

Article title: A 12-Week, Open-Label, Multicenter Pilot Study to Evaluate the Efficacy and Safety of Lemborexant in Patients with Insomnia Comorbid with Depressive Episodes (SELENADE)

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Authors: Yoshikazu Takaesu*, Hiroyuki Muraoka, Masahiro Takeshima, Masaki Kato, Hirofumi Hirakawa, Hikaru Hori, Ken Inada, Hitoshi Sakurai, Motohiro Ozone, Yosuke Koshikawa, Tomohiko Murao, Takeshi Terao, Koichiro Watanabe, Haruka Yokoyama, Michinori Koebisu, Yuka Kawatsu, Yoshiteru Takekita

*Corresponding author

Yoshikazu Takaesu

Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

e-mail: takaesuy@med.u-ryukyu.ac.jp

ORCID: <https://orcid.org/0000-0002-9169-3249>

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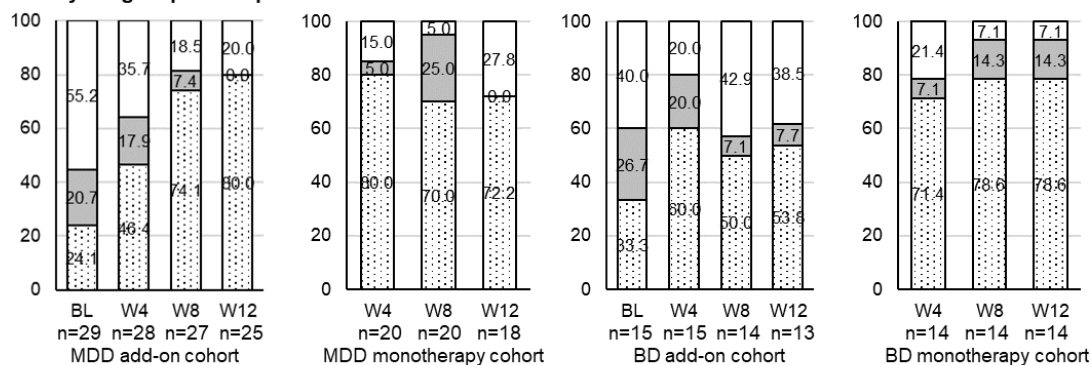
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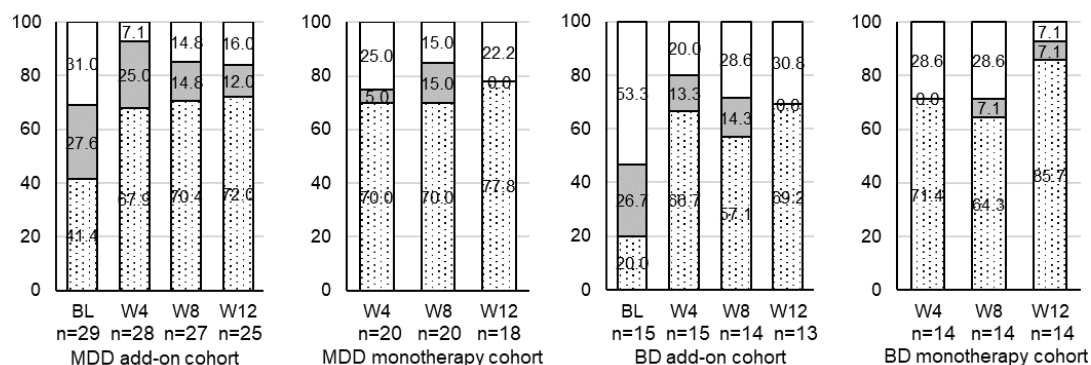
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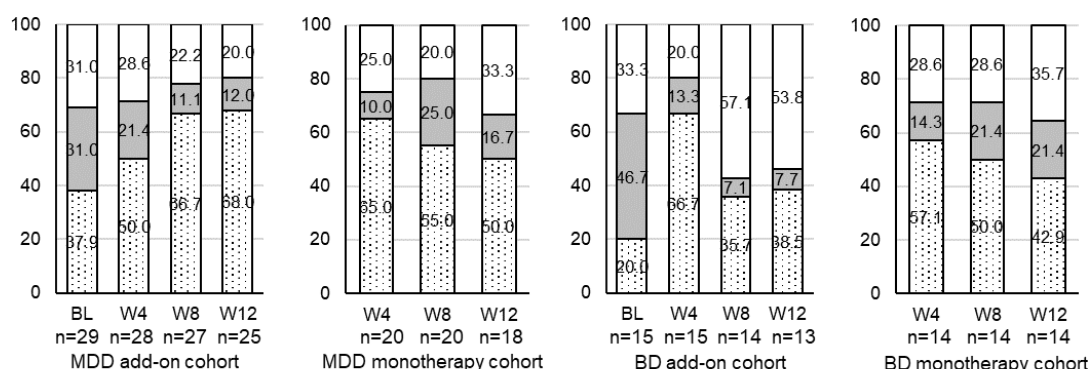
a. Study drug helped sleep



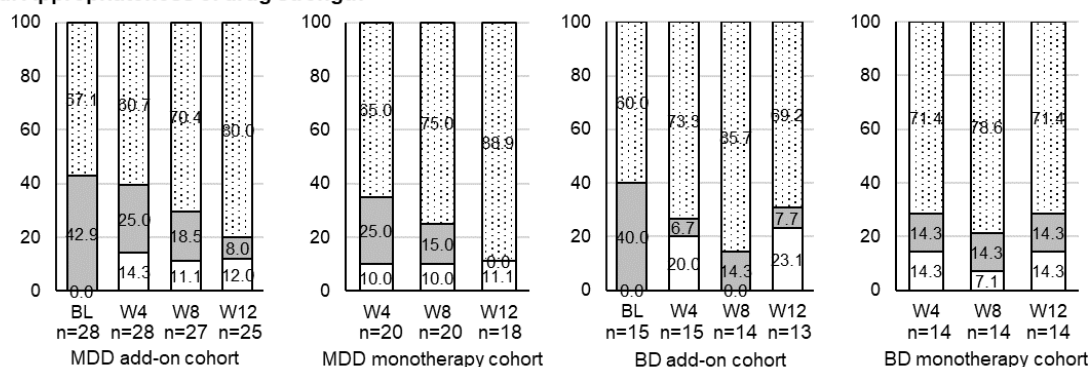
b. Study drug decreased time to fall asleep



c. Study drug increased total sleep time



d. Appropriateness of drug strength



Supplementary Fig.1 Changes in the Patient Global Impression of Insomnia (PGI-I) score after lemborexant treatment

The proportion of answers to each questionnaire was calculated at each evaluation time point. For items a to c, the choices are dot = positive, gray = negative, white = neutral. For item d, the choices are dot = just right, gray = too weak, and white = too strong. Percentages were calculated by dividing the number of patients who responded to each item by the number of patients evaluated at each time point (given as “n = ” at the bottom of each figure). Thus, the percentages do not total 100.

Abbreviations: PGI-I, Patient Global Impression of Insomnia; MDD, major depressive disorder; BD, bipolar disorder; BL, baseline; W4, W8, or W12, 4 weeks, 8 weeks, or 12 weeks after administration of the study drug, respectively.

Supplementary Table 1. Insomnia Severity Index (ISI) total scores (7 items) after lemborexant treatment

Cohort	Time point	N	Actual Value		Change from Baseline			
			Mean	SD	Mean	SD	95% CI	p-value
MDD add-on cohort	Baseline	29	14.5	4.8				
	Week 4	28	12.1	4.7	-2.3	4.2	-3.9 -0.7	0.0065
	Week 8	27	10.6	5.6	-3.6	6.5	-6.2 -1.1	
	Week 12	25	8.9	4.5	-5.6	5.1	-7.7 -3.4	
MDD monotherapy cohort	Baseline	23	13.2	5.5				
	Week 4	22	9.8	6.3	-3.2	4.2	-5.0 -1.3	0.0018
	Week 8	20	10.1	6.9	-2.7	4.8	-4.9 -0.5	
	Week 12	18	8.5	7.3	-4.2	5.6	-7.0 -1.4	
BD add-on cohort	Baseline	14	13.5	6.0				
	Week 4	15	8.5	5.4	-5.2	4.7	-7.9 -2.5	0.0012
	Week 8	14	10.2	5.5	-3.7	6.8	-7.8 0.4	
	Week 12	13	8.7	5.9	-5.0	5.6	-8.6 -1.4	
BD monotherapy cohort	Baseline	15	11.8	4.6				
	Week 4	15	7.3	3.3	-4.5	3.4	-6.3 -2.6	0.0001
	Week 8	14	6.5	4.1	-5.4	3.8	-7.5 -3.2	
	Week 12	14	6.0	4.0	-5.9	3.8	-8.0 -3.7	

Abbreviations: ISI, insomnia severity index; SD, standard deviation; CI, confidence interval; MDD, major depressive disorder; BD, bipolar disorder.

Supplementary Table 2. HAM-D-17 total scores (17 items) and HAM-D-17 subtotal scores (excluding sleep-related items) after lemborexant treatment

Item	Cohort	Time point	N	Actual value		Change from baseline			
				Mean	SD	Mean	SD	95% CI	
HAM-D-17 Total score (Item1 - 17)	MDD add-on cohort	Baseline	28	13.6	5.1				
		Week 4	27	9.4	4.7	-3.8	4.1	-5.4	-2.1
		Week 8	27	8.6	4.9	-4.6	3.9	-6.2	-3.0
		Week 12	25	6.9	4.0	-6.4	3.5	-7.8	-4.9
	MDD monotherapy cohort	Baseline	23	12.6	5.1				
		Week 4	22	9.5	5.1	-3.2	3.5	-4.7	-1.6
		Week 8	19	7.4	5.0	-5.4	4.2	-7.5	-3.4
		Week 12	18	5.4	3.9	-6.2	3.1	-7.7	-4.6
	BD add-on cohort	Baseline	15	13.9	4.3				
		Week 4	15	8.4	6.1	-5.5	3.2	-7.2	-3.7
		Week 8	13	8.1	4.6	-5.8	3.8	-8.1	-3.5
		Week 12	13	9.2	5.7	-5.2	5.2	-8.4	-2.1
	BD monotherapy cohort	Baseline	15	11.4	3.4				
		Week 4	15	6.4	4.0	-5.0	4.9	-7.7	-2.3
		Week 8	14	6.4	3.4	-5.1	3.8	-7.3	-2.9
		Week 12	14	6.2	3.8	-5.4	3.2	-7.2	-3.5
HAM-D-17 Subtotal score excluding items related to sleep (Items 1–3 and 7–17)	MDD add-on cohort	Baseline	28	10.1	4.5				
		Week 4	27	7.7	4.0	-2.2	3.4	-3.5	-0.8
		Week 8	27	7.0	4.2	-2.8	3.5	-4.2	-1.4
		Week 12	25	5.9	3.6	-4.0	3.1	-5.3	-2.7
	MDD monotherapy cohort	Baseline	23	9.1	4.5				
		Week 4	22	7.8	4.2	-1.5	3.3	-2.9	0.0
		Week 8	20	5.9	3.9	-3.4	3.5	-5.0	-1.8
		Week 12	18	4.7	3.2	-3.6	2.8	-4.9	-2.2
	BD add-on cohort	Baseline	15	10.7	3.5				
		Week 4	15	7.4	5.4	-3.3	3.2	-5.1	-1.5
		Week 8	13	6.7	3.7	-3.9	2.9	-5.7	-2.2
		Week 12	13	7.8	4.6	-3.5	3.9	-5.9	-1.2
	BD monotherapy cohort	Baseline	15	8.4	3.7				
		Week 4	15	4.9	3.4	-3.5	4.2	-5.8	-1.1
		Week 8	14	5.3	2.9	-3.3	3.3	-5.2	-1.4
		Week 12	14	5.2	3.3	-3.4	3.0	-5.1	-1.6

Abbreviations: HAM-D-17, Hamilton Rating Scale for Depression 17 items; SD, standard deviation; CI, confidence interval; MDD, major depressive disorder; BD, bipolar disorder.

Supplementary Table 3. Young Mania Rating Scale (YMRS) total scores after lemborexant treatment

Cohort	Time point	N	Actual value		Change from baseline		
			Mean	SD	Mean	SD	95% CI
BD add-on cohort	Baseline	15	1.1	1.8			
	Week 4	15	0.5	0.8	-0.7	1.8	-1.6 0.3
	Week 8	14	0.7	1.3	-0.5	1.5	-1.4 0.4
	Week12	13	0.6	1.3	-0.7	2.0	-1.9 0.5
BD monotherapy cohort	Baseline	14	2.3	2.5			
	Week 4	15	0.9	1.3	-1.3	2.3	-2.6 0
	Week 8	14	0.6	1.3	-1.6	2.1	-2.9 -0.4
	Week12	14	0.8	1.1	-1.5	2.2	-2.8 -0.2

Abbreviations: YMRS, Young Mania Rating Scale; SD, standard deviation; CI, confidence interval; BD, bipolar disorder.

Supplementary Table 4. Concomitant drugs

	MDD add-on cohort		MDD monotherapy cohort		BD add-on cohort		BD monotherapy cohort	
	n = 29		n = 23		n = 15		n = 15	
	n	(%)	n	(%)	n	(%)	n	(%)
Drugs for insomnia								
Brotizolam	5	(17.2)	0	(0.0)	0	(0.0)	0	(0.0)
Estazolam	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Eszopiclone	9	(31.0)	0	(0.0)	7	(46.7)	0	(0.0)
Ethyl loflazepate	3	(10.3)	0	(0.0)	0	(0.0)	0	(0.0)
Flunitrazepam	3	(10.3)	0	(0.0)	3	(20.0)	0	(0.0)
Quazepam	0	(0.0)	0	(0.0)	2	(13.3)	0	(0.0)
Ramelteon	2	(6.9)	0	(0.0)	2	(13.3)	0	(0.0)
Triazolam	2	(6.9)	0	(0.0)	0	(0.0)	0	(0.0)
Zolpidem tartrate	4	(13.8)	0	(0.0)	0	(0.0)	0	(0.0)
Zopiclone	1	(3.4)	0	(0.0)	0	(0.0)	0	(0.0)
Drug for mood disorders								
Aripiprazole	6	(20.7)	0	(0.0)	0	(0.0)	2	(13.3)
Brexiprazole	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)
Clonazepam	1	(3.4)	0	(0.0)	0	(0.0)	1	(6.7)
Duloxetine hydrochloride	6	(20.7)	1	(4.3)	0	(0.0)	0	(0.0)
Escitalopram oxalate	5	(17.2)	7	(30.4)	0	(0.0)	1	(6.7)
Fluvoxamine maleate	0	(0.0)	1	(4.3)	0	(0.0)	0	(0.0)
Lamotrigine	0	(0.0)	0	(0.0)	2	(13.3)	4	(26.7)
Lithium carbonate	0	(0.0)	0	(0.0)	4	(26.7)	6	(40.0)
Lurasidone hydrochloride	2	(6.9)	0	(0.0)	6	(40.0)	3	(20.0)
Milnacipran hydrochloride	0	(0.0)	1	(4.3)	0	(0.0)	0	(0.0)
Mirtazapine	9	(31.0)	9	(39.1)	0	(0.0)	2	(13.3)
Nortriptyline hydrochloride	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Olanzapine	0	(0.0)	1	(4.3)	1	(6.7)	1	(6.7)
Paroxetine hydrochloride hydrate	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)
Quetiapine fumarate	0	(0.0)	0	(0.0)	4	(26.7)	3	(20.0)
Risperidone	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Sertraline hydrochloride	1	(3.4)	3	(13.0)	0	(0.0)	0	(0.0)
Sodium valproate	1	(3.4)	1	(4.3)	4	(26.7)	2	(13.3)
Tandospirone citrate	0	(0.0)	2	(8.7)	1	(6.7)	1	(6.7)
Trazodone hydrochloride	7	(24.1)	4	(17.4)	1	(6.7)	3	(20.0)
Venlafaxine hydrochloride	5	(17.2)	2	(8.7)	0	(0.0)	1	(6.7)
Vortioxetine hydrobromide	5	(17.2)	3	(13.0)	1	(6.7)	0	(0.0)
Drugs for other psychiatric disorders								
Guanfacine hydrochloride	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Tofisopam	0	(0.0)	1	(4.3)	0	(0.0)	0	(0.0)

Abbreviations: MDD, major depressive disorder; BD, bipolar disorder.

Supplementary Table 5. Adherence to the study drug

		MDD add-on cohort		MDD monotherapy cohort		BD add-on cohort		BD monotherapy cohort	
		n = 29		n = 23		n = 16		n = 15	
Discontinuation of study drug, yes	n (%)	4	(13.8)	3	(13.0)	2	(12.5)	0	(0.0)
Continuation of treatment for insomnia including lemborexant after 12 weeks	n (%)	25	(100.0)	18	(90.0)	14	(100.0)	13	(86.7)
Percent days adherent for study drug (%)	Mean (SD)	98.52	(4.05)	85.43	(25.34)	98.73	(3.05)	92.25	(14.16)
≥80% adherence to study drug	n (%)	29	(100.0)	17	(73.9)	16	(100.0)	13	(86.7)
Duration of study drug administration (days)	Mean (SD)	77.0	(17.4)	77.9	(17.5)	81.6	(8.6)	86.0	(5.3)
Actual number of days the study drug was administered (days)	Mean (SD)	76.2	(18.2)	69.7	(25.2)	80.6	(8.6)	79.3	(12.8)
Average daily dose of study drug (mg/day)	Mean (SD)	5.78	(1.18)	5.34	(1.68)	5.64	(1.27)	5.12	(0.78)

Abbreviations: MDD, major depressive disorder; BD, bipolar disorder; SD, standard deviation.

Supplementary Table 6. ISI total scores (7 items) by experience of lemborexant dose escalation

Cohort	Experience of increasing	Time point		N	Mean	Standard deviation	Minimum	Q1	Median	Q3	Maximum	95% CI	
												Lower	Upper
MDD add-on	No	Baseline	Value	18	13.9	3.8	6	12.0	14.5	17.0	19	12.0	15.8
		Week 4	Value	17	11.4	4.8	5	7.0	12.0	14.0	21	8.9	13.9
			Change from baseline	17	-2.3	3.7	-13	-3.0	-2.0	0.0	3	-4.2	-0.4
		Week 8	Value	16	10.4	5.2	4	7.0	9.0	14.5	20	7.6	13.1
			Change from baseline	16	-3.0	4.9	-11	-8.0	-2.5	-0.5	8	-5.6	-0.4
		Week 12	Value	16	9.1	4.7	3	6.0	7.0	12.5	19	6.6	11.5
			Change from baseline	16	-4.3	5.5	-13	-8.5	-4.0	-1.5	7	-7.2	-1.4
	Yes	Baseline	Value	11	15.5	6.1	3	11.0	17.0	21.0	22	11.4	19.5
		Week 4	Value	11	13.1	4.6	6	10.0	12.0	18.0	21	10.0	16.2
			Change from baseline	11	-2.4	5.0	-11	-4.0	-3.0	0.0	8	-5.7	1.0
		Week 8	Value	11	10.9	6.4	2	5.0	11.0	18.0	20	6.6	15.2
			Change from baseline	11	-4.5	8.5	-15	-11.0	-6.0	-1.0	17	-10.2	1.2
		Week 12	Value	9	8.7	4.3	2	7.0	8.0	12.0	14	5.3	12.0
			Change from baseline	9	-7.8	3.7	-14	-10.0	-8.0	-5.0	-2	-10.6	-4.9
MDD mono	No	Baseline	Value	14	12.1	5.4	6	6.0	11.5	17.0	20	9.0	15.2
		Week 4	Value	13	6.5	5.2	1	3.0	6.0	8.0	18	3.4	9.7
			Change from baseline	13	-5.1	4.2	-14	-6.0	-5.0	-3.0	1	-7.6	-2.6
		Week 8	Value	13	8.3	5.3	1	6.0	8.0	10.0	20	5.1	11.5
			Change from baseline	13	-3.3	5.1	-13	-5.0	-3.0	0.0	4	-6.4	-0.3
		Week 12	Value	12	5.8	5.4	1	2.0	3.0	8.5	20	2.4	9.3
			Change from baseline	12	-5.3	5.7	-17	-8.5	-4.0	-2.0	4	-9.0	-1.7
	Yes	Baseline	Value	9	14.9	5.4	7	11.0	14.0	18.0	24	10.7	19.1
		Week 4	Value	9	14.4	4.8	5	12.0	15.0	18.0	20	10.7	18.2
			Change from baseline	9	-0.4	2.4	-4	-2.0	0.0	0.0	4	-2.3	1.4
		Week 8	Value	7	13.4	8.7	1	7.0	10.0	22.0	25	5.4	21.5
			Change from baseline	7	-1.6	4.4	-6	-5.0	-4.0	4.0	5	-5.7	2.5
		Week 12	Value	6	13.8	8.0	1	9.0	15.5	21.0	21	5.4	22.2
			Change from baseline	6	-1.8	5.1	-6	-6.0	-3.5	1.0	7	-7.2	3.5
BD add-on	No	Baseline	Value	6	17.0	3.8	12	15.0	16.0	21.0	22	13.0	21.0
		Week 4	Value	7	9.4	4.2	2	7.0	10.0	13.0	14	5.6	13.3
			Change from baseline	6	-8.0	5.1	-14	-12.0	-9.0	-3.0	-1	-13.4	-2.6
		Week 8	Value	7	9.7	2.7	6	7.0	10.0	13.0	13	7.2	12.2
			Change from baseline	6	-7.8	4.9	-14	-12.0	-8.0	-3.0	-2	-13.0	-2.7
		Week 12	Value	6	9.7	3.8	4	8.0	9.0	14.0	14	5.6	13.7
			Change from baseline	5	-8.4	6.5	-17	-13.0	-7.0	-3.0	-2	-16.4	-0.4
	Yes	Baseline	Value	8	10.9	6.2	0	7.5	11.0	14.5	21	5.7	16.1
		Week 4	Value	8	7.8	6.5	0	3.5	8.0	9.0	21	2.3	13.2
			Change from baseline	8	-3.1	3.3	-7	-6.5	-3.0	0.0	1	-5.9	-0.4
		Week 8	Value	7	10.7	7.6	0	2.0	14.0	17.0	18	3.7	17.8
			Change from baseline	7	-0.1	6.5	-7	-6.0	-1.0	7.0	10	-6.1	5.8
		Week 12	Value	7	7.9	7.4	0	0.0	11.0	13.0	18	1.0	14.7
			Change from baseline	7	-2.6	3.7	-7	-7.0	-3.0	1.0	2	-6.0	0.8
BD mono	No	Baseline	Value	13	11.4	4.6	4	9.0	10.0	13.0	19	8.6	14.1
		Week 4	Value	13	6.8	3.3	3	5.0	6.0	8.0	14	4.8	8.8
			Change from baseline	13	-4.5	3.4	-11	-6.0	-5.0	-4.0	3	-6.6	-2.5
		Week 8	Value	12	5.5	3.3	0	3.5	6.0	7.0	11	3.4	7.6
			Change from baseline	12	-5.9	3.8	-13	-7.5	-5.5	-3.0	-1	-8.3	-3.5
		Week 12	Value	12	4.9	2.9	1	2.0	5.0	7.5	9	3.1	6.8
			Change from baseline	12	-6.5	3.7	-11	-9.5	-6.5	-3.5	0	-8.8	-4.2
	Yes	Baseline	Value	2	14.5	4.9	11	11.0	14.5	18.0	18	-30.0	59.0
		Week 4	Value	2	10.5	0.7	10	10.0	10.5	11.0	11	4.1	16.9
			Change from baseline	2	-4.0	4.2	-7	-7.0	-4.0	-1.0	-1	-42.1	34.1
		Week 8	Value	2	12.5	3.5	10	10.0	12.5	15.0	15	-19.3	44.3
			Change from baseline	2	-2.0	1.4	-3	-3.0	-2.0	-1.0	-1	-14.7	10.7
		Week 12	Value	2	12.5	3.5	10	10.0	12.5	15.0	15	-19.3	44.3
			Change from baseline	2	-2.0	1.4	-3	-3.0	-2.0	-1.0	-1	-14.7	10.7

Abbreviations: MDD, major depressive disorder; BD, bipolar disorder; CI, confidence interval.

Supplementary Table 7. Subjective sleep parameters

Item	Cohort	Time point	N	Actual value		Change from baseline			
				Mean	SD	Mean	SD	95% CI	
Subjective sleep onset latency (sSOL)	MDD add-on cohort	Baseline	26	71.9	51.8				
		Week 4	27	45.6	32.2	-24.6	44.9	-43.1	-6.1
	MDD monotherapy cohort	Baseline	22	63.6	38.4				
		Week 4	20	45.4	43.2	-16.5	30.6	-30.9	-2.2
	BD add-on cohort	Baseline	15	51.5	41.8				
		Week 4	14	35.1	28.2	-13.3	34.4	-33.2	6.5
	BD monotherapy cohort	Baseline	13	35.5	40.8				
		Week 4	13	30.6	39.2	-4.9	20.3	-17.1	7.3
Subjective wake after sleep onset (sWASO)	MDD add-on cohort	Baseline	26	102.4	62.7				
		Week 4	27	104.9	71.8	16.9	47.2	-2.6	36.4
	MDD monotherapy cohort	Baseline	21	77.9	45.5				
		Week 4	19	75.7	52.0	0.4	48.7	-23.1	23.9
	BD add-on cohort	Baseline	14	105.8	106.8				
		Week 4	13	60.8	67.1	-37.9	60.2	-74.3	-1.5
	BD monotherapy cohort	Baseline	13	55.6	37.0				
		Week 4	13	62.7	63.8	7.2	58.4	-28.1	42.5
Subjective perception of number of awakening	MDD add-on cohort	Baseline	26	1.8	1.5				
		Week 4	27	1.6	1.1	-0.1	1.1	-0.6	0.4
	MDD monotherapy cohort	Baseline	22	2.1	1.2				
		Week 4	20	1.9	1.3	-0.2	1.0	-0.7	0.3
	BD add-on cohort	Baseline	15	1.5	1.1				
		Week 4	14	1.4	1.4	-0.1	0.4	-0.3	0.2
	BD monotherapy cohort	Baseline	13	1.0	0.8				
		Week 4	13	1.1	0.8	0.0	0.5	-0.3	0.3
Subjective total sleep time (sTST)	MDD add-on cohort	Baseline	26	356.3	106.0				
		Week 4	27	351.4	99.6	-7.1	63.1	-33.1	19.0
	MDD monotherapy cohort	Baseline	21	340.0	126.3				
		Week 4	19	397.1	125.2	43.6	49.8	19.5	67.6
	BD add-on cohort	Baseline	14	383.1	129.7				
		Week 4	13	451.5	100.3	54.1	55.2	20.8	87.4
	BD monotherapy cohort	Baseline	13	363.7	81.8				
		Week 4	13	381.9	121.4	18.2	69.4	-23.7	60.1
Subjective sleep efficiency (sSE)	MDD add-on cohort	Baseline	26	67.439	15.206				
		Week 4	27	70.282	16.932	0.593	10.381	-3.692	4.878
	MDD monotherapy cohort	Baseline	21	69.945	18.315				
		Week 4	19	76.532	17.006	4.829	11.232	-0.584	10.243
	BD add-on cohort	Baseline	14	71.543	21.199				
		Week 4	13	82.597	13.704	8.733	9.530	2.974	14.492
	BD monotherapy cohort	Baseline	13	81.010	13.053				
		Week 4	13	80.753	20.966	-0.257	11.323	-7.099	6.586
Quality of sleep	MDD add-on cohort	Baseline	26	3.9	1.2				
		Week 4	27	4.2	1.3	0.4	1.2	-0.1	0.9
	MDD monotherapy cohort	Baseline	22	4.1	1.6				
		Week 4	20	4.8	1.5	0.6	0.9	0.1	1.0
	BD add-on cohort	Baseline	15	4.2	1.5				
		Week 4	15	4.6	1.8	0.3	0.7	0.0	0.7
	BD monotherapy cohort	Baseline	13	4.7	1.5				
		Week 4	13	5.2	1.1	0.5	1.6	-0.5	1.4
Morning alertness	MDD add-on cohort	Baseline	26	3.4	0.9				
		Week 4	27	3.7	1.3	0.3	1.1	-0.1	0.8
	MDD monotherapy cohort	Baseline	22	3.9	1.4				
		Week 4	20	4.4	1.7	0.5	0.9	0.1	1.0
	BD add-on cohort	Baseline	15	3.5	1.1				
		Week 4	15	3.6	1.6	0.0	1.1	-0.6	0.6
	BD monotherapy cohort	Baseline	13	4.3	1.4				
		Week 4	13	4.4	1.1	0.2	1.4	-0.7	1.0
Morning mood	MDD add-on cohort	Baseline	26	4.0	1.2				
		Week 4	27	4.4	1.2	0.4	1.1	0.0	0.9
	MDD monotherapy cohort	Baseline	22	4.2	1.6				
		Week 4	20	4.7	1.5	0.5	0.6	0.2	0.8
	BD add-on cohort	Baseline	15	4.1	1.4				
		Week 4	15	4.4	1.8	0.4	1.1	-0.2	1.0
	BD monotherapy cohort	Baseline	13	4.6	1.4				
		Week 4	13	4.9	1.1	0.3	1.2	-0.4	1.0

Abbreviations: SD, standard deviation; CI, confidence interval; MDD, major depressive disorder; BD, bipolar disorder.