THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

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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DOI Number: https://doi.org/10.4088/JCP.20m13795

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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)
sSOL 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)
sWASO 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)
sSOL 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)
sWASO 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]sSOL responder, alternate definition, defined as ≥ 15% improvement in mean sSOL; this outcome is available for suvorexant (10).
[e]sWASO responder, alternate definition5 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; 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

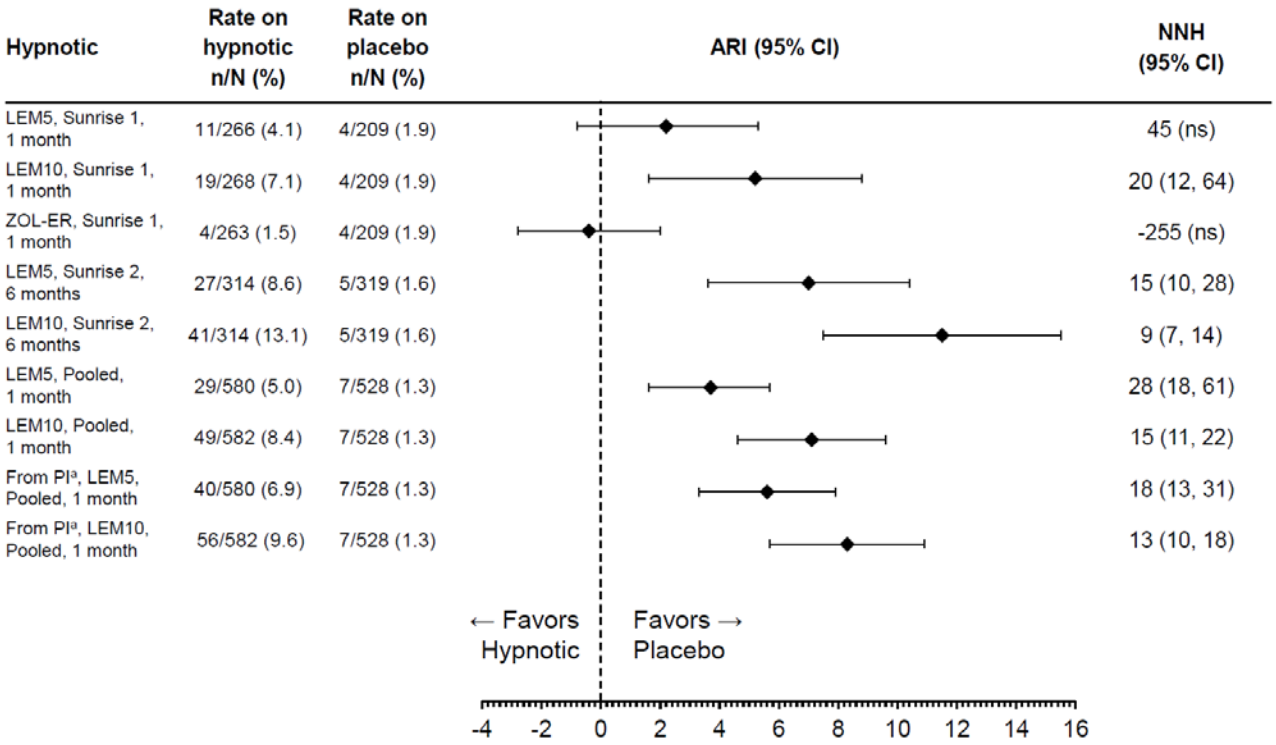
Abbreviations
CGI: Clinical Global Impression); ISI: Insomnia Severity Index; LPS: latency to persistent sleep; PGI-I: Patient Global Impression – Insomnia; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; WASO: wake after sleep onset

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