Lemborexant and Daridorexant for the Treatment of Insomnia:

An Indirect Comparison Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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Abstract

Objective: To determine if there are differences in the number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH) between lemborexant and daridorexant and to compare lemborexant with daridorexant indirectly.

Methods: Dichotomous efficacy and tolerability outcomes reported for Phase 3 daridorexant trials (conducted May 29, 2018–May 14, 2020) for months 1 and 3 were identified from published literature and regulatory documents. Analogous data were extracted for lemborexant from Phase 3 studies (conducted May 31, 2016–January 8, 2019). NNT, NNH, and LHH were then calculated.

Results: Lemborexant 5 mg and 10 mg had clinically relevant therapeutic effect sizes, evidenced by most NNT values versus placebo <10 for Insomnia Severity Index, subjective total sleep time, and polysomnography outcomes. NNH values for adverse events (AEs) were >10, suggesting relative tolerability. Somnolence was the most common AE. Discontinuation rates of lemborexant because of an AE were low, including for somnolence. Efficacy outcomes for daridorexant 25-mg and 50-mg doses pooled resulted in most NNT values versus placebo ≥10, with more robust NNT estimates for the 50-mg dose than for the 25-mg dose. Discontinuation rate because of an AE at month 3 was higher for placebo than for daridorexant, rendering favorable LHH calculations. Daridorexant evidenced low rates of somnolence or fatigue.

Conclusions: In Phase 3 trials, the benefit-risk ratios for both lemborexant and daridorexant were favorable as measured by NNT, NNH, and LHH. Indirect comparisons of lemborexant with daridorexant suggest an efficacy advantage for lemborexant and a tolerability advantage for daridorexant.

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Insomnia disorder is characterized by ongoing difficulties with initiating or maintaining sleep occurring at least 3 times per week, persisting for at least 3 months, and associated with daytime impairment.[1] Insomnia is commonly reported in the general population and is often chronic, persisting for years.[2,3] Additionally, insomnia is a regularly reported comorbidity with other medical and psychiatric disorders.[2] It is also a risk factor for a wide range of disorders, including depression, anxiety, suicidality, Alzheimer's disease, chronic pain, and cardiometabolic disease.[3–5] Whether insomnia is reported independently or in conjunction with another condition, treatments aim to improve sleep quality and quantity as well as improve daytime impairments.[6] Treatment strategies may include nonpharmacologic options and pharmacologic approaches.[1,3] Recommended first-line treatment is a nonpharmacologic option—cognitive-behavioral therapy for insomnia (CBT-I). However, access to CBT-I may be limited, and there is heterogeneity in CBT-I treatment response depending on disease phenotype.[7,8] A variety of pharmacologic treatments are available, which target a range of receptors including γ-aminobutyric acid A ($GABA_A$), melatonin, histamine, and orexin receptors.[9] The medications that target orexin receptors constitute a new generation of agents that specifically target the excessive wakefulness and arousal signaling observed in people with insomnia.[1] To date, 3 different dual orexin receptor antagonists (DORAs) for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or

Clinical Points

- Many pharmacologic and nonpharmacologic options are available to treat insomnia, a common and chronic condition, and each option has associated benefits and risks.
- Using number needed to treat and number needed to harm analyses may help place new insomnia medications into clinical perspective with other treatment options.

maintenance have been approved by the US Food and Drug Administration (FDA): suvorexant in 2014,[10] lemborexant in 2019,[11] and daridorexant in 2022.[12]

In the absence of direct head-to-head clinical trial data, it can be challenging to understand the potential therapeutic role for the different treatment options available, especially for new agents that may be unfamiliar to clinicians and patients. A possible solution to better inform clinical decision-making is the calculation of effect sizes such as 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.[13–15] The ratio of NNH to NNT can further describe the benefit-risk ratio and is called "likelihood to be helped or harmed" (LHH).[14] A recent report described insomnia treatment options using NNT, NNH, and LHH and compared lemborexant to other hypnotic agents, including suvorexant, doxepin, ramelteon, zolpidem, eszopiclone, zaleplon, and selected benzodiazepines.[16] With daridorexant now available, the aim of this study is to describe the relative efficacy and safety of lemborexant and daridorexant using the metrics of NNT, NNH, and LHH.

METHODS

Data Sources

Categorical data from pivotal trials of daridorexant (NCT03545191, NCT03575104) were identified and extracted from product labeling,[12] FDA regulatory Drug Approval Packages,[17] and published literature.[18] Corresponding data were then extracted from published and unpublished data of Phase 3 randomized placebo-controlled trials of lemborexant—the SUNRISE 1 (NCT02783729)[19] and SUNRISE 2 (NCT02952820)[20] trials. As documented in the source publications, all studies included in this analysis had protocols approved by the relevant institutional review boards or ethics committees and were conducted in accordance with the *Guideline for Good Clinical Practice* and the Declaration of Helsinki, and all participants provided written informed consent.[18–20]

Description of Studies

Lemborexant Study: SUNRISE 1 (Study E2006-G000-304, NCT02783729, EudraCT 2015–004347-39). The SUNRISE 1 Phase 3 clinical study was a 1-month, global, randomized, double-blind, placebo- and active comparator–controlled trial conducted from May 31, 2016, to January 30, 2018, at 67 sites in North America and Europe. A detailed description of the study design has been published previously.[19] Briefly, eligible participants (women aged ≥ 55 years, men aged ≥ 65 years) met *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[21] insomnia disorder criteria characterized by sleep maintenance difficulties (with or without sleep onset difficulties) that were confirmed using sleep diary, sleep history, and polysomnography (PSG). Insomnia Severity Index (ISI)[22] scores were required to be ≥ 13. Following a 2-week placebo-only run-in treatment period, participants were randomized 5:5:5:4 to 30 days treatment at bedtime with lemborexant 5 mg, lemborexant 10 mg, zolpidem extended release (ER) 6.25 mg, or placebo. The primary endpoint was the change from baseline in latency to persistent sleep (LPS) for lemborexant therapy versus placebo, measured using PSG after nights 29 and 30 of treatment. PSG measures were recorded separately and averaged across pairs of consecutive nights.

There were 1,006 participants randomized (lemborexant 5 mg, 266; lemborexant 10 mg, 269; zolpidem ER, 263; placebo, 208) with a median age of 63 years (range, 55–88 years); 869 participants (86.4%) were women. Both doses of lemborexant therapy improved the primary endpoint, objective sleep onset compared with placebo as assessed by LPS.

Lemborexant Study: SUNRISE 2 (Study E2006-G000-303, NCT02952820, EudraCT 2015–001463-39). The SUNRISE 2 Phase 3 clinical study was a 12-month (placebo-controlled for 6 months), global, randomized, double-blind, parallel-group trial conducted from November 15, 2016, to January 8, 2019, at 119 sites in North America, Europe, Asia, and Oceania. A detailed description of the study design has been published previously.[20] Briefly, eligible participants (aged ≥ 18 years) met *DSM-5* insomnia disorder criteria characterized by sleep maintenance difficulties and/or sleep onset difficulties, which were confirmed using sleep diary, sleep history, and questionnaires. ISI scores were required to be ≥ 15. Participants were randomized 1:1:1 to treatment with lemborexant 5 mg, lemborexant 10 mg, or placebo at bedtime for a 6-month placebo-controlled treatment period. The primary endpoint was mean change from baseline in subjective sleep onset latency (sSOL) at the end of month 6.

For the placebo-controlled period (ie, first 6 months), there were 949 participants randomized in the full analysis set (lemborexant 5 mg, 316; lemborexant 10 mg, 315; placebo, 318), with a median age of 55.0 years (range,

18–88 years); 647 participants (68.2%) were women. Both doses of lemborexant therapy significantly improved the primary outcome, sSOL, compared with placebo.

Daridorexant Study 1: NCT03545191 (Study ID-078A301). This Phase 3 clinical study was a global, randomized, double-blind, placebo-controlled, parallel-group trial conducted from June 4, 2018, to February 25, 2020, at 75 sites in North America, Europe, and Australia. A detailed description of the study design has been published previously.[18] Briefly, eligible participants (aged ≥ 18 years) with *DSM-5*–diagnosed[21] insomnia disorder that was moderate or severe in intensity (ISI score ≥ 15) were randomized 1:1:1 to daridorexant 25 mg, daridorexant 50 mg, or placebo every evening for 3 months. The primary endpoints were PSG-measured change from baseline in wake after sleep onset (WASO) and LPS at month 1 and month 3.

There were 930 participants randomized (daridorexant 25 mg, 310; daridorexant 50 mg, 310; placebo, 310); 364 participants (39%) were aged ≥ 65 years, and 624 participants (67%) were women. Both doses of daridorexant significantly improved the 2 primary endpoints, WASO and LPS, at month 1 and month 3 compared with placebo.

Daridorexant Study 2: NCT03575104 (Study ID-078A302). This Phase 3 clinical study was a global, randomized, double-blind, placebo-controlled, parallel-group trial conducted from May 29, 2018, to May 14, 2020, at 81 sites in North America, Europe, and Asia. A detailed description of the study design has been published previously.[18] Briefly, eligible participants (aged ≥ 18 years) with *DSM-5* diagnosed insomnia disorder that was moderate or severe in intensity (ISI score ≥ 15) were randomized 1:1:1 to daridorexant 10 mg, daridorexant 25 mg, or placebo every evening for 3 months. Primary efficacy endpoints were as described for Study 1 (NCT03545191). The 10-mg dose investigated in this study is considered subtherapeutic and is not an FDA-approved dose, and thus it was not included in this analysis.

There were 924 participants randomized (daridorexant 10 mg, 307; daridorexant 25 mg, 309; placebo, 308); 363 participants (39%) were aged ≥ 65 years, and 638 participants (69%) were women. Treatment with daridorexant 25 mg significantly improved WASO at month 1 and month 3 compared with placebo. Daridorexant 25 mg did not improve LPS at month 1 or month 3 compared with placebo.

Outcomes

The selection of the categorical efficacy outcomes of clinical interest that were examined for this analysis was based on publicly available data for daridorexant[17,18] and when the same measures were used in SUNRISE 1 and/or SUNRISE 2 (Supplementary Table 1).

Reported data for daridorexant included subjective response defined by total ISI score (ISI score < 10 [subthreshold insomnia], ISI score ≤ 7 [absent insomnia], and ISI score ≥ 6-point decrease from baseline [clinically relevant improvement]). Response was also reported for subjective total sleep time (sTST), as defined by > 80-minute increase from baseline. Data for these outcomes were then extracted from the lemborexant clinical trial database for SUNRISE 1 and SUNRISE 2, by study arm, at the same time points as reported for the registrational studies of daridorexant (month 1 for SUNRISE 1, months 1 and 3 for SUNRISE 2). The population (denominator for calculation) was the number of randomized participants who received ≥ 1 dose of study drug and had ≥ 1 post-baseline assessment on the efficacy outcome of interest. Categorical outcomes for ISI score ≤ 7 and ISI score ≥ 6-point decrease from baseline were previously calculated and reported for lemborexant.[16]

Regarding objective outcomes, PSG measures of LPS and WASO for daridorexant studies were reported in regulatory documents at month 1 and month 3.[18] Categorical response thresholds included ≥ 50% improvement from baseline and ≥ 75% improvement from baseline for both LPS and WASO. Corresponding objective PSG response at month 1 was assessed for the SUNRISE 1 study from baseline (averaged from the testing done during the run-in period before receiving randomized study medication) to the end of treatment (day 29 and day 30 averaged). PSG was not conducted in SUNRISE 2.

Tolerability and safety outcomes of clinical interest occurring at any time during 3-month double-blind treatment, including AEs and discontinuation due to an AE, were assessed for daridorexant. Data were extracted by study arm from published literature.[18] The population (denominator) was the number of all randomized participants who received ≥ 1 dose of study drug. Tolerability and safety outcomes of clinical interest have been previously extracted and reported for lemborexant[16] through month 1 (SUNRISE 1 and SUNRISE 2) and month 3 (SUNRISE 2).

Data Analysis

NNT and NNH, with their respective 95% CIs, were calculated for daridorexant versus placebo and lemborexant versus placebo in each individual study. Study data were also pooled as appropriate. The daridorexant 10-mg dose group was not included in analyses or in dose group pooling as it is not an approved dose. LHH was calculated to illustrate potential trade-offs for efficacy (response) and tolerability outcomes (commonly encountered AEs).

In this analysis, the use of the terms *statistically significant* and *non–statistically significant* is descriptive rather than inferential. In all instances, if the 95% CI included "infinity," the result is considered not statistically significant at the $P < .05$ threshold. The notation "NS" (ie, not significant) is used rather than showing the non-continuous 95% CIs generated when statistical significance

Table 1.

Lemborexant Efficacy Outcomes at End of Month 1 (Pooled SUNRISE 1 and SUNRISE 2)

Outcome at Month 1	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	%			
ISI score < 10	192	558	34.4	195	540	36.1	107	494	21.7	8 (6–14)	7 (5–12)	8 (6–12)
ISI score ≤ 7	140	558	25.1	140	540	25.9	65	494	13.2	9 (6–14)	8 (6–13)	9 (7–12)
ISI score ≥ 6-point decrease from baseline	326	558	58.4	313	540	58.0	215	494	43.5	7 (5–12)	7 (5–12)	7 (5–11)
sTST > 80-min increase from baseline	149	529	28.2	188	526	35.7	97	481	20.2	13 (8–37)	7 (5–10)	9 (7–14)

Abbreviations: ISI = Insomnia Severity Index, NNT = number needed to treat, NS = not significant, sTST = subjective total sleep time.

is not achieved. In general, a NNT versus placebo < 10 is considered to be a clinically relevant effect size difference, with a NNT < 5 being considered even more desirable.[14,15] A NNH versus placebo > 10 is generally considered acceptable, with a NNH > 20 deemed more desirable. A negative value for a NNH versus placebo can occur when an AE is more common with placebo than with study drug. In this instance, "no difference" (ND) has been noted to avoid interpreting such difference as a tolerability advantage over placebo. Because a meaningful LHH cannot be calculated with a zero or negative NNH value, for negative NNH estimates, a NNH of 1,000 was used as an approximation for LHH calculations.[23,24] A LHH > 1 indicates that a treatment is more likely to help than harm.[14]

Formulae Used

The absolute risk increase (ARI) was calculated as the incidence on medication (f_1) less the incidence on placebo (f_2) (ARI = $f_1 - f_2$). The corresponding 95% CI was calculated by the equations below, for which $z = 1.96$ for a 95% CI.

$$\textit{Lower bound of the CI} = ARI - z\sqrt{\frac{f_1(1-f_1)}{n_1} + \frac{f_2(1-f_2)}{n_2}}$$

$$\textit{Upper bound of the CI} = ARI + z\sqrt{\frac{f_1(1-f_1)}{n_1} + \frac{f_2(1-f_2)}{n_2}}$$

NNT or NNH were calculated as the reciprocal of ARI (1/ARI) and rounded up to the next highest whole number. The 95% 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 was calculated as the ratio of NNH to NNT (LHH = NNH/NNT).

RESULTS

Lemborexant

Efficacy—NNT. The categorical efficacy outcomes at the end of the SUNRISE 1 study at month 1 demonstrated a statistically significantly higher responder rate with either lemborexant 5 mg or 10 mg compared with placebo for a variety of response definitions: ISI score < 10, ISI score ≤ 7, ISI score ≥ 6-point decrease from baseline, and sTST > 80-minute increase from baseline (Supplementary Table 2). Significant improvements were also observed for PSG response of ≥ 50% LPS or WASO improvement from baseline for both lemborexant doses and ≥ 75% LPS or WASO improvement for lemborexant 10 mg (Supplementary Table 2). Most NNT values versus placebo for lemborexant were ≤ 10, with the most robust NNT being 5 for ≥ 50% WASO improvement (5 mg and 10 mg) and sTST improvement > 80 minutes (10 mg). A negative NNT for the active control, zolpidem ER 6.25 mg, for LPS outcomes indicates placebo outperformed zolpidem ER on these measures. Efficacy results for SUNRISE 2 showed similar trends of significance of NNT for both lemborexant doses versus placebo for ISI measures, with generally more robust NNT estimates at month 3 compared with month 1 (Supplementary Table 3).

In pooled efficacy data from SUNRISE 1 and SUNRISE 2, NNT values versus placebo at the end of month 1 for pooled lemborexant 5-mg and 10-mg dose groups were < 10 for all relevant outcomes: ISI score < 10, ISI score ≤ 7, ISI score ≥ 6-point decrease from baseline, and sTST > 80-minute increase from baseline (Table 1). There was a potential dose response for the sTST outcome (NNT vs placebo: lemborexant 10 mg, 7; lemborexant 5 mg, 13) with a NNT for the lemborexant 10-mg group versus 5-mg group of 14 (95% CI, 8–51).

Tolerability—NNH. In pooled tolerability analysis of SUNRISE 1 and SUNRISE 2 through month 1 (Table 2),[16,19,20] there were no NNH values versus placebo for lemborexant that were < 10. The lowest significant NNH estimates reported for pooled lemborexant 5-mg and 10-mg doses were for somnolence (19) and fatigue (56). The NNH for somnolence (lemborexant 10 mg, 15; lemborexant 5 mg, 28) indicated a potential dose response (NNH for somnolence in lemborexant 10-mg group vs 5-mg group, 30 [95% CI, 16–182]). Rates of discontinuation due to any AE, including somnolence, were low and not statistically significant through month 1, with NNH values versus placebo of approximately 100 or higher for these outcomes regardless of dose (Table 2). Month 3 tolerability outcomes were available

Table 2.

Lemborexant Tolerability Through Month 1 (Pooled SUNRISE 1 and SUNRISE 2) and Month 3 (SUNRISE 2)[a]

Outcome at Month 1	SUNRISE 1 and SUNRISE 2 Lemborexant 5 mg (n = 580) n	%	SUNRISE 1 and SUNRISE 2 Lemborexant 10 mg (n = 582) n	%	SUNRISE 1 and SUNRISE 2 Placebo (n = 528) n	%	SUNRISE 1 and SUNRISE 2 Lemborexant 5 mg vs Placebo NNH (95% CI)	SUNRISE 1 and SUNRISE 2 Lemborexant 10 mg vs Placebo NNH (95% CI)	SUNRISE 1 and SUNRISE 2 Pooled Lemborexant vs Placebo NNH (95% CI)
Discontinuation because of an AE	8	1.4	15	2.6	8	1.5	ND	95 (NS)	216 (NS)
Discontinuation because of AE of somnolence	4	0.7	6	1.0	2	0.4	322 (NS)	154 (NS)	208 (NS)
AE somnolence	29	5.0	49	8.4	7	1.3	28 (18–61)	15 (11–22)	19 (14–28)
AE headache	35	6.0	27	4.6	21	4.0	49 (NS)	152 (NS)	74 (NS)
AE urinary tract infection	4	0.7	12	2.1	6	1.1	ND	109 (NS)	416 (NS)
AE nasopharyngitis	16	2.8	10	1.7	5	0.9	56 (30–411)	130 (NS)	78 (41–953)
AE fatigue	12	2.1	9	1.5	0	0	49 (31–110)	65 (40–184)	56 (39–96)
AE back pain	4	0.7	6	1.0	3	0.6	824 (NS)	217 (NS)	342 (NS)
AE nightmare	3	0.5	6	1.0	2	0.4	723 (NS)	154 (NS)	253 (NS)
AE abnormal dreams	2	0.3	6	1.0	4	0.8	ND	366 (NS)	ND
AE sleep paralysis	1	0.2	5	0.9	0	0	580 (NS)	117 (63–915)	194 (108–960)
AE nausea	8	1.4	4	0.7	1	0.2	84 (46–586)	201 (NS)	119 (66–651)
AE upper respiratory tract infection	7	1.2	4	0.7	5	0.9	385 (NS)	ND	ND
AE dizziness	5	0.9	4	0.7	7	1.3	ND	ND	ND
AE fall	4	0.7	0	0	3	0.6	824 (NS)	ND	ND
Outcome at Month 3[b]	**SUNRISE 2 Lemborexant 5 mg (n = 314) n**	**%**	**SUNRISE 2 Lemborexant 10 mg (n = 314) n**	**%**	**SUNRISE 2 Placebo (n = 319) n**	**%**	**SUNRISE 2 Lemborexant 5 mg vs Placebo NNH (95% CI)**	**SUNRISE 2 Lemborexant 10 mg vs Placebo NNH (95% CI)**	**SUNRISE 2 Pooled Lemborexant vs Placebo NNH (95% CI)**
Discontinuation because of an AE	9	2.9	17	5.4	7	2.2	149 (NS)	32 (17–409)	52 (NS)
Discontinuation because of AE of somnolence	3	1.0	7	2.2	1	0.3	156 (NS)	53 (28–584)	79 (42–810)
Discontinuation because of AE of nightmare	1	0.3	3	1.0	0	0	314 (NS)	105 (NS)	157 (80–6789)
AE somnolence	26	8.3	38	12.1	4	1.3	15 (10–27)	10 (7–15)	12 (9–16)
AE nasopharyngitis	17	5.4	20	6.4	26	8.2	ND	ND	ND
AE headache	24	7.6	17	5.4	13	4.1	28 (NS)	75 (NS)	41 (NS)
AE fatigue	12	3.8	10	3.2	0	0	27 (17–59)	32 (20-81)	29 (21–49)
AE influenza	5	1.6	10	3.2	6	1.9	ND	77 (NS)	197 (NS)
AE back pain	7	2.2	8	2.5	4	1.3	103 (NS)	78 (NS)	89 (NS)
AE nightmare	2	0.6	6	1.9	1	0.3	310 (NS)	63 (NS)	105 (NS)
AE urinary tract infection	4	1.3	6	1.9	5	1.6	ND	292 (NS)	4007 (NS)
AE gastroenteritis	1	0.3	5	1.6	3	0.9	ND	154 (NS)	6678 (NS)
AE upper respiratory tract infection	7	2.2	5	1.6	6	1.9	287 (NS)	ND	3339 (NS)
AE nausea	6	1.9	4	1.3	0	0	53 (30–253)	79 (40–2,990)	63 (39–164)
AE fall	2	0.6	2	0.6	7	2.2	ND	ND	ND
AE sinusitis	2	0.6	2	0.6	5	1.6	ND	ND	ND
AE arthralgia	5	1.6	0	0	7	2.2	ND	ND	ND

[a]Table adapted with permission from Citrome et al.[16]
[b]AEs ≥ 2% in any group through month 3.
Abbreviations: AE = adverse event, ND = no difference (rate on medication ≤ placebo), NNH = number needed to harm, NS = not significant.

only in SUNRISE 2 (Table 2). At month 3 for commonly reported AEs (≥ 2% in any group) there were no NNH values < 10. As at month 1, significant NNHs for pooled 5-mg and 10-mg lemborexant doses were lowest for somnolence (12) and fatigue (29), with a potential dose response for somnolence (lemborexant 10 mg, 10; lemborexant 5 mg, 15; NNH for somnolence in lemborexant 10-mg group vs 5-mg group, 27 [NS]).

LHH. Calculating the LHH for discontinuation due to an AE for pooled lemborexant 5-mg and 10-mg doses versus placebo at month 1 (NNH = 216 [NS]) using the range of statistically significant NNTs versus placebo (5–14) equated to a LHH range of 15.4–43.2. At month 3 (NNH = 52 [NS]; NNT range, 5–10), the LHH range was 5.2–10.4. As there were fewer discontinuations due to an AE in the lemborexant 5-mg group compared with the 10-mg group, the LHH range for the 5-mg group alone was more advantageous (LHH range for discontinuation due to an AE: month 1, 76.9–200; month 3, 13.5–298). The month 3 LHH with pooled lemborexant 5-mg and 10-mg doses for an AE of fatigue (NNH = 29) or an AE of somnolence (NNH = 12) versus ISI score ≥ 6-point decrease from baseline (NNT = 5) or sTST > 80-minute increase (NNT = 10) ranged from 1.2 to 5.8.

Table 3.

Daridorexant Efficacy Outcomes at End of Month 1 and Month 3 (Study 1 [NCT03545191])[a]

Outcome	Daridorexant 25 mg			Daridorexant 50 mg			Placebo			Daridorexant 25 mg vs Placebo NNT (95% CI)	Daridorexant 50 mg vs Placebo NNT (95% CI)	Daridorexant 25 mg + 50 mg vs Placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%			
Month 1												
ISI < 10	56	292	19.2	61	299	20.4	33	297	11.1	13 (8–44)	11 (7–29)	12 (8–26)
ISI ≤ 7	30	292	10.3	34	299	11.4	15	297	5.1	20 (11–107)	16 (10–52)	18 (11–45)
ISI ≥ 6-point decrease from baseline	103	292	35.3	120	299	40.1	85	297	28.6	15 (NS)	9 (6–26)	11 (7–38)
sTST > 80-min increase from baseline	54	303	17.8	69	304	22.7	31	302	10.3	14 (8–49)	8 (6–16)	10 (7–19)
LPS ≥ 50% improvement from baseline (PSG)	144	298	48.3	156	305	51.1	96	299	32.1	7 (5–12)	6 (4–9)	6 (5–10)
LPS ≥ 75% improvement from baseline (PSG)	52	298	17.4	62	305	20.3	31	299	10.4	15 (8–65)	10 (7–24)	12 (8–26)
WASO ≥ 50% improvement from baseline (PSG)	53	298	17.8	86	305	28.2	30	299	10.0	13 (8–45)	6 (5–9)	8 (6–13)
WASO ≥ 75% improvement from baseline (PSG)	7	298	2.3	16	305	5.2	3	299	1.0	75 (NS)	24 (15–67)	36 (22–110)
Month 3												
ISI < 10	98	286	34.3	100	283	35.3	71	281	25.3	12 (7–67)	10 (6–40)	11 (7–33)
ISI ≤ 7	69	286	24.1	74	283	26.1	46	281	16.4	13 (7–86)	11 (7–33)	12 (7–32)
ISI ≥ 6-point decrease from baseline	145	286	50.7	160	283	56.5	131	281	46.6	25 (NS)	11 (6–59)	15 (NS)
sTST > 80-min increase from baseline	81	292	27.7	98	289	33.9	60	289	20.8	15 (8–3,027)	8 (5–17)	10 (7–25)

[a]Data from Mignot et al[18] and the integrated review in US Food and Drug Administration.[17] When denominators were unavailable in the integrated review[17] for ISI outcomes, denominators were used per other ISI outcomes in Mignot et al.[18]

Abbreviations: ISI = Insomnia Severity Index, LPS = latency to persistent sleep, NNT = number needed to treat, NS = not significant, PSG = polysomnography, sTST = subjective total sleep time, WASO = wake after sleep onset.

Daridorexant

Efficacy—NNT. The categorical efficacy outcomes for Study 1 at the end of month 1 and month 3 (Table 3) demonstrated consistently statistically significant NNT values versus placebo for daridorexant 50 mg for a variety of response definitions including ISI score < 10, ISI score ≤ 7, ISI score ≥ 6-point decrease from baseline, and sTST improved by > 80 minutes from baseline. NNT estimates were not statistically significant for daridorexant 25 mg for ISI score ≥ 6-point decrease from baseline, suggesting a clinically relevant dose response. Additionally, the NNT versus placebo was numerically more robust for daridorexant 50 mg compared with daridorexant 25 mg at either month 1 or month 3 for all efficacy outcomes (PSG outcomes were reported only at month 1; Table 3). NNT estimates that were < 10 in Study 1 for daridorexant 50 mg were ISI score ≥ 6-point decrease from baseline at month 1, sTST > 80-minute increase from baseline at month 1 and month 3, WASO ≥ 50% improvement from baseline at month 1, and LPS ≥ 50% improvement from baseline at month 1. The 25-mg daridorexant group also had a NNT < 10 for LPS ≥ 50% improvement from baseline at month 1. NNT estimates for ISI score ≤ 7 were more robust at month 3 than at month 1. For daridorexant Study 2 (Supplementary Table 4), no NNT values versus placebo were < 10 for the daridorexant 25-mg dose group. NNT values versus placebo were statistically significant for daridorexant 25 mg for ISI score < 10 and sTST > 80-minute increase from baseline. NNT estimates were generally more robust at month 3 than at month 1.

Pooled efficacy data from daridorexant Study 1 and Study 2 are shown in Supplementary Table 5 and do not include the 10-mg dose group, as it is not commercially available and is considered subtherapeutic. For pooled doses of 25 mg and 50 mg, no NNT values versus placebo were < 10. Estimates were more robust at month 3 than at month 1 for ISI score < 10 and sTST > 80-minute increase from baseline.

Tolerability—NNH. Rates for discontinuation because of an AE were higher for the placebo groups than for any of the daridorexant dose groups in Study 1 (Supplementary Table 6) or Study 2 (Supplementary Table 7). Hence, the NNH values versus placebo for this outcome were negative numbers. In Study 1, all NNH estimates for AEs were > 10; for the non-pooled daridorexant dose groups, the NHH estimates versus placebo were not statistically significant. In the pooled 25-mg and 50-mg dose groups, AEs of fatigue (NNH = 62) and dizziness (NNH = 69) were statistically significant, but the NNH values versus placebo were weak in terms of effect size (ie, much greater than 10; see Supplementary Table 6). The AE of somnolence was not statistically significant (NNH = 155). In Study 2, all NNH estimates were > 10 (Supplementary Table 7). A statistically significant NNH value versus placebo was reported for fatigue for daridorexant 25 mg (NNH = 35). The NNH for an AE of somnolence was not significant for daridorexant 25 mg (NNH = 52). In pooled 25-mg and 50-mg dose groups from Study 1 and Study 2 (Table 4), all NNH estimates were > 10; the most robust statistically significant NNH versus placebo was reported for fatigue (NNH = 49), and the NNH for an AE of somnolence (NNH = 85) was not significant.

LHH. Comparing the NNH versus placebo for discontinuation due to an AE for pooled daridorexant 25-

Table 4.

Pooled Daridorexant Tolerability Outcomes Through Month 3 (Study 1 and Study 2)[a]

Outcome	Daridorexant 25 mg (n = 618)		Daridorexant 25 mg + 50 mg (n = 926)		Placebo (n = 615)		Daridorexant 25 mg vs Placebo NNH (95% CI)	Daridorexant 25 mg + 50 mg vs Placebo NNH (95% CI)
	n	%	n	%	n	%		
Discontinuation because of AE	11	1.8	14	1.5	17	2.8	ND	ND
Nasopharyngitis	34	5.5	54	5.8	36	5.9	ND	ND
Headache	31	5.0	50	5.4	23	3.7	79 (NS)	61 (NS)
Accidental overdose	8	1.3	16	1.7	6	1.0	314 (NS)	133 (NS)
Fatigue	18	2.9	25	2.7	4	0.7	45 (27–127)	49 (31–121)
Dizziness	12	1.9	19	2.1	6	1.0	104 (NS)	93 (NS)
Nausea	3	0.5	10	1.1	6	1.0	ND	959 (NS)
Somnolence	21	3.4	26	2.8	10	1.6	57 (29–3,501)	85 (NS)
Fall	4	0.6	5	0.5	11	1.8	ND	ND
Upper respiratory tract infection	4	0.6	5	0.5	9	1.5	ND	ND
Excessive daytime sleepiness	6	1.0	7	0.8	2	0.3	155 (NS)	233 (NS)
Sleep paralysis	3	0.5	4	0.4	0	0.0	206 (NS)	232 (117–10,467)
Hallucinations	4	0.6	4	0.4	0	0.0	155 (79–6,667)	232 (117–10,567)
Suicidal injury or self-injury	1	0.2	1	0.1	0	0.0	618 (NS)	926 (NS)

[a]Data from Mignot et al.[18]
Abbreviations: AE = adverse event, ND = no difference (rate on medication ≤ placebo), NNH = number needed to harm, NS = not significant.

mg and 50-mg doses (imputed to be 1,000) to the range of statistically significant NNTs versus placebo (10–13) equates to a LHH range of 76.9–100 at month 3. Efficacy outcomes were more robust for the daridorexant 50-mg group alone, with statistically significant NNT estimates versus placebo of 8–11 (excluding ISI score < 22), resulting in a LHH at month 3 ranging from 90.9 to 125. The month 3 LHH for the pooled daridorexant 25-mg and 50-mg doses for an AE of fatigue (NNH = 49) or an AE of somnolence (NNH = 85) versus ISI score ≥ 6-point decrease from baseline (NNT = 13) or sTST > 80-minute increase (NNT = 10) ranged from 3.8 to 8.5.

Indirect Comparisons

The efficacy outcome NNT estimates for ISI and sTST for the available commercial dose strengths of lemborexant and daridorexant are compared in Figure 1. For most outcomes, the NNT effect sizes were more robust for lemborexant than for daridorexant at month 1 and month 3.

PSG measures were available for comparison only at month 1 and indicated similar NNT ranges for lemborexant and daridorexant for LPS improvement of ≥ 50% or ≥ 75% from baseline (Figure 1). NNT estimates for WASO improvement of ≥ 50% from baseline were more robust for lemborexant than for daridorexant, whereas NNT estimates for WASO improvement of ≥ 75% demonstrated small effect size differences from placebo (Figure 1).

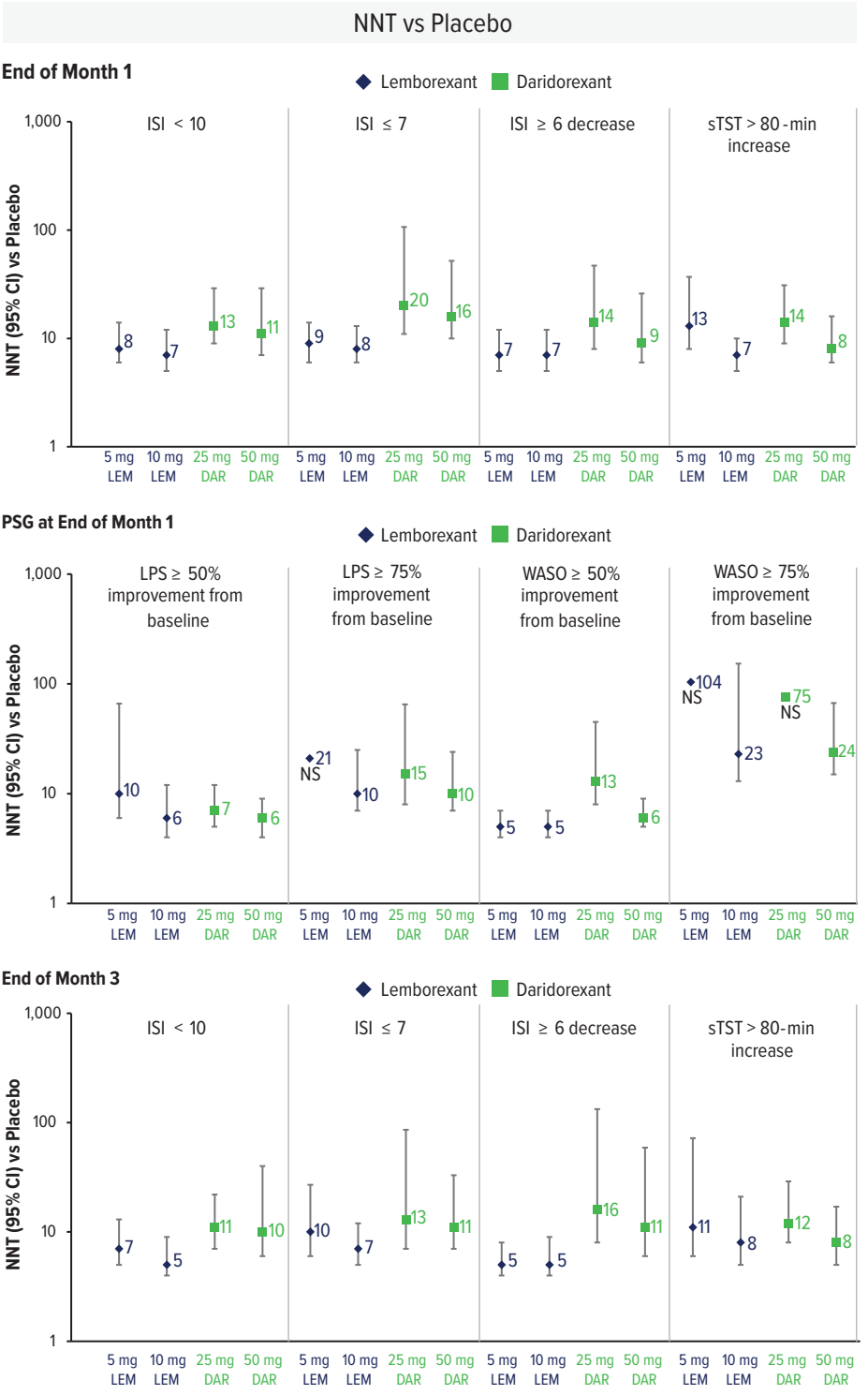
For lemborexant, the discontinuation rates due to an AE through month 3 (data source: SUNRISE 2) were higher than for placebo (Table 2); the NNH was quantifiable but not statistically significant. For the pooled daridorexant studies, the discontinuation rates due to an AE through month 3 were higher for placebo than for daridorexant, yielding an imputed NNH of 1,000 that was used for the LHH calculations (Table 4). These differences in discontinuation rates due to an AE resulted in more favorable LHH calculations for daridorexant than for lemborexant despite less robust NNT for efficacy outcomes for daridorexant (Figure 1). The 3-month NNH for pooled daridorexant doses (Study 1 and 2 pooled) was more favorable than that for the pooled lemborexant doses (in SUNRISE 2) for AEs of fatigue (pooled daridorexant = 49; pooled lemborexant = 29) and somnolence (pooled daridorexant = 85; pooled lemborexant = 12). The LHH values contrasting efficacy (ISI score ≥ 6-point decrease from baseline and sTST > 80-minute increase from baseline) and tolerability (AEs of somnolence and fatigue) were > 1 for both daridorexant and lemborexant (Figure 1).

DISCUSSION

The goal of an insomnia medication is to allow patients to fall asleep, stay asleep, wake, and function well.[6] For insomnia medications, some of the key pharmacokinetic properties that may impact efficacy (eg, onset and maintenance) and safety (eg, duration of action and next day effects) may include absorption, receptor interaction, half-life curve, and endogenous orexin levels (which are highest upon awakening[25]). Each DORA has unique characteristics in terms of absorption, time to receptor occupancy (K_{on} and K_{off}), time to onset of action,

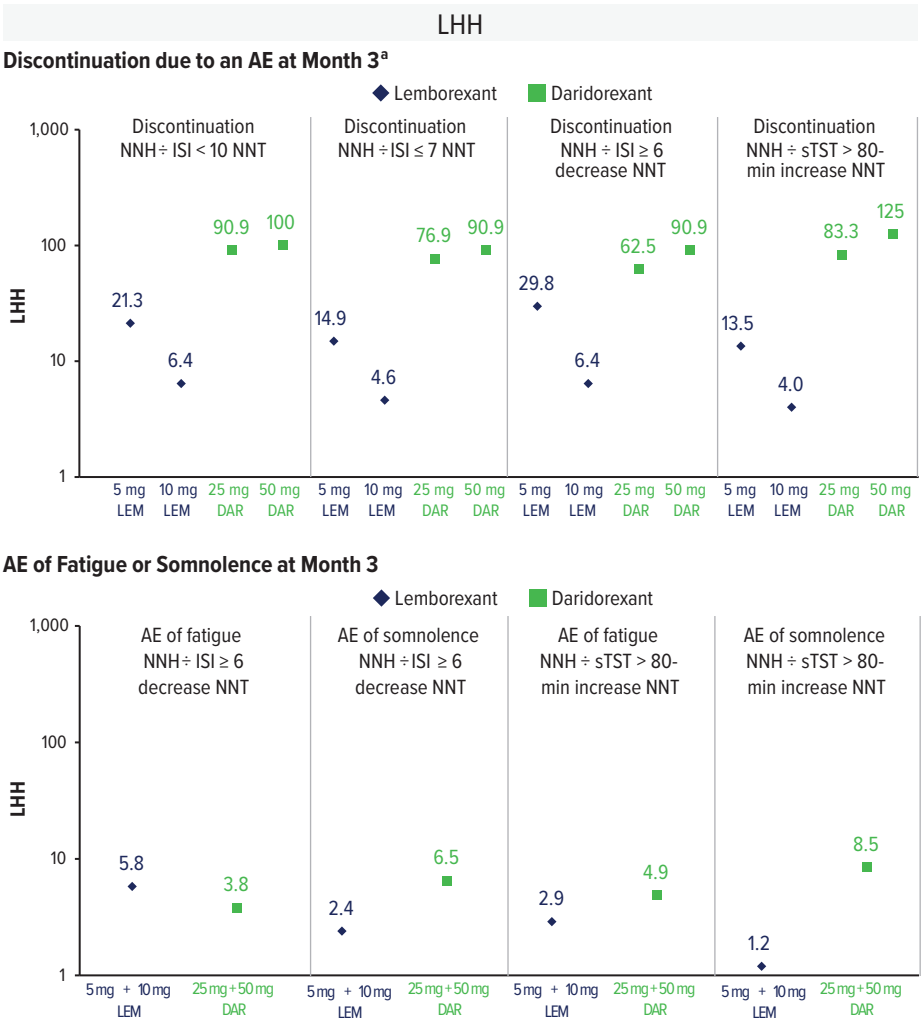
Figure 1.

Indirect Comparisons of NNTs (95% CI) vs Placebo and LHH for Different Efficacy Outcomes for Lemborexant and Daridorexant



(continued)

Figure 1. Continued



[a]Daridorexant NNH imputed as 1,000. Data from the US Food and Drug Administration[17] and Mignot et al.[18]
Abbreviations: AE = adverse event, DAR = daridorexant, ISI = Insomnia Severity Index, LEM = lemborexant, LHH = likelihood to be helped or harmed, LPS = latency to persistent sleep, NNH = number needed to harm, NNT = number needed to treat, NS = not significant, PSG = polysomnography, sTST = subjective total sleep time, WASO = wake after sleep onset.

half-life, and accumulation at steady state[10-12]; these pharmacokinetic profiles are published elsewhere.[26,27] However, the clinical impacts of these different characteristics have not been tested, and head-to-head studies of DORAs have not been conducted. As such, this analysis to indirectly compare clinical trial data of lemborexant and daridorexant using NNT, NNH, and LHH assessments is relevant to aid clinical decision-making.

A NNT of < 10 is desirable and clinically relevant, as it indicates that fewer than 10 patients would require treatment to observe a benefit compared with placebo.[14] A NNT of < 10 was observed more consistently with lemborexant than with daridorexant for subjectively reported ISI and sTST measures, indicating a more robust clinical effect with lemborexant. Larger effect sizes were reported for lemborexant than for daridorexant at month 1 and month 3, with the most robust improvements at month 3. In a previous report comparing hypnotics for insomnia treatment, the NNT estimates for different categorical efficacy outcomes were also generally < 10 at month 1 and month 3 (when available) for lemborexant (5 mg or 10 mg), zolpidem ER (6.25 mg or 12.5 mg), doxepin (3 mg or 6 mg), and eszopiclone (2 mg).[16] The most robust NNT effect sizes (NNT = 5) were reported for ISI score ≥ 6-point decrease for all doses of lemborexant at month 3 and for ISI score < 10 for lemborexant 10 mg. Categorial data regarding an ISI score ≥ 6-point decrease are also available for suvorexant.[16] NNT estimates for an ISI ≥ 6-point decrease from baseline with suvorexant 15 mg or 20 mg at month 1 (10 [95% CI, 7–19]) and month 3 (8 [95% CI, 6–14]) were intermediate between the NNT ranges for pooled lemborexant doses (5–7) and pooled daridorexant doses (12–13). For PSG outcomes, only available for comparison at month 1, NNT estimates for lemborexant

were similar to those for daridorexant. For many of the efficacy outcomes, the 95% CIs for lemborexant and daridorexant overlapped, indicating an appropriately designed trial including both treatments would be needed to more precisely compare their efficacy profiles.

Generally, a NNH > 10 is desirable, although a NNH < 10 may still be accepted for an AE that is mild, is temporary, does not result in discontinuation, does not pose a serious health risk, or causes minimal distress.[14] Both lemborexant and daridorexant had NNH ≥ 10 indicative of a favorable tolerability profile compared with placebo. At month 3, rates of discontinuation due to an AE were not significant for either pooled lemborexant doses or pooled daridorexant doses, with higher discontinuation rates with placebo than observed with daridorexant. NNH versus placebo for both fatigue and somnolence favored daridorexant over lemborexant. NNH versus placebo for somnolence with daridorexant was also more favorable than those reported previously for other hypnotics (except ramelteon 8 mg).[16] Somnolence with lemborexant was dose-dependent, and the prescribing information for lemborexant recommends a dose of lemborexant 5 mg, to be increased up to 10 mg based on clinical response and tolerability.[11] Nonetheless, rates of discontinuation due to an AE of somnolence were low with lemborexant.

LHH ratios may help place NNH and NNT in a broader context and may reflect instances in which a lower NNH may be acceptable if a treatment has a desirable NNT (< 10). A LHH of much greater than 1 was observed for discontinuation due to an AE at month 3 for both lemborexant and daridorexant, with higher LHH reported with daridorexant across the subjectively reported outcomes. LHHs for sTST > 80-minute increase and ISI ≥ 6-point decrease from baseline were > 1 for both daridorexant and lemborexant for AEs of fatigue and somnolence, indicating the treatments are more likely to be efficacious than cause these AEs.

A limitation of this analysis includes the potential for introduced biases. Indirect comparisons can be biased by heterogeneity in study design between trials that may include differences in baseline characteristics, outcome definitions, medication dosing, trial duration, and timing of assessments.[28] Trials included in this analysis had different study designs for lemborexant and daridorexant and the enrollment of similar yet different populations (Supplementary Table 1). For example, the lemborexant SUNRISE 1 study was limited to older adults, ≥ 55 years old, with an ISI score ≥ 13, while the other 3 studies were open to adults ≥ 18 years old with an ISI score ≥ 15. In SUNRISE 1, participants were not required to have sleep onset difficulties, whereas the daridorexant studies were limited to patients with a history of sSOL ≥ 30 minutes. Moreover, the mean baseline LPS in SUNRISE 1 (range, 44.6–44.9 minutes) was shorter than the mean baseline LPS in studies of daridorexant (range, 63.6–71.8 min). Despite this population difference, the NNT for LPS ≥ 50% improvement at month 1 with pooled lemborexant was still significant in SUNRISE 1 (Supplementary Table 2). Population differences also exist regarding ethnic diversity, with the lemborexant SUNRISE 1 and SUNRISE 2 studies including 25.4% and 28.5% non-White participants, respectively, compared with 10%–12% for daridorexant studies 1 and 2. Additionally, objective PSG measures to confirm severity for study inclusion were not required for all of the trials. These variabilities in study design limit the ability to make definitive statements based on the results of these analyses. Further research using direct head-to-head clinical trials among DORAs would be beneficial to provide more robust evidence for the relative efficacy and safety of lemborexant and daridorexant.

An additional limitation is that the data from this study were limited to categorical outcomes that were reported previously in the literature and regulatory documents for daridorexant. For example, data for subjective WASO and sSOL were not available for daridorexant, thereby preventing comparison. As available dichotomous data for suvorexant differed, it was not possible to conduct an in-depth comparison of all 3 FDA-approved DORAs. As is commonly a concern when interpreting clinical trial data for daily practice, results may not be generalizable to the real-world treatment population due to the strict inclusion and exclusion criteria of clinical studies, which often exclude patients with comorbidities. NNH versus placebo for discontinuation specifically may not always generalize to overall tolerability, as the reasons for clinical trial discontinuation are complex. Additionally, due to the short-term duration and small sample sizes of many trials, the NNH for delayed adverse outcomes or uncommon AEs were likely not captured. Lastly, not all AEs leading to discontinuation are associated with study drug. Generalizability to the real-world population is further limited by the short duration of some of the trials included in this analysis, which did not capture long-term outcomes. As long-term data for insomnia treatments were not required by regulatory agencies until recent years, the majority of clinical trials for insomnia treatments do not report long-term outcomes.[29] While the SUNRISE 2 study investigated long-term lemborexant treatment for up to 12 months (6 months placebo-controlled), future long-term trials would be required to characterize and compare the long-term safety and efficacy of lemborexant and daridorexant.

CONCLUSION

This analysis supports the use of lemborexant and daridorexant for the treatment of adults with insomnia, with a more favorable NNT efficacy profile for lemborexant and more favorable NNH estimates for discontinuation due to an AE for daridorexant. For both agents, NNH estimates for discontinuation due to an AE were not significant. The LHH for an AE of somnolence indicated

a tolerability advantage for daridorexant. Definitive statements on relative benefits between the 2 treatments, however, should be made with caution. Well-designed direct head-to-head clinical trials among the DORAs would be helpful to further characterize any potential differences in their efficacy and safety profiles.

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Supplementary Material

Article Title: Lemborexant and Daridorexant for the Treatment of Insomnia: An Indirect Comparison Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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Supplementary Table 1. Summary of Study Designs

	Lemborexant		Daridorexant	
	SUNRISE 1	**SUNRISE 2**	**Study 1**	**Study 2**
Diagnosis Inclusion Criteria	DSM-5 insomnia disorder with ISI ≥13	DSM-5 insomnia disorder with ISI ≥15	DSM-5 insomnia disorder with ISI ≥15	DSM-5 insomnia disorder with ISI ≥15
PSG Inclusion Criteria	WASO ≥60 min, neither night <45 min	none	LPS ≥20 min, WASO ≥30 min, TST <7 h	LPS ≥20 min, WASO ≥30 min, TST <7 h
Self-Reported Inclusion Criteria	sWASO ≥60 min ≥3 nights/week in previous 4 weeks	sSOL ≥30 min and/or sWASO ≥60 min ≥3 nights/week in previous 4 weeks	sSOL ≥30 min and sWASO ≥30 min and sTST ≤6.5 h for ≥3 nights/week for ≥3 months	sSOL ≥30 min and sWASO ≥30 min and sTST ≤6.5 h for ≥3 nights/week for ≥3 months
Patients randomized	1006	949	930	924
Age ≥65 years, %	45	28	39	39
Women, %	86	68	67	69
Baseline LPS	Baseline LPS, mean (SD), min 44.5 (35.5)	Baseline LPS, range of mean (SD) for treatment groups, min 25.1 (16.7)-37.4 (32.5)		
Study Duration	~2-week placebo run-in period, 30-day treatment period, 14–18-day follow-up	14–17-day placebo run-in period, 6-month placebo-controlled treatment period, 6-month extension period[a]	13–24-day placebo run-in period, 3-month treatment period, 7-day placebo run-out period, 23-day follow up or extension trial	13–24-day placebo run-in period, 3-month treatment period, 7-day placebo run-out period, 23-day follow up or extension trial
Dosing	Placebo, zolpidem tartrate extended release (6.25 mg), or lemborexant (5 mg or 10 mg) at bedtime	Placebo or lemborexant (5 mg or 10 mg) ≤5 min of bedtime	Placebo or daridorexant (25 mg or 50 mg) in the evening	Placebo or daridorexant (10 mg or 25 mg) in the evening
Efficacy Outcomes	*Primary*: LPS *Secondary:* SE, WASO, WASO2H, sSE, sSOL, sWASO, ISI	*Primary:* sSOL *Secondary:* sSE, sWASO, sTST	*Primary:* WASO, LPS *Secondary:* sTST, IDSIQ, sWASO, sSOL, TST	*Primary:* WASO, LPS *Secondary*: sTST, IDSIQ, sWASO, sSOL, TST
Efficacy Assessment Schedule	Electronic sleep diary daily ≤1 h of waking; PSG nights 1/2 and 29/30	Electronic sleep diary daily; outcomes assessed at 7 days, month 1, month 3, month 6	Electronic sleep diary daily; PSG at placebo run in, month 1 end, month 3 end, placebo run-out	Electronic sleep diary daily; PSG at placebo run in, month 1 end, month 3 end, placebo run-out

[a]The 6-month extension period was not included in this analysis

DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth edition; IDSIQ: Insomnia Daytime Symptoms and Impacts Questionnaire; ISI: Insomnia Severity Index; LPS: latency to persistent sleep; PSG: polysomnography; SE: sleep efficiency; sSE: subjective sleep efficiency; sSOL: subjective sleep onset latency; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset; TST: total sleep time; WASO: wake after sleep onset; WASO2H, wake after sleep onset in the second half of the night.

Supplementary Table 2. Lemborexant Efficacy Outcomes at End of Month 1 (SUNRISE 1)

Outcome	Lemborexant 5 mg			Lemborexant 10 mg			Zolpidem tartrate ER 6.25 mg			Placebo			Lemborexant 5 mg vs placebo NNT (95% CI)	Lemborexant 10 mg vs placebo NNT (95% CI)	Lemborexant 5 mg + 10 mg vs placebo NNT (95% CI)	Zolpidem tartrate ER vs placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%	n	N	%				
ISI <10	96	257	37.4	97	253	38.3	99	244	40.6	51	198	25.8	9 (5-33)	8 (5-25)	9 (6-22)	7 (5-17)
ISI ≤7	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 ≥6 points decrease from baseline	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 (4-11)
sTST >80 minutes increase from baseline	89	245	36.3	106	244	43.4	98	235	41.7	44	190	23.2	8 (5-22)	5 (4-9)	6 (5-11)	6 (4-11)
LPS ≥50% improvement from baseline (PSG, averaged from Day 29 and Day 30)	106	260	40.8	124	260	47.7	68	250	27.2	61	200	30.5	10 (6-66)	6 (4-12)	8 (5-17)	-27 (ns)
LPS ≥75% improvement from baseline (PSG, averaged from Day 29 and Day 30)	36	260	13.8	50	260	19.2	19	250	7.6	18	200	9.0	21 (ns)	10 (7-25)	14 (8-41)	-72 (ns)
WASO ≥50% improvement from baseline (PSG averaged from Day 29 and Day 30)	95	260	36.5	100	260	38.5	71	250	28.4	29	200	14.5	5 (47)	5 (4-7)	5 (4-6)	8 (5-16)
WASO ≥75% improvement from baseline (PSG, averaged from Day 29 and Day 30)	9	260	3.5	18	260	6.9	8	250	3.2	5	200	2.5	104 (ns)	23 (13-153)	38 (ns)	143 (ns)

Denominator (N) is the number of randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline assessment on the efficacy outcome of interest at any time after randomization (and thus N can vary from outcome to outcome if not all patients had this test done). PSG baseline are the averaged values from the testing done during the run-in period before receiving randomized study medication.

Abbreviations: ER: extended release; ISI: Insomnia Severity Index; LPS: latency to persistent sleep; NNT: number needed to treat; ns: not significant; PSG: polysomnography; sTST: subjective total sleep time; WASO: wake after sleep onset.

Supplementary Table 3. Lemborexant Efficacy Outcomes at End of Month 1 and Month 3 (SUNRISE 2)

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	%			
MONTH 1												
ISI <10	96	301	31.9	98	287	34.1	56	296	18.9	8 (5-17)	7 (5-13)	8 (5-13)
ISI ≤7	69	301	22.9	70	287	24.4	36	296	12.2	10 (6-22)	9 (6-17)	9 (6-16)
ISI ≥6 points decrease from baseline	164	301	54.5	160	287	55.7	116	296	39.2	7 (5-14)	6 (5-12)	7 (5-11)
sTST >80 minutes increase from baseline	60	284	21.1	82	282	29.1	53	291	18.2	35 (ns)	10 (6-26)	15 (8-85)
MONTH 3												
ISI <10	120	274	43.8	124	259	47.9	79	283	27.9	7 (5-13)	5 (4-9)	6 (5-9)
ISI ≤7	82	274	29.9	92	259	35.5	54	283	19.1	10 (6-27)	7 (5-12)	8 (6-14)
ISI ≥6 points decrease from baseline	187	274	68.2	176	259	68.0	135	283	47.7	5 (4-8)	5 (4-9)	5 (4-8)
sTST >80 minutes increase from baseline	92	258	35.7	98	250	39.2	71	269	26.4	11 (6-72)	8 (5-21)	10 (6-24)

Denominator (N) is the number of randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline assessment on the efficacy outcome of interest at any time after randomization (and thus N can vary from outcome to outcome if not all patients had this test done).

Abbreviations: ISI: Insomnia Severity Index; NNT: number needed to treat; ns: not significant; sTST: subjective total sleep time.

Supplementary Table 4. Daridorexant Efficacy Outcomes at End of Month 1 and Month 3 (Study 2 [NCT03575104])

Outcome	Daridorexant 25 mg			Placebo			Daridorexant 25 mg vs placebo NNT (95% CI)
	n	N	%	n	N	%	
MONTH 1							
ISI <10	60	287	20.9	40	294	13.6	14 (8-85)
ISI ≥6 points decrease from baseline	109	287	38.0	87	294	29.6	12 (7-139)
sTST >80 minutes increase from baseline	69	297	23.2	47	297	15.8	14 (8-95)
MONTH 3							
ISI <10	95	280	33.9	64	277	23.1	10 (6-30)
ISI ≥6 points decrease from baseline	154	280	55.0	127	277	45.8	11 (6-114)
sTST >80 minutes increase from baseline	83	285	29.1	55	287	19.2	10 (6-34)

Data from [18] and [17] Integrated Review.

Abbreviations: ISI: Insomnia Severity Index; NNT: number needed to treat; ns: not significant; sTST: subjective total sleep time.

Supplementary Table 5. Daridorexant Efficacy Outcomes at End of Month 1 and Month 3 (Pooled Study 1 and Study 2)

Outcome	Daridorexant 25 mg			Daridorexant 25 mg + 50 mg			Placebo			Daridorexant 25 mg vs placebo NNT (95% CI)	Daridorexant 25 mg + 50 mg vs placebo NNT (95% CI)
	n	N	%	n	N	%	n	N	%		
MONTH 1											
ISI <10	116	579	20.0	177	878	20.2	73	591	12.4	13 (9-29)	13 (9-25)
ISI ≥6 points decrease from baseline	212	579	36.6	332	878	37.8	172	591	29.1	14 (8-47)	12 (8-26)
sTST >80 minutes increase from baseline	123	600	20.5	192	904	21.2	78	599	13.0	14 (9-31)	13 (9-23)
MONTH 3											
ISI <10	193	566	34.1	293	849	34.5	135	558	24.2	11 (7-22)	10 (7-19)
ISI ≥6 points decrease from baseline	299	566	52.8	459	849	54.1	258	558	46.2	16 (8-133)	13 (8-40)
sTST >80 minutes increase from baseline	164	577	28.4	262	866	30.3	115	576	20.0	12 (8-29)	10 (7-18)

Data from [18] and [17] Integrated Review.

Abbreviations: ISI: Insomnia Severity Index; NNT: number needed to treat; ns: not significant; sTST: subjective total sleep time.

Supplementary Table 6. Daridorexant Tolerability Outcomes Through Month 3 (Study 1 [NCT03545191])

Outcome	Daridorexant 25 mg			Daridorexant 50 mg			Placebo			Daridorexant 25 mg vs placebo NNH (95% CI)	Daridorexant 50 mg vs placebo NNH (95% CI)	Daridorexant 25 mg + 50 mg vs placebo NNH (95% CI)
	n	N	%	n	N	%	n	N	%			
Discontinuation because of AE	7	310	2.3	3	308	1.0	10	309	3.2	ND	ND	ND
Nasopharyngitis	21	310	6.8	20	308	6.5	20	309	6.5	332 (ns)	4759 (ns)	618 (ns)
Headache	16	310	5.2	19	308	6.2	12	309	3.9	79 (ns)	44 (ns)	57 (ns)
Accidental overdose	4	310	1.3	8	308	2.6	5	309	1.6	ND	103 (ns)	309 (ns)
Fatigue	7	310	2.3	7	308	2.3	2	309	0.6	63 (ns)	62 (ns)	62 (33-699)
Dizziness	6	310	1.9	7	308	2.3	2	309	0.6	78 (ns)	62 (ns)	69 (35-7025)
Nausea	1	310	0.3	7	308	2.3	3	309	1.0	ND	77 (ns)	309 (ns)
Somnolence	11	310	3.5	5	308	1.6	6	309	1.9	63 (ns)	ND	155 (ns)
Fall	1	310	0.3	1	308	0.3	8	309	2.6	ND	ND	ND
Upper respiratory tract infection	1	310	0.3	1	308	0.3	3	309	1.0	ND	ND	ND
Excessive daytime sleepiness	2	310	0.6	1	308	0.3	1	309	0.3	311 (ns)	95172 (ns)	618 (ns)
Sleep paralysis	1	310	0.3	1	308	0.3	0	309	0.0	310 (ns)	308 (ns)	309 (ns)
Hallucinations	1	310	0.3	0	308	0.0	0	309	0.0	310 (ns)	ND	618 (ns)
Suicidal injury or self-injury	0	310	0.0	0	308	0.0	0	309	0.0	ND	ND	ND

Table reprinted in part from [18]. Reprinted from *The Lancet Neurology*, Vol 21(2), Mignot E, Mayleben D, Fietze I, et al. , Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials., Page 125-139, Copyright 2022, with permission from Elsevier.

Abbreviations: AE: adverse event; ND: no difference (rate on medication ≤ placebo); NNH: number needed to harm; ns: not significant.

Supplementary Table 7. Daridorexant Tolerability Outcomes Through Month 3 (Study 2 [NCT03575104])

Outcome	Daridorexant 25 mg			Placebo			Daridorexant 25 mg vs placebo NNH (95% CI)
	n	N	%	n	N	%	
Discontinuation because of AE	4	308	1.3	7	306	2.3	ND
Nasopharyngitis	13	308	4.2	16	306	5.2	ND
Headache	15	308	4.9	11	306	3.6	79 (ns)
Accidental overdose	4	308	1.3	1	306	0.3	103 (ns)
Fatigue	11	308	3.6	2	306	0.7	35 (20-153)
Dizziness	6	308	1.9	4	306	1.3	156 (ns)
Nausea	2	308	0.6	3	306	1.0	ND
Somnolence	10	308	3.2	4	306	1.3	52 (ns)
Fall	3	308	1.0	3	306	1.0	ND
Upper respiratory tract infection	3	308	1.0	6	306	2.0	ND
Excessive daytime sleepiness	4	308	1.3	1	306	0.3	103 (ns)
Sleep paralysis	2	308	0.6	0	306	0.0	154 (ns)
Hallucinations	3	308	1.0	0	306	0.0	103 (ns)
Suicidal injury or self-injury	1	308	0.3	0	306	0.0	308 (ns)

Table reprinted in part from [18]. Reprinted from *The Lancet Neurology*, Vol 21(2), Mignot E, Mayleben D, Fietze I, et al. , Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials., Page 125-139., Copyright 2022, with permission from Elsevier.

Abbreviations: AE: adverse event; ND: no difference (rate on medication ≤ placebo); NNH: number needed to harm; ns: not significant