The Journal of Clinical Psychiatry

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

Author(s): Leslie Citrome, MD, MPH; Timothy R. Juday, PhD, MPA; and Christie Lundwall, PhD

DOI Number: https://doi.org/10.4088/JCP.23m14851

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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