Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder

Summary

EudraCT number	2015-004347-39
Trial protocol	GB DE ES IT
Global end of trial date	30 January 2018

Results information

Result version number	v1
This version publication date	15 February 2019
First version publication date	15 February 2019

Trial information

Trial identification

Sponsor protocol code	E2006-G000-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02783729
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	Woodcliff Lake, New jersey, United States, 07677
Public contact	Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate using polysomnography (PSG) that lemborexant (lemborexant 10 milligram [mg] [LEM 10] and lemborexant 5 mg [LEM 5]) is superior to placebo (PBO) on objective sleep onset as assessed by latency to persisted sleep (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Germany: 68
Country: Number of subjects enrolled	Spain: 71
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 843
Worldwide total number of subjects	1006
EEA total number of subjects	143

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	553
From 65 to 84 years	449
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 67 investigative sites in the United States, Spain, Germany, Canada, United Kingdom, and Italy from 31 May 2016 to 30 January 2018.

Pre-assignment

Screening details:

A total of 3537 subjects were screened, of which 1006 subjects were randomized to the treatment period. All subjects who were subsequently randomized completed a Run-in Period before randomization to treatment period.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received lemborexant-matched placebo and zolpidem matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Arm type	Placebo
Investigational medicinal product name	Zolpidem-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Investigational medicinal product name	Lemborexant-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Arm title	Zolpidem Tartrate Extended Release 6.25 mg

Arm description:

Subjects received zolpidem tartrate extended release (ZOL ER) 6.25 mg and lemborexant-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment period.

Arm type	Active comparator
Investigational medicinal product name	Lemborexant-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant-matched placebo, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment period.

Investigational medicinal product name	Zolpidem Tartrate Extended Release
Investigational medicinal product code	
Other name	Ambien CR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received zolpidem tartrate extended release 6.25 mg, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment period.

Arm title	Lemborexant 5 mg

Arm description:

Subjects received Lemborexant 5 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Zolpidem-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received zolpidem-matched placebo, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Investigational medicinal product name	Lemborexant 5 mg
Investigational medicinal product code	E2006
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant 5 mg, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Arm title	Lemborexant 10 mg

Arm description:

Subjects received lemborexant 10 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Zolpidem-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received zolpidem-matched placebo, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Investigational medicinal product name	Lemborexant 10 mg
Investigational medicinal product code	E2006
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant 10 mg, tablet, orally, once daily from Day 1 up to Day 30 in the Treatment Period.

Number of subjects in period 1	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg
Started	208	263	266
Completed	198	246	258
Not completed	10	17	8
Consent withdrawn by subject	2	3	1
Adverse event, non-fatal	2	6	2
Unspecified	1	6	2
Lost to follow-up	2	1	1
Subject choice	2	1	2
Lack of efficacy	1	-	-

Number of subjects in period 1	Lemborexant 10 mg
Started	269
Completed	260
Not completed	9
Consent withdrawn by subject	2
Adverse event, non-fatal	3
Unspecified	3
Lost to follow-up	-
Subject choice	1
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received lemborexant-matched placebo and zolpidem matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	
Reporting group title	Zolpidem Tartrate Extended Release 6.25 mg
Reporting group description:	
Subjects received zolpidem tartrate extended release (ZOL ER) 6.25 mg and lemborexant-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment period.	
Reporting group title	Lemborexant 5 mg
Reporting group description:	
Subjects received Lemborexant 5 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	
Reporting group title	Lemborexant 10 mg
Reporting group description:	
Subjects received lemborexant 10 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	

Reporting group values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg
Number of subjects	208	263	266
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.4	64.3	63.7
standard deviation	± 6.36	± 7.12	± 6.78
Gender categorical			
Units: Subjects			
Female	184	226	229
Male	24	37	37
Ethnicity			
Units: Subjects			
Hispanic or Latino	35	32	51
Not Hispanic or Latino	173	231	215
Race			
Units: Subjects			
White	153	173	199
Black or African American	51	80	63
Japanese	1	1	0
Chinese	1	0	0
Other Asian	0	4	2
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	2	0
Other	2	3	2

LPS			
The baseline values for LPS were analysed in the full analysis set (FAS) defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	43.89	44.52	44.86
standard deviation	± 33.596	± 38.349	± 36.528
Sleep Efficiency (SE)			
The baseline values for SE were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	68.89	68.13	68.36
standard deviation	± 9.639	± 11.419	± 11.268
Wake After Sleep Onset (WASO)			
The baseline values for WASO were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	111.75	114.31	113.44
standard deviation	± 37.179	± 39.992	± 38.953
Wake After Sleep Onset in Second Half of Night (WASO2H)			
The baseline values for WASO2H were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	74.44	78.04	76.60
standard deviation	± 30.109	± 33.849	± 32.903
Body Sway			
The baseline values for body sway were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 199, 239, 245, and 243.			
Units: one-third degree of angle of arc			
arithmetic mean	23.08	26.96	26.40
standard deviation	± 17.506	± 26.502	± 20.781
Total Sleep Time (TST)			
The baseline values for TST were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	330.67	326.99	328.00
standard deviation	± 46.268	± 54.852	± 54.224
Subjective Sleep Onset Latency (sSOL)			
The baseline values for sSol were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 206, 258, 263,			

and 269.			
Units: minutes			
arithmetic mean	55.90	60.54	65.79
standard deviation	± 37.389	± 36.350	± 43.530
Subjective Wake After Sleep Onset (sWASO)			
The baseline values for sWASO were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 206, 259, 264, and 266.			
Units: minutes			
arithmetic mean	170.89	173.06	166.76
standard deviation	± 80.676	± 77.212	± 82.047
Subjective Sleep Efficiency (sSE)			
The baseline values for sSE were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 201, 247, 253, and 258.			
Units: minutes			
arithmetic mean	56.08	55.49	56.05
standard deviation	± 17.343	± 15.802	± 17.094
Subjective Total Sleep Time (sTST)			
The baseline values for sTST were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 201, 247, 253, and 258.			
Units: minutes			
arithmetic mean	276.23	273.07	275.74
standard deviation	± 87.649	± 81.207	± 83.650
Insomnia Severity Index (ISI)			
The baseline values for ISI were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 263, 266, and 269.			
Units: score in scale			
arithmetic mean	11.21	11.06	10.91
standard deviation	± 2.436	± 2.508	± 2.419
Fatigue Severity Scale (FSS)			
The baseline values for FSS were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 263, 266, and 269.			
Units: score on scale			
arithmetic mean	37.48	37.15	37.47
standard deviation	± 13.602	± 13.788	± 13.518
Power of Attention (POA)			
The baseline values for POA were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 249, and 246.			
Units: millisecond			
arithmetic mean	1421.0	1418.7	1452.9
standard deviation	± 210.27	± 195.95	± 263.04
Speed of Memory Retrieval (SOMT)			
The baseline values for SOMT were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy			

measurement. The baseline characteristic was assessed for the following "n" population: 195, 238, 246, and 246.			
Units: milliseconds			
arithmetic mean	4507.7	4513.8	4674.3
standard deviation	± 1098.73	± 1097.65	± 1174.74
Quality of Memory (QOM)			
The baseline values for QOM were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 248, and 246.			
Units: units on scale			
arithmetic mean	342.2	350.0	345.7
standard deviation	± 66.03	± 65.30	± 67.60
Continuity of Attention (COA)			
The baseline values for COA were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 249, and 246.			
Units: units on scale			
arithmetic mean	90.7	90.6	91.0
standard deviation	± 4.77	± 6.0	± 5.15

Reporting group values	Lemborexant 10 mg	Total	
Number of subjects	269	1006	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.2		
standard deviation	± 6.88	-	
Gender categorical			
Units: Subjects			
Female	230	869	
Male	39	137	
Ethnicity			
Units: Subjects			
Hispanic or Latino	47	165	
Not Hispanic or Latino	222	841	
Race			
Units: Subjects			
White	202	727	
Black or African American	62	256	
Japanese	0	2	
Chinese	1	2	
Other Asian	4	10	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	2	
Other	0	7	
LPS			
The baseline values for LPS were analysed in the full analysis set (FAS) defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n"			

population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	44.61		
standard deviation	± 32.986	-	
Sleep Efficiency (SE)			
The baseline values for SE were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	67.85		
standard deviation	± 10.849	-	
Wake After Sleep Onset (WASO)			
The baseline values for WASO were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	114.83		
standard deviation	± 39.997	-	
Wake After Sleep Onset in Second Half of Night (WASO2H)			
The baseline values for WASO2H were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	76.88		
standard deviation	± 32.126	-	
Body Sway			
The baseline values for body sway were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 199, 239, 245, and 243.			
Units: one-third degree of angle of arc			
arithmetic mean	36.29		
standard deviation	± 197.282	-	
Total Sleep Time (TST)			
The baseline values for TST were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 262, 266, and 269.			
Units: minutes			
arithmetic mean	325.07		
standard deviation	± 52.819	-	
Subjective Sleep Onset Latency (sSOL)			
The baseline values for sSol were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 206, 258, 263, and 269.			
Units: minutes			

arithmetic mean	60.88		
standard deviation	± 42.514	-	
Subjective Wake After Sleep Onset (sWASO)			
The baseline values for sWASO were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 206, 259, 264, and 266.			
Units: minutes			
arithmetic mean	175.35		
standard deviation	± 83.453	-	
Subjective Sleep Efficiency (sSE)			
The baseline values for sSE were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 201, 247, 253, and 258.			
Units: minutes			
arithmetic mean	54.31		
standard deviation	± 18.318	-	
Subjective Total Sleep Time (sTST)			
The baseline values for sTST were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 201, 247, 253, and 258.			
Units: minutes			
arithmetic mean	266.10		
standard deviation	± 92.164	-	
Insomnia Severity Index (ISI)			
The baseline values for ISI were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 263, 266, and 269.			
Units: score in scale			
arithmetic mean	10.84		
standard deviation	± 2.334	-	
Fatigue Severity Scale (FSS)			
The baseline values for FSS were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 208, 263, 266, and 269.			
Units: score on scale			
arithmetic mean	37.42		
standard deviation	± 13.111	-	
Power of Attention (POA)			
The baseline values for POA were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 249, and 246.			
Units: millisecond			
arithmetic mean	1399.2		
standard deviation	± 192.47	-	
Speed of Memory Retrieval (SOMT)			
The baseline values for SOMT were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 238, 246, and 246.			
Units: milliseconds			

arithmetic mean	4619.8		
standard deviation	± 1065.00	-	
Quality of Memory (QOM)			
The baseline values for QOM were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 248, and 246.			
Units: units on scale			
arithmetic mean	340.7		
standard deviation	± 72.75	-	
Continuity of Attention (COA)			
The baseline values for COA were analysed in the FAS defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The baseline characteristic was assessed for the following "n" population: 195, 239, 249, and 246.			
Units: units on scale			
arithmetic mean	91.3		
standard deviation	± 4.15	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received lemborexant-matched placebo and zolpidem matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	
Reporting group title	Zolpidem Tartrate Extended Release 6.25 mg
Reporting group description:	
Subjects received zolpidem tartrate extended release (ZOL ER) 6.25 mg and lemborexant-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment period.	
Reporting group title	Lemborexant 5 mg
Reporting group description:	
Subjects received Lemborexant 5 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	
Reporting group title	Lemborexant 10 mg
Reporting group description:	
Subjects received lemborexant 10 mg and zolpidem-matched placebo, tablets, orally, once daily from Day 1 up to Day 30 in the Treatment Period.	

Primary: Change From Baseline in Mean LPS of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30

End point title	Change From Baseline in Mean LPS of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30[1]
End point description:	
LPS is defined as the time in minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness as measured by PSG. Change from baseline to average LPS on Day 29 and 30 was reported. FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.	
End point type	Primary
End point timeframe:	
Baseline, Days 29/30	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	260	260	
Units: minutes				
arithmetic mean (standard deviation)	-7.93 (± 31.946)	-19.53 (± 33.054)	-21.46 (± 32.436)	

Statistical analyses

Statistical analysis title	Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [2]
Method	MMRM
Parameter estimate	Least Squares Geometric Mean(LSGM) Ratio
Point estimate	0.773
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.672
upper limit	0.889

Notes:

[2] - Based on mixed effect model repeated measurement (MMRM) model with log transformation of LPS and factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	MMRM
Parameter estimate	LSGM Ratio
Point estimate	0.723
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.628
upper limit	0.832

Notes:

[3] - Based on MMRM model with log transformation of LPS and factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Secondary: Change From Baseline in Mean SE of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30

End point title	Change From Baseline in Mean SE of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30[4]

End point description:

SE is defined as percentage of time spent asleep per time in bed (TIB), calculated as total sleep time (TST) divided by interval from lights off until lights on as measured by PSG. Change from baseline to average SE on Day 29 and 30 was reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Secondary

End point timeframe:

Baseline, Days 29/30

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	260	260	
Units: minutes				
arithmetic mean (standard deviation)	5.35 (± 9.897)	12.93 (± 9.741)	14.09 (± 10.514)	

Statistical analyses

Statistical analysis title	Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant 5 mg v Placebo
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	MMRM
Parameter estimate	Least Squares Mean (LSM) Difference
Point estimate	7.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.61
upper limit	8.54
Variability estimate	Standard error of the mean
Dispersion value	0.746

Notes:

[5] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline SE as a covariate.

Statistical analysis title	Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	8.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.57
upper limit	9.49
Variability estimate	Standard error of the mean
Dispersion value	0.746

Notes:

[6] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline SE as a covariate.

Secondary: Change From Baseline in Mean WASO of Lemborexant 10 mg and

Lemborexant 5 mg Compared to Placebo on Days 29/30

End point title	Change From Baseline in Mean WASO of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30[7]

End point description:

WASO is defined as minutes of wake from the onset of persistent sleep until lights on as measured by PSG. Change from baseline to average WASO on Days 29 and 30 was reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Secondary

End point timeframe:

Baseline, Days 29/30

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	260	260	
Units: minutes				
arithmetic mean (standard deviation)	-18.58 (± 41.931)	-43.89 (± 39.264)	-46.43 (± 39.595)	

Statistical analyses

Statistical analysis title	Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-23.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.98
upper limit	-17.95
Variability estimate	Standard error of the mean
Dispersion value	3.068

Notes:

[8] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO as a covariate.

Statistical analysis title	Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-25.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.36
upper limit	-19.34
Variability estimate	Standard error of the mean
Dispersion value	3.067

Notes:

[9] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO as a covariate.

Secondary: Change From Baseline in WASO in the Second Half of the Night WASO2H of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER on Days 29/30

End point title	Change From Baseline in WASO in the Second Half of the Night WASO2H of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER on Days 29/30[10]

End point description:

WASO2H is defined as time in minutes of wake during the interval from 240 minutes after lights off until lights on as measured by PSG. Change from baseline to average WASO2H on Days 29 and 30 was reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Secondary

End point timeframe:

Baseline, Days 29/30

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Zolpidem ER 6.25 mg, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	250	260	260	
Units: minutes				
arithmetic mean (standard deviation)	-21.42 (± 36.257)	-27.19 (± 33.047)	-28.84 (± 33.138)	

Statistical analyses

Statistical analysis title	Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5

	mg
Number of subjects included in analysis	510
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038 [11]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-6.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.15
upper limit	-2.15
Variability estimate	Standard error of the mean
Dispersion value	2.298

Notes:

[11] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	510
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [12]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.53
upper limit	-3.47
Variability estimate	Standard error of the mean
Dispersion value	2.309

Notes:

[12] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Other pre-specified: Change from Baseline in Mean Body Sway upon Awakening in the Morning for Lemborexant 5 mg and Lemborexant 10 mg Compared to Zolpidem ER on Days 2/3

End point title	Change from Baseline in Mean Body Sway upon Awakening in the Morning for Lemborexant 5 mg and Lemborexant 10 mg Compared to Zolpidem ER on Days 2/3[13]

End point description:

Body sway is detected through a cable around the subject's waist by the ataxia meter. Body sway is measured in units of 1/3° of the angle of arc. For ease in reporting, these are called arbitrary units, with a higher number indicating more body sway (less postural stability). Change from baseline in mean body sway on Days 2 and 3 was reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 2/3

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only planned to be analyse for the following reporting groups: Zolpidem ER 6.25 mg, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	234	237	234	
Units: one-third degree of angle of arc				
arithmetic mean (standard deviation)	8.47 (± 69.894)	-0.82 (± 20.383)	-8.97 (± 146.679)	

Statistical analyses

Statistical analysis title	Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0171 [14]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-9.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.53
upper limit	-1.72
Variability estimate	Standard error of the mean
Dispersion value	4.029

Notes:

[14] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline posture stability of body sway as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg

Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [15]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-10.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.67
upper limit	-2.81
Variability estimate	Standard error of the mean
Dispersion value	4.04

Notes:

[15] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline posture stability of body sway as a covariate.

Other pre-specified: Change from Baseline in Mean LPS, WASO, and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER on Days 1/2 and Days 29/30

End point title	Change from Baseline in Mean LPS, WASO, and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER on Days 1/2 and Days 29/30[16]

End point description:

LPS is defined as the time in minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness as measured by the PSG. WASO is defined as minutes of wake from the onset of persistent sleep until lights on as measured by PSG. TST is defined as the amount of sleep in minutes from LPS until terminal awakening as measured by PSG. Change from baseline to average LPS, WASO, and TST on Days 1 and 2, and Days 29 and 30 were reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. Here "n" were subjects who were evaluable for the outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 1/2, and Days 29/30

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Zolpidem ER 6.25 mg, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	263	266	269	
Units: minutes				
arithmetic mean (standard deviation)				
LPS: Days 1/2 (n=262, 266, 269)	-12.56 (± 32.506)	-16.59 (± 28.742)	-19.48 (± 31.809)	
LPS: Days 29/30 (n=250, 260, 260)	-7.51 (± 35.065)	-19.53 (± 33.047)	-21.46 (± 32.436)	
WASO: Days 1/2 (n =262, 266, 269)	-44.36 (± 38.074)	-49.96 (± 39.578)	-59.59 (± 37.749)	

WASO: Days 29/30 (n=250, 260, 260)	-36.50 (± 43.406)	-43.89 (± 39.264)	-46.43 (± 39.595)	
TST: Days 1/2 (n=262, 266, 269)	55.31 (± 48.138)	65.22 (± 46.695)	79.58 (± 47.350)	
TST: Days 29/30 (n=250, 260, 260)	43.34 (± 54.012)	61.99 (± 46.817)	67.86 (± 52.117)	

Statistical analyses

Statistical analysis title	LPS, Days 1/2: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0218 [17]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.874
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.981

Notes:

[17] - Based on MMRM model with log transformation of LPS and factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	LPS, Days 1/2: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [18]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.818
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.729
upper limit	0.917

Notes:

[18] - Based on MMRM model with log transformation of LPS and factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	LPS, Days 29/30: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.634
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.556
upper limit	0.724

Notes:

[19] - Based on MMRM model with log transformation of LPS and factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	LPS, Days 29/30: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.594
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.521
upper limit	0.677

Notes:

[20] - Based on MMRM model with log transformation of LPS and factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	WASO, Days 1/2: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0154 [21]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-6.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.15
upper limit	-1.17
Variability estimate	Standard error of the mean
Dispersion value	2.544

Notes:

[21] - Based on MMRM model with factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline WASO as a covariate.

Statistical analysis title	WASO, Days 1/2: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-15.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.01
upper limit	-10.05
Variability estimate	Standard error of the mean
Dispersion value	2.542

Notes:

[22] - Based on MMRM model with factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline WASO as a covariate.

Statistical analysis title	WASO, Days 29/30: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073 [23]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-7.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.36
upper limit	-2.08
Variability estimate	Standard error of the mean
Dispersion value	2.876

Notes:

[23] - Based on MMRM model with factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline WASO as a covariate.

Statistical analysis title	WASO, Days 29/30: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg

Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [24]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.75
upper limit	-3.45
Variability estimate	Standard error of the mean
Dispersion value	2.883

Notes:

[24] - Based on MMRM model with factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline WASO as a covariate.

Statistical analysis title	TST, Days 1/2: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [25]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	10.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.18
upper limit	16.32
Variability estimate	Standard error of the mean
Dispersion value	3.094

Notes:

[25] - Based on MMRM model with factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline TST as a covariate.

Statistical analysis title	TST, Days 1/2: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	23.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	17.04
upper limit	29.15
Variability estimate	Standard error of the mean
Dispersion value	3.085

Notes:

[26] - Based on MMRM model with factors for age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline TST as a covariate.

Statistical analysis title	TST, Days 29/30: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	19.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.63
upper limit	26.2
Variability estimate	Standard error of the mean
Dispersion value	3.457

Notes:

[27] - Based on MMRM model with factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline TST as a covariate.

Statistical analysis title	TST, Days 29/30: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.32
upper limit	30.88
Variability estimate	Standard error of the mean
Dispersion value	3.456

Notes:

[28] - Based on MMRM model with factors for age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline TST as a covariate.

Other pre-specified: Change From Baseline in sSOL, sWASO, sSE, and sTST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER

End point title	Change From Baseline in sSOL, sWASO, sSE, and sTST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER[29]

End point description:

sSOL: estimated minutes from time attempted to sleep to sleep onset. sWASO: estimated minutes of wake at night after initial sleep onset to time stopped trying to sleep for the night. sSE: percentage of sTST per subjective time spent in bed (time attempted to sleep to time stopped trying to sleep for the night, and time spent asleep derived from subjective time spent in bed minus sWASO). sTST: minutes of sleep from sleep onset to time stopped trying to sleep for the night. sSOL, sSE, sWASO, sTST were analyzed with diary handling rules (DHR) on an electronic sleep diary. Subjective measures were derived from sleep diaries entries, collected daily and analyzed at appropriate intervals. FAS: group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. "n": subjects who were evaluable for outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

First 7 nights (approximately Week 1) and Last 7 nights (approximately Week 4)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Zolpidem ER 6.25 mg, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	263	266	269	
Units: minutes				
arithmetic mean (standard deviation)				
sSOL: 1st 7 nights: With DHR(n=251, 259, 266)	-16.23 (± 29.531)	-22.54 (± 32.812)	-21.88 (± 29.269)	
sSOL: last 7 nights: With DHR(n=246, 252, 258)	-17.04 (± 30.683)	-25.20 (± 34.854)	-24.79 (± 34.068)	
sWASO: 1st 7 nights: With DHR(n=253, 261, 262)	-48.91 (± 51.761)	-39.33 (± 55.022)	-55.06 (± 66.696)	
sWASO: last 7 nights: With DHR(n=247, 253, 253)	-63.52 (± 64.161)	-44.51 (± 58.090)	-57.96 (± 72.791)	
sSE: 1st 7 nights: With DHR(n=240, 251, 254)	11.96 (± 12.526)	10.56 (± 12.296)	13.97 (± 14.188)	
sSE: last 7 nights: With DHR(n=235, 245, 244)	14.83 (± 15.011)	12.92 (± 13.884)	16.12 (± 16.300)	
sTST: 1st 7 nights: With DHR(n=240, 251, 254)	56.99 (± 62.880)	50.30 (± 60.065)	67.80 (± 71.134)	
sTST: last 7 nights: With DHR(n=235, 245, 244)	71.01 (± 76.574)	62.41 (± 68.555)	79.95 (± 81.211)	

Statistical analyses

Statistical analysis title	sSOL,First 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122 [30]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.898
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.825
upper limit	0.977

Notes:

[30] - Based on MMRM model model with log transformation of sSOL and factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,First7 nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	0.902

Notes:

[31] - Based on MMRM model model with log transformation of sSOL and factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effect, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,Last 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0176 [32]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.796
upper limit	0.978

Notes:

[32] - Based on MMRM model model with log transformation of sSOL and factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,Last 7 nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.811
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	0.899

Notes:

[33] - Based on MMRM model model with log transformation of sSOL and with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sWASO,First7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0706 [34]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	8.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	16.91
Variability estimate	Standard error of the mean
Dispersion value	4.484

Notes:

[34] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,First7 nights: Zolpidem ER,Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg

Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1949 [35]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-5.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.61
upper limit	2.98
Variability estimate	Standard error of the mean
Dispersion value	4.481

Notes:

[35] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,Last 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059 [36]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	14.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.16
upper limit	24.73
Variability estimate	Standard error of the mean
Dispersion value	5.241

Notes:

[36] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,Last 7 nights:Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3064 [37]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	5.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	15.65
Variability estimate	Standard error of the mean
Dispersion value	5.241

Notes:

[37] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sSE,First 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1963 [38]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	0.71
Variability estimate	Standard error of the mean
Dispersion value	1.063

Notes:

[38] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sSE,First 7 nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1093 [39]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	3.78
Variability estimate	Standard error of the mean
Dispersion value	1.06

Notes:

[39] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sSE,Last 7 nights:Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2196 [40]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	1.247

Notes:

[40] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sSE,Last 7 nights:Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4013 [41]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.49
Variability estimate	Standard error of the mean
Dispersion value	1.246

Notes:

[41] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sTST,First 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2174 [42]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-6.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.02
upper limit	3.88
Variability estimate	Standard error of the mean
Dispersion value	5.325

Notes:

[42] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baselines sTST as a covariate.

Statistical analysis title	sTST,First7 nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0949 [43]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	8.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.55
upper limit	19.31
Variability estimate	Standard error of the mean
Dispersion value	5.313

Notes:

[43] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sTST as a covariate.

Statistical analysis title	sTST,Last 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2718 [44]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-6.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.01
upper limit	5.36
Variability estimate	Standard error of the mean
Dispersion value	6.207

Notes:

[44] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sTST as a covariate.

Statistical analysis title	sTST,Last 7 nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2317 [45]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	7.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.75
upper limit	19.61
Variability estimate	Standard error of the mean
Dispersion value	6.206

Notes:

[45] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sTST as a covariate.

Other pre-specified: Change From Baseline in Mean LPS, SE, WASO, WASO2H, and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 1/2

End point title	Change From Baseline in Mean LPS, SE, WASO, WASO2H, and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 1/2[46]

End point description:

LPS: amount of time in minutes from lights off to first epoch of 20 consecutive epochs of non-wakefulness. SE: percentage of time spent asleep per time in bed (TIB), calculated as TST divided by interval from lights off until lights on. WASO: amount of time in minutes of wake from the onset of persistent sleep until lights. WASO2H: amount of time in minutes of wake during the interval from 240 minutes after lights off until lights on. TST: amount of time in minutes of sleep from sleep onset until terminal awakening. LPS, SE, WASO, WASO2H, and TST were measured by PSG. Change from baseline to average LPS, SE, WASO, WASO2H, and TST on Day 1 and 2 were reported. FAS: group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 1/2

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208	266	269	
Units: minutes				
arithmetic mean (standard deviation)				
LPS: Days 1/2	-6.45 (± 32.618)	-16.59 (± 28.742)	-19.48 (± 31.809)	
SE: Days 1/2	4.22 (± 9.033)	13.60 (± 9.725)	16.48 (± 9.623)	

WASO: Days 1/2	-15.07 (± 36.938)	-49.96 (± 39.578)	-59.59 (± 37.749)	
WASO2H: Days 1/2	-7.06 (± 31.097)	-30.28 (± 32.056)	-37.10 (± 30.815)	
TST: Days 1/2	19.44 (± 43.348)	65.22 (± 46.695)	79.58 (± 47.350)	

Statistical analyses

Statistical analysis title	LPS: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0092 [47]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.752
upper limit	0.961

Notes:

[47] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	LPS: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [48]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.795
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.704
upper limit	0.899

Notes:

[48] - Based on MMRM model with factors of age group, region, treatment, visit (Days1/2), and treatment-by-visit interaction as fixed effects, and the baseline LPS as a covariate.

Statistical analysis title	SE: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	9.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	10.31
Variability estimate	Standard error of the mean
Dispersion value	0.666

Notes:

[49] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline SE as a covariate.

Statistical analysis title	SE: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [50]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.3
upper limit	12.9
Variability estimate	Standard error of the mean
Dispersion value	0.664

Notes:

[50] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline SE as a covariate.

Statistical analysis title	WASO: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [51]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.71
upper limit	-28.09

Variability estimate	Standard error of the mean
Dispersion value	2.711

Notes:

[51] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline WASO as a covariate.

Statistical analysis title	WASO: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [52]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-42.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.57
upper limit	-36.97
Variability estimate	Standard error of the mean
Dispersion value	2.705

Notes:

[52] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline WASO as a covariate.

Statistical analysis title	WASO2H: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [53]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-21.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.01
upper limit	-17.3
Variability estimate	Standard error of the mean
Dispersion value	2.221

Notes:

[53] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Statistical analysis title	WASO2H: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [54]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-28.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.68
upper limit	-23.98
Variability estimate	Standard error of the mean
Dispersion value	2.219

Notes:

[54] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Statistical analysis title	TST: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [55]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	44.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.59
upper limit	50.51
Variability estimate	Standard error of the mean
Dispersion value	3.291

Notes:

[55] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline TST as a covariate.

Statistical analysis title	TST: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [56]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	56.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.46
upper limit	63.34

Variability estimate	Standard error of the mean
Dispersion value	3.284

Notes:

[56] - Based on MMRM model with factors of age group, region, treatment, visit (Days 1/2), and treatment-by-visit interaction as fixed effect, and the baseline TST as a covariate.

Other pre-specified: Change From Baseline in Mean WASO2H and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30

End point title	Change From Baseline in Mean WASO2H and TST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo on Days 29/30[57]

End point description:

WASO2H is defined as the time in minutes of wake during the interval from 240 minutes after lights off until lights on. TST is defined as the amount of sleep in minutes from sleep onset until terminal awakening. WASO and TST were measured by PSG. Change from baseline to average WASO and TST on Day 29 and 30 were reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 29/30

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	260	260	
Units: minutes				
arithmetic mean (standard deviation)				
WASO2H: Days 29 /30	-8.92 (± 31.909)	-27.19 (± 33.047)	-28.84 (± 33.138)	
TST: Days 29/30	25.65 (± 47.587)	61.99 (± 46.817)	67.86 (± 52.117)	

Statistical analyses

Statistical analysis title	WASO2H: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [58]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-16.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.23
upper limit	-11.6
Variability estimate	Standard error of the mean
Dispersion value	2.457

Notes:

[58] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Statistical analysis title	WASO2H: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [59]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-17.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.57
upper limit	-12.96
Variability estimate	Standard error of the mean
Dispersion value	2.451

Notes:

[59] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as a covariate.

Statistical analysis title	TST: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [60]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	34.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.95
upper limit	41.36
Variability estimate	Standard error of the mean
Dispersion value	3.673

Notes:

[60] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline TST as a covariate.

Statistical analysis title	TST: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [61]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	38.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.64
upper limit	46.05
Variability estimate	Standard error of the mean
Dispersion value	3.672

Notes:

[61] - Based on MMRM model with factors of age group, region, treatment, visit (Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline TST as a covariate.

Other pre-specified: Change From Baseline in Mean sSOL, sWASO, sSE, and sTST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo

End point title	Change From Baseline in Mean sSOL, sWASO, sSE, and sTST of Lemborexant 10 mg and Lemborexant 5 mg Compared to Placebo[62]

End point description:

sSOL: estimated minutes from time attempted to sleep to sleep onset. sWASO: estimated minutes of wake at night after initial sleep onset to time stopped trying to sleep for the night. sSE: percentage of sTST per subjective time spent in bed (time attempted to sleep to time stopped trying to sleep for the night, and time spent asleep derived from subjective time spent in bed minus sWASO). sTST: minutes of sleep from sleep onset to time stopped trying to sleep for the night. sSOL, sSE, sWASO, sTST were analyzed with diary handling rules (DHR) on an electronic sleep diary. Subjective measures were derived from sleep diaries entries, collected daily and analyzed at appropriate intervals. FAS: group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. "n": subjects who were evaluable for outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

First 7 nights (approximately Week 1) and Last 7 nights (approximately Week 4)

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only planned to be analyse for the following reporting groups: Placebo, Lemborexant 5 mg, and Lemborexant 10 mg.

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208	266	269	
Units: minutes				
arithmetic mean (standard deviation)				
sSOL: 1st 7 nights :With DHR(n=202, 259, 266)	-6.83 (± 23.040)	-22.54 (± 32.812)	-21.88 (± 29.269)	
sSOL: last 7 nights: With DHR(n=196, 252, 258)	-8.10 (± 27.447)	-25.20 (± 34.854)	-24.79 (± 34.068)	
sWASO: 1st 7 nights: With DHR(n=202, 261, 262)	-27.92 (± 45.201)	-39.33 (± 55.022)	-55.06 (± 66.696)	
sWASO: last 7 nights: With DHR(n=196, 253, 253)	-36.01 (± 57.584)	-44.51 (± 58.090)	-57.96 (± 72.791)	

sSE: 1st 7 nights: With DHR(n=197, 251, 254)	6.73 (± 10.930)	10.56 (± 12.296)	13.97 (± 14.188)	
sSE: last 7 nights: With DHR(n=190, 245, 244)	8.35 (± 13.273)	12.92 (± 13.884)	16.12 (± 16.300)	
sTST: 1st 7 nights: With DHR(n=197, 251, 254)	30.86 (± 57.437)	50.30 (± 60.065)	67.80 (± 71.134)	
sTST: last 7 nights: With DHR(n=190, 245, 244)	38.98 (± 66.174)	62.41 (± 68.555)	79.95 (± 81.211)	

Statistical analyses

Statistical analysis title	sSOL,First 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [63]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.815
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.745
upper limit	0.891

Notes:

[63] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [64]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.753
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.689
upper limit	0.823

Notes:

[64] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,Last 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [65]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.671
upper limit	0.837

Notes:

[65] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sSOL,Last 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [66]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.689
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	0.769

Notes:

[66] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSOL as a covariate.

Statistical analysis title	sWASO,First 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0093 [67]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-12.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.76
upper limit	-3.06
Variability estimate	Standard error of the mean
Dispersion value	4.764

Notes:

[67] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [68]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-26.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.68
upper limit	-16.99
Variability estimate	Standard error of the mean
Dispersion value	4.762

Notes:

[68] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,Last 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0396 [69]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-11.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.42
upper limit	-0.55
Variability estimate	Standard error of the mean
Dispersion value	5.573

Notes:

[69] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sWASO,Last 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [70]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-20.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.51
upper limit	-9.63
Variability estimate	Standard error of the mean
Dispersion value	5.574

Notes:

[70] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sWASO as a covariate.

Statistical analysis title	sSE,First 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [71]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	5.97
Variability estimate	Standard error of the mean
Dispersion value	1.122

Notes:

[71] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sSE,First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [72]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	6.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.64
upper limit	9.04
Variability estimate	Standard error of the mean
Dispersion value	1.12

Notes:

[72] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sSE,Last 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [73]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	4.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	7.19
Variability estimate	Standard error of the mean
Dispersion value	1.319

Notes:

[73] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effect, and the baseline sSE as a covariate.

Statistical analysis title	sSE,Last 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [74]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	7.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	9.77
Variability estimate	Standard error of the mean
Dispersion value	1.319

Notes:

[74] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sSE as a covariate.

Statistical analysis title	sTST,First 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [75]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	19.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.03
upper limit	30.08

Variability estimate	Standard error of the mean
Dispersion value	5.619

Notes:

[75] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baselines sTST as a covariate.

Statistical analysis title	sTST,First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [76]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	34.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.5
upper limit	45.52
Variability estimate	Standard error of the mean
Dispersion value	5.609

Notes:

[76] - Based on MMRM model with factors of age group, region, treatment, visit (First 7 Nights), and treatment-by-visit interaction as fixed effects, and the baselines sTST as a covariate.

Statistical analysis title	sTST,Last 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [77]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	23.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.68
upper limit	36.45
Variability estimate	Standard error of the mean
Dispersion value	6.565

Notes:

[77] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sTST as a covariate.

Statistical analysis title	sTST,Last 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [78]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	37.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.94
upper limit	50.71
Variability estimate	Standard error of the mean
Dispersion value	6.565

Notes:

[78] - Based on MMRM model with factors of age group, region, treatment, visit (Last 7 Nights), and treatment-by-visit interaction as fixed effects, and the baseline sTST as a covariate.

Other pre-specified: Percentage of Responders With Objective and Subjective Sleep Onset Response, and Objective and Subjective Sleep Maintenance Response

End point title	Percentage of Responders With Objective and Subjective Sleep Onset Response, and Objective and Subjective Sleep Maintenance Response

End point description:

Objective sleep onset response: LPS less than or equal to (<=) 20 minutes (mins) provided baseline LPS was greater than(>) 30 mins. Subjective sleep onset response: sSOL <=20 mins provided mean baseline sSOL was >30 mins. Objective sleep maintenance response: WASO <=60 minutes provided baseline WASO was > 60 mins and was reduced by >10 mins compared to baseline. Subjective sleep maintenance response: sWASO <=60 mins provided mean WASO was >60 mins and was reduced by >10 mins compared to baseline. Subjective measures were derived from sleep diaries entries, collected daily and analyzed at appropriate intervals. Average data for first and last 7 nights of treatment period was reported. FAS: group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. "n": subjects who were evaluable for the outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

Days 1/2, Days 29/30, first 7 night (approximately Week 1), and Last seven nights (approximately Week 4)

End point values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	263	266	269
Units: percentage of subjects				
number (not applicable)				
LPS: Days 1/2	15.4	10.3	15.8	17.8
LPS: Days 29/30	15.9	11.4	20.3	22.3
sSOL: First 7 nights (with DHR)	2.9	7.6	9.8	10.4
sSOL: Last 7 nights (with DHR)	7.2	8.7	16.9	14.5
WASO: Days 1/2	16.8	46.0	51.1	64.3
WASO: Days 29/30	22.1	34.6	44.4	46.1

sWASO: First 7 nights (with DHR)	9.6	16.7	16.9	20.4
sWASO: Last 7 nights (with DHR)	15.4	23.2	23.3	23.0

Statistical analyses

Statistical analysis title	LPS, Days 1/2: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9028 [79]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.22
upper limit	7.04

Notes:

[79] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS,Days 1/2: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4699 [80]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	9.18

Notes:

[80] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 1/2: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0566 [81]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	5.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	11.31

Notes:

[81] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 1/2: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122 [82]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	13.44

Notes:

[82] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 29/30: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2176 [83]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	4.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	11.34

Notes:

[83] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 29/30: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0773 [84]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	6.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	13.49

Notes:

[84] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 29/30: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054 [85]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	8.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.68
upper limit	15.02

Notes:

[85] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	LPS, Days 29/30: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [86]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	10.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.61
upper limit	17.17

Notes:
[86] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, First 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [87]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.66
upper limit	11.14

Notes:
[87] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [88]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.19
upper limit	11.81

Notes:
[88] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, First 7 nights: Zolpidem, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3643 [89]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	2.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	7.01

Notes:

[89] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, First 7 nights: Zolpidem, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2553 [90]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	7.66

Notes:

[90] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, Last 7 nights: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [91]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	9.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.98
upper limit	15.4

Notes:

[91] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, Last 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0128 [92]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	12.79

Notes:

[92] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, Last 7 nights: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg v Lemborexant 5 mg
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051 [93]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	8.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.51
upper limit	13.81

Notes:

[93] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sSOL, Last 7nights: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0389 [94]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	5.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	11.18

Notes:

[94] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 1/2: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [95]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	34.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.46
upper limit	42.06

Notes:

[95] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 1/2: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [96]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	47.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.02
upper limit	55.13

Notes:

[96] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 1/2: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2534 [97]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	4.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	13.28

Notes:
[97] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO: Days 1/2: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [98]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	18.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.1
upper limit	26.4

Notes:
[98] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 29/30: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [99]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	22.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.06
upper limit	30.35

Notes:
[99] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 29/30: Placebo, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [100]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	24.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.16
upper limit	32.1

Notes:

[100] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 29/30: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [101]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	9.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	17.81

Notes:

[101] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	WASO, Days 29/30: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [102]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	11.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.38
upper limit	19.48

Notes:

[102] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO,First7 nights: Placebo,Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0222 [103]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	13.33

Notes:

[103] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO, First 7 nights: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013 [104]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	10.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.57
upper limit	17.11

Notes:

[104] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO,First7 nights:Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9495 [105]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.17
upper limit	6.58

Notes:

[105] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO: First7 nights:Zolpidem ER, Lemborexant 10mg
Comparison groups	Lemborexant 10 mg v Zolpidem Tartrate Extended Release 6.25 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2708 [106]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	10.32

Notes:

[106] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO, Last7nights: Placebo,Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0322 [107]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	14.96

Notes:

[107] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO,Last7 nights:Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0363 [108]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	7.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	14.71

Notes:

[108] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO, Last7 nights:Zolpidem ER,Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9885 [109]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.14
upper limit	7.24

Notes:

[109] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Statistical analysis title	sWASO, Last7 nights:Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9651 [110]
Method	Cochran-Mantel-Haenszel
Parameter estimate	LSM Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.31
upper limit	6.99

Notes:

[110] - Based on Cochran-Mantel-Haenszel test stratified by age group.

Other pre-specified: Change From Baseline in Score From Items 4 to 7 on the ISI of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER and Placebo on Day 31

End point title	Change From Baseline in Score From Items 4 to 7 on the ISI of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER and Placebo on Day 31

End point description:

The ISI is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The dimensions evaluated were: severity of sleep onset; sleep maintenance; early morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning; noticeability of the sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale was used to rate each item (from 0 = no problem to 4 = very severe problem) yielding a total score from 0 to 28. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement at given time points.

End point type	Other pre-specified
End point timeframe:	
Baseline and Day 31	

End point values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	198	244	257	253
Units: score in scale				
arithmetic mean (standard deviation)	-3.88 (± 3.559)	-5.24 (± 3.764)	-4.83 (± 3.593)	-4.77 (± 3.735)

Statistical analyses

Statistical analysis title	Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [111]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	-0.47
Variability estimate	Standard error of the mean
Dispersion value	0.319

Notes:

[111] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Statistical analysis title	Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [112]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[112] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2951 [113]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.301

Notes:

[113] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2744 [114]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.303

Notes:

[114] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Other pre-specified: Change From Baseline in FSS Score of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER and Placebo on Day 31

End point title	Change From Baseline in FSS Score of Lemborexant 10 mg and Lemborexant 5 mg Compared to Zolpidem ER and Placebo on Day 31

End point description:

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree, and "7" indicates strongly agree. The FSS total score was the sum of all responses to the 9 questions. The FSS average item score was the average of the score for each item. Higher total scores and higher average item scores indicated greater fatigue. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The FAS was the group of subjects where data was available at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline and Day 31

End point values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	198	244	257	253
Units: score on scale				
arithmetic mean (standard deviation)	-6.75 (± 11.916)	-7.80 (± 12.879)	-8.14 (± 13.411)	-8.00 (± 14.058)

Statistical analyses

Statistical analysis title	Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2348 [115]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	1.063

Notes:

[115] - Based on ANCOVA model with factors of age group, region, treatment and the baseline FSS as a covariate.

Statistical analysis title	Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2745 [116]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	0.93
Variability estimate	Standard error of the mean
Dispersion value	1.067

Notes:

[116] - Based on ANCOVA model with factors of age group, region, treatment and the baseline FSS as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711 [117]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	1.005

Notes:

[117] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Statistical analysis title	Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7854 [118]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	1.71
Variability estimate	Standard error of the mean
Dispersion value	1.009

Notes:

[118] - Based on ANCOVA model with factors of age group, region, treatment and the baseline ISI as a covariate.

Other pre-specified: Change From Baseline in Mean POA and SOMT on Days 2/3

End point title	Change From Baseline in Mean POA and SOMT on Days 2/3

End point description:

POA reflects the ability to focus attention and process information. POA is calculated from the sum of simple reaction time, choice reaction time and digit vigilance. SOMT reflects time taken to retrieve information from working and episodic memory. SOMT is a composite score created by combining numerical working memory and spatial working memory and word recognition and picture recognition. Cognitive performance assessment was done by a computerized performance assessment battery (PAB) which was administered on a laptop computer. A positive change from baseline reflects impairment and a lower value of decrease from baseline indicates better performance. Change from baseline to average POA and SOMT on Days 2 and 3 was reported. The FAS was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. Here "n" were subjects who were evaluable for the outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 2/3

End point values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	263	266	269
Units: millisecond				
arithmetic mean (standard deviation)				
POA (n=186, 233, 240, 236)	-14.2 (± 149.31)	37.1 (± 107.15)	8.9 (± 154.33)	31.1 (± 142.38)
SOMT (n=186, 232, 237, 235)	-177.9 (± 668.77)	60.7 (± 749.12)	-185.1 (± 645.18)	-152.8 (± 722.49)

Statistical analyses

Statistical analysis title	POA: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141 [119]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	30.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.23
upper limit	55.31
Variability estimate	Standard error of the mean
Dispersion value	12.505

Notes:

[119] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline POA as a covariate.

Statistical analysis title	POA: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [120]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	39.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.05
upper limit	64.29
Variability estimate	Standard error of the mean
Dispersion value	12.542

Notes:

[120] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline POA as a covariate.

Statistical analysis title	POA: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1031 [121]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-19.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.34
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	11.779

Notes:

[121] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline POA as a covariate.

Statistical analysis title	POA: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3825 [122]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-10.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.5
upper limit	12.86
Variability estimate	Standard error of the mean
Dispersion value	11.813

Notes:

[122] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline POA as a covariate.

Statistical analysis title	SOMT: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6348 [123]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	28.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-90.18
upper limit	147.8
Variability estimate	Standard error of the mean
Dispersion value	60.626

Notes:

[123] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline SOMT as a covariate.

Statistical analysis title	SOMT: Placebo, Lemborexant 10 mg

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4026 [124]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	50.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.3
upper limit	169.97
Variability estimate	Standard error of the mean
Dispersion value	60.702

Notes:

[124] -
Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline SOMT as a covariate.

Statistical analysis title	SOMT: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [125]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-203.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-315.56
upper limit	-91.15
Variability estimate	Standard error of the mean
Dispersion value	57.171

Notes:

[125] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline SOMT as a covariate.

Statistical analysis title	SOMT: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [126]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-181.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-293.71
upper limit	-68.96
Variability estimate	Standard error of the mean
Dispersion value	57.255

Notes:

[126] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline SOMT as a covariate.

Other pre-specified: Change From Baseline in Mean QOM and COA on Days 2/3

End point title	Change From Baseline in Mean QOM and COA on Days 2/3

End point description:

QOM: ability to store information in memory and subsequently retrieve it. It is a composite score created by combining accuracy measures from 2 sets of working memory and 4 sets of episodic memory. 2 sets of working memory were included: numerical and spatial working memory, and ranges from -2 to 2. 4 sets of episodic memory were included: immediate and delayed word recall, and word and picture recognition, and ranges from -200 to 400. COA is ability to sustain attention. Number of correct responses (out of 50) for choice reaction time was added to total number of targets correctly identified (out of 45) digit vigilance minus number of false alarms (total score of -45 to 95). Higher values were better. Change from baseline to average QOM and COA on Days 2 and 3 was reported. FAS: group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. "n": subjects who were evaluable for outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 2/3

End point values	Placebo	Zolpidem Tartrate Extended Release 6.25 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	263	266	269
Units: units on scale				
arithmetic mean (standard deviation)				
QOM (n=185, 233, 239, 235)	3.5 (± 45.20)	-12.1 (± 46.94)	1.4 (± 44.21)	-2.8 (± 44.11)
COA (n=186, 233, 240, 236)	0.0 (± 4.16)	-1.0 (± 4.48)	0.2 (± 4.95)	-0.7 (± 3.92)

Statistical analyses

Statistical analysis title	QOM: Placebo, Lemborexant 5 mg
Comparison groups	Placebo v Lemborexant 5 mg

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9936 [127]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.16
upper limit	8.09
Variability estimate	Standard error of the mean
Dispersion value	4.141

Notes:

[127] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline QOM as a covariate.

Statistical analysis title	QOM: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1595 [128]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-5.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	4.154

Notes:

[128] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline QOM as a covariate.

Statistical analysis title	QOM: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [129]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	12.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.09
upper limit	20.38

Variability estimate	Standard error of the mean
Dispersion value	3.894

Notes:

[129] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline QOM as a covariate.

Statistical analysis title	QOM: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0774 [130]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	6.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	14.6
Variability estimate	Standard error of the mean
Dispersion value	3.913

Notes:

[130] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline QOM as a covariate.

Statistical analysis title	COA: Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant 5 mg v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3726 [131]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.393

Notes:

[131] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline COA as a covariate.

Statistical analysis title	COA: Placebo, Lemborexant 10 mg
Comparison groups	Placebo v Lemborexant 10 mg

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2579 [132]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.394

Notes:

[132] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline COA as a covariate.

Statistical analysis title	COA: Zolpidem ER, Lemborexant 5 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 5 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [133]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	2.11
Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[133] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline COA as a covariate.

Statistical analysis title	COA: Zolpidem ER, Lemborexant 10 mg
Comparison groups	Zolpidem Tartrate Extended Release 6.25 mg v Lemborexant 10 mg
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112 [134]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.32
Variability estimate	Standard error of the mean
Dispersion value	0.372

Notes:

[134] - Based on MMRM model with factors of age group, region, treatment, visit (Days 2/3), and treatment-by-visit interaction as fixed effect, and the baseline COA as a covariate.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Run-in Phase (Day -7) up to End of treatment (Day 44)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Zolpidem tartrate
Reporting group description:	
Subjects received ZOL ER 6.25 mg and LEM-matched PBO, tablets, orally, once on each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep of treatment period.	
Reporting group title	Lemborexant 5 mg
Reporting group description:	
Subjects received LEM 5 and ZOL ER -matched PBO, tablets, orally, once on each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep of treatment period.	
Reporting group title	Placebo
Reporting group description:	
Subjects received LEM-matched PBO and ZOL ER-matched PBO, tablets, orally once on each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep of treatment period.	
Reporting group title	Lemborexant 10 mg
Reporting group description:	
Subjects received LEM 10 mg (LEM 10) and ZOL ER-matched PBO, tablets, orally, once on each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep of treatment period.	
Reporting group title	Run -in Period Placebo
Reporting group description:	
Subjects received LEM-matched PBO and ZOL ER-matched PBO, tablets, orally, once on each night for 7 consecutive nights up to Baseline (Day 1), immediately before the time the subject intended to try to sleep of run-in period.	

Serious adverse events	Zolpidem tartrate	Lemborexant 5 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 263 (1.52%)	2 / 266 (0.75%)	0 / 209 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			

subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lemborexant 10 mg	Run -in Period Placebo	
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 268 (0.00%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Zolpidem tartrate	Lemborexant 5 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 263 (6.84%)	27 / 266 (10.15%)	16 / 209 (7.66%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 263 (5.32%)	17 / 266 (6.39%)	13 / 209 (6.22%)
occurrences (all)	21	21	13
Somnolence			
subjects affected / exposed	4 / 263 (1.52%)	11 / 266 (4.14%)	4 / 209 (1.91%)
occurrences (all)	5	11	4

Non-serious adverse events	Lemborexant 10 mg	Run -in Period Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 268 (10.45%)	34 / 1006 (3.38%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 268 (4.85%)	34 / 1006 (3.38%)	
occurrences (all)	15	34	
Somnolence			
subjects affected / exposed	19 / 268 (7.09%)	0 / 1006 (0.00%)	
occurrences (all)	20	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2016	Amendment 01: The protocol was amended to update that exclusion criteria include current diagnosis of obstructive sleep apnea, prohibition of strong CYP3A inhibitors from being used any time during study, even if intermittently, added sleep onset latency as a PSG variable and moved analysis of cognitive PAB tasks from exploratory to secondary analyses.
16 February 2017	Amendment 02: The protocol was amended to update screening period from up to -28 days to up to -35 days, inclusion and exclusion criteria, requirement for monitoring of seizures and falls and T-BWSQ assessment description such that scores above 20 will not be considered clinically significant and that the symptoms will no longer be summarized separately from all other AEs.
16 June 2017	Amendment 03: The protocol was amended to update WASO1H as a sleep architecture parameter (efficacy) and age groups for analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported