – Study (33), 3 weeks											
Discontinuation because of an AE	NA	NA	NA	6	102	5.9	2	110	1.8	NA	25 (ns)
AE nervous system disorders	NA	NA	NA	41	102	40.2	24	110	21.8	NA	6 (4-17)
AE psychiatric disorders	NA	NA	NA	18	102	17.6	11	110	10.0	NA	14 (ns)
AE gastrointestinal disorders	NA	NA	NA	12	102	11.8	14	110	12.7	NA	ND
AE musculoskeletal and connective tissue disorders	NA	NA	NA	11	102	10.8	7	110	6.4	NA	23 (ns)
AE eye disorders	NA	NA	NA	8	102	7.8	2	110	1.8	NA	17 (9-416)
AE general disorders, administration site conditions	NA	NA	NA	7	102	6.9	7	110	6.4	NA	201 (ns)
AE headache	NA	NA	NA	19	102	18.6	18	110	16.4	NA	45 (ns)
AE somnolence	NA	NA	NA	15	102	14.7	2	110	1.8	NA	8 (5-18)
AE dizziness	NA	NA	NA	12	102	11.8	6	110	5.5	NA	16 (ns)
AE nausea	NA	NA	NA	7	102	6.9	4	110	3.6	NA	31 (ns)
Tolerability – Study (42), 3 weeks											
Discontinuation because of an AE	1	99	1	NA	NA	NA	0	106	0	99 (ns)	NA
AE headache	14	99	14	NA	NA	NA	12	106	11	36 (ns)	NA
AE dizziness	8	99	8	NA	NA	NA	3	106	3	19 (ns)	NA
AE somnolence	6	99	6	NA	NA	NA	5	106	5	75 (ns)	NA
AE nasopharyngitis	6	99	6	NA	NA	NA	4	106	4	44 (ns)	NA
AE anxiety	3	99	3	NA	NA	NA	2	106	2	88 (ns)	NA
AE psychomotor retardation	2	99	2	NA	NA	NA	0	106	0	50 (ns)	NA
AE palpitations	2	99	2	NA	NA	NA	0	106	0	50 (ns)	NA
AE arthralgia	2	99	2	NA	NA	NA	0	106	0	50 (ns)	NA
AE muscle cramp	2	99	2	NA	NA	NA	1	106	1	93 (ns)	NA
AE neck pain	2	99	2	NA	NA	NA	0	106	0	50 (ns)	NA
Tolerability – Study (32), 6 months											
Discontinuation because of an AE	NA	NA	NA	55	669	8.2	16	349	4.6	NA	28 (15-164)
AE headache	NA	NA	NA	70	669	10.5	33	349	9.5	NA	100 (ns)
AE anxiety	NA	NA	NA	42	669	6.3	9	349	2.6	NA	27 (17-82)
AE somnolence	NA	NA	NA	38	669	5.7	7	349	2.0	NA	28 (17-73)
AE dizziness	NA	NA	NA	32	669	4.8	7	349	2.0	NA	36 (21-170)
AE fatigue	NA	NA	NA	30	669	4.5	11	349	3.2	NA	76 (ns)
AE disturbance in attention	NA	NA	NA	29	669	4.3	6	349	1.7	NA	39 (22-180)
AE irritability	NA	NA	NA	25	669	3.7	10	349	2.9	NA	115 (ns)
AE nausea	NA	NA	NA	23	669	3.4	8	349	2.3	NA	88 (ns)

AE sinusitis	NA	NA	NA	22	669	3.3	3	349	0.9	NA	42 (25-131)

Abbreviations
AE: adverse event; CGI: Clinical Global Impression); CI: confidence interval; NA: not applicable; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; ns: not significant; PGI: Patient Global Impression)

Supplementary Table 18. Triazolam tolerability (NNH) outcomes. Data taken from (25). Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold. The product label (25) includes adverse events from placebo-controlled clinical trials lasting 1 to 42 days; the numerators were calculated from the percentages provided. The recommended dosage is 0.25 mg once daily before bedtime. A dosage of 0.125 mg once daily may be sufficient for some patients (e.g., patients with low body weight). A dosage of 0.5 mg should be used only for patients who do not respond adequately to a trial of a lower dose. The maximum recommended dosage is 0.5 mg once daily. Elderly patients have an increased risk of dose-related adverse reactions and thus in geriatric patients, the recommended dosage is 0.125 mg to 0.25 mg once daily.

Outcome	Triazolam (all doses)			Placebo			Triazolam vs. placebo NNH (95% CI)
	n	N	%	n	N	%	
Tolerability, 1 to 42 days							
Discontinuation because of an AE	NA	1003	NA	NA	997	NA	NA
AE drowsiness	~140	1003	14.0	~64	997	6.4	14 (10-21)
AE headache	~97	1003	9.7	~84	997	8.4	77 (ns)
AE dizziness	~79	1003	7.8	~31	997	3.1	22 (15-37)
AE nervousness	~52	1003	5.2	~45	997	4.5	143 (ns)
AE light-headedness	~49	1003	4.9	~9	997	0.9	25 (19-40)
AE coordination disorders/ataxia	~46	1003	4.6	~8	997	0.8	27 (20-42)
AE nausea/vomiting	~46	1003	4.6	~37	997	3.7	112 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; NA: not available; NNH: number needed to harm; ns: not significant

Supplementary Table 19. Temazepam tolerability (NNH) outcomes. Data taken from (26). Results for the NNH are bolded when statistical significance is achieved at the P < .05 threshold. The product label (26) includes adverse events from placebo-controlled clinical trials; the numerators were calculated from the percentages provided. The clinical trials performed in support of efficacy were 2 weeks in duration with the final formal assessment of sleep latency performed at the end of treatment. While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients, and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency. In elderly or debilitated patients, it is recommended that therapy be initiated with 7.5 mg until individual responses are determined.

Outcome	Temazepam (all doses)			Placebo			Temazepam vs. placebo NNH (95% CI)
	n	N	%	n	N	%	
Tolerability (duration not specified)							
Discontinuation because of an AE	NA	1076	NA	NA	783	NA	NA
AE drowsiness	~98	1076	9.1	~44	783	5.6	**29 (18-88)**
AE headache	~91	1076	8.5	~71	783	9.1	ND
AE fatigue	~52	1076	4.8	~37	783	4.7	1000 (ns)
AE nervousness	~49	1076	4.6	~64	783	8.2	ND
AE lethargy	~48	1076	4.5	~27	783	3.4	91 (ns)
AE dizziness	~48	1076	4.5	~26	783	3.3	84 (ns)
AE nausea	~33	1076	3.1	~30	783	3.8	ND
AE hangover	~27	1076	2.5	~9	783	1.1	**72 (39-465)**
AE anxiety	~22	1076	2.0	~12	783	1.5	200 (ns)
AE depression	~18	1076	1.7	~14	783	1.8	ND
AE dry mouth	~18	1076	1.7	~17	783	2.2	ND
AE diarrhea	~18	1076	1.7	~9	783	1.1	167 (ns)
AE abdominal discomfort	~16	1076	1.5	~15	783	1.9	ND
AE euphoria	~16	1076	1.5	~3	783	0.4	**91 (52-401)**
AE weakness	~15	1076	1.4	~7	783	0.9	200 (ns)
AE confusion	~14	1076	1.3	~4	783	0.5	125 (ns)
AE blurred vision	~14	1076	1.3	~10	783	1.3	ND
AE nightmares	~13	1076	1.2	~13	783	1.7	ND
AE vertigo	~13	1076	1.2	~6	783	0.8	250 (ns)

Abbreviations
AE: adverse event; CI: confidence interval; NA: not available; ND: no difference or rate with placebo was higher than the rate for medication; NNH: number needed to harm; ns: not significant

Supplementary Table 20. Examples of likelihood to be helped or harmed (LHH) for hypnotics where statistically significant number needed to treat (NNT) vs. placebo for any efficacy measure and number needed to harm (NNH) vs. placebo for somnolence are available.

Hypnotic (dose)	NNT vs. placebo	NHH vs. placebo	LHH
Lemborexant (5/10mg)	Day 30 WASO response in the SUNRISE 1 study (Supplementary Table 1) and the Month 6 subjective outcome of PGI-I = 1 for decreased time to fall asleep for the SUNRISE 2 study (Supplementary Table 4), both having a NNT of 4	Somnolence up to Month 1, NNH 19	4.8
Suvorexant (15/20 mg)	sSOL responder (≥ 15% improvement in mean sSOL) at Week 1, sTST responder(≥ 15% improvement in mean sTST) at Month 1, and ISI with a ≥ 6-point improvement (clinically relevant improvement) at Month 3 (Supplementary Table 11), all having a NNT of 8	Somnolence up to Month 3, NNH 28	3.5
Doxepin (6 mg)	PGI helped sleep at Week 4 (Supplementary Table 12), NNT 6	Somnolence/sedation up to Week 4, NNH 19	3.2
Eszopiclone (3 mg)	ISI ≤ 7 (no insomnia) at Month 6 (Supplementary Table 14a), NNT 4	Somnolence up to Month 6, NNH 17	4.2
Zolpidem extended release (12.5 mg)	PGI helped sleep or shortened onset at Week 3 (Supplementary Table 17), NNT 3	Somnolence up to Week 3, NNH 8	2.7

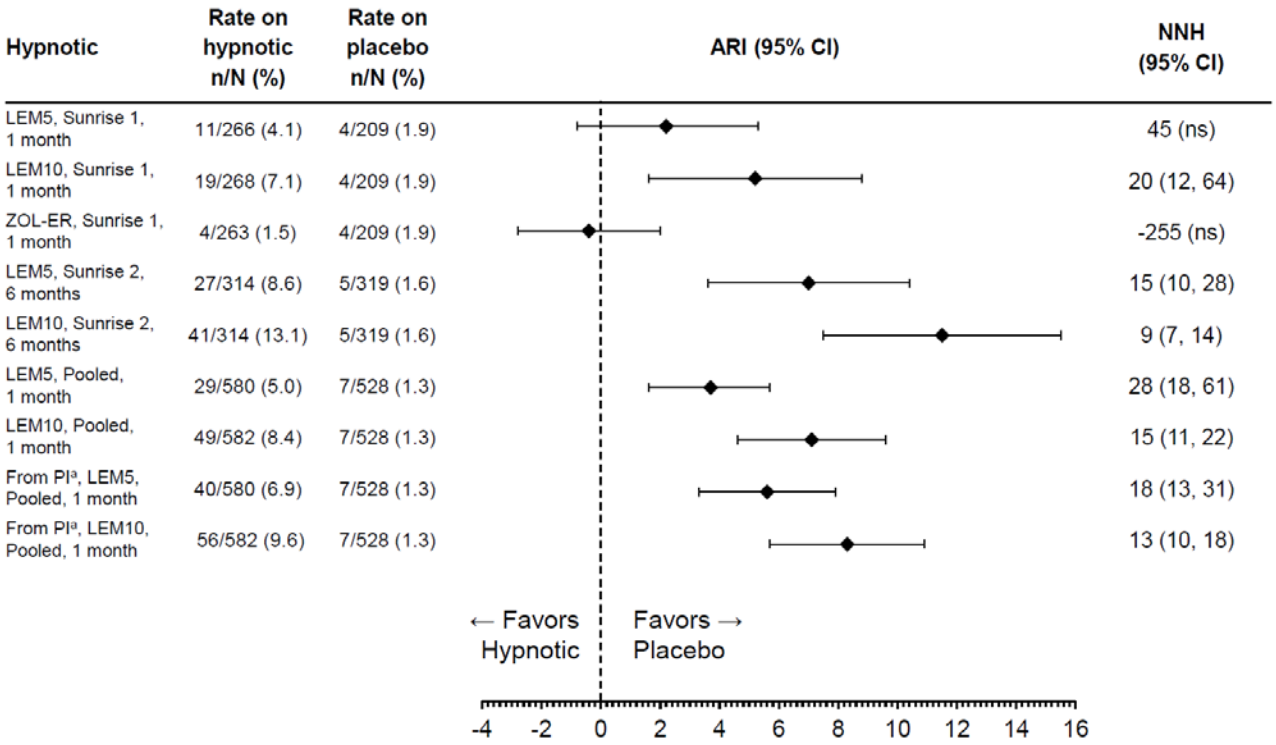
Abbreviations
CGI: Clinical Global Impression); ISI: Insomnia Severity Index; LPS: latency to persistent sleep; PGI-I: Patient Global Impression – Insomnia; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; WASO: wake after sleep onset

Supplementary Table 21. Likelihood to be helped or harmed (LHH) for lemborexant 5 and 10 mg and suvorexant 15 and 20 mg based on number needed to treat (NNT) vs. placebo for response measured by sTST, sSOL, sWASO or ISI and number needed to harm (NNH) vs. placebo for somnolence, at Month 3 (Supplementary Tables 4 and 11, and text).

Response	Lemborexant 5 and 10 mg			Suvorexant 15 and 20 mg		
	NNT	NNH	LHH	NNT	NNH	LHH
sTST ≥ 15% improvement	7	12	1.7	13	28	2.2
sSOL ≥ 15% improvement	6	12	2.0	26	28	1.1
sWASO ≥ 15% improvement	10	12	1.2	16	28	1.8
ISI ≥ 6-point improvement	5	12	2.4	8	28	3.5

Abbreviations
ISI: Insomnia Severity Index; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset

Supplementary Figure 1. Adverse event of somnolence: absolute risk increase (ARI) and number needed to harm (NNH) vs placebo, SUNRISE 1, SUNRISE 2, pooled. A negative NNH occurs when the adverse event rate is lower for the test medication vs. placebo.



[a]From the Product Insert (PI) using the combined terms of somnolence, lethargy, fatigue, sluggishness

Abbreviations
LEM5: lemborexant 5 mg; LEM10: lemborexant 10 mg; ns: not significant; ZOL-ER: zolpidem extended release 6.25 mg