



Clinical trial results:

A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel-Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder

Summary

EudraCT number	2015-001463-39
Trial protocol	DE FI PL ES
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	E2006-G000-303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02952820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Medical Information, Eisai, Inc., +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Medical Information, Eisai, Inc., +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	08 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of lemborexant 5 mg (LEM5) and 10 mg (LEM10) compared to placebo (PBO) on subjective sleep onset latency (sSOL) after 6 months of treatment in subjects 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	15 November 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	Poland: 61
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Germany: 124
Country: Number of subjects enrolled	Japan: 161
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 3
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	Romania: 52
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	United States: 310
Country: Number of subjects enrolled	Finland: 206

Worldwide total number of subjects	971
EEA total number of subjects	471

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)	709
From 65 to 84 years	259
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 119 investigative sites in Japan, Korea, Finland, Germany, Italy, New Zealand, Poland, Romania, Spain, Canada, Mexico, and the United States from 15 November 2016 to 08 January 2019.

Pre-assignment

Screening details:

A total of 2059 subjects were screened, of which 1088 were screen failures and 971 subjects were randomized to receive study treatment.

Period 1

Period 1 title	Placebo -Controlled Treatment (6 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received lemborexant-matched placebo, tablet, orally, once daily for up to Month 6 in the placebo-controlled treatment period. Then they were re-randomized to lemborexant 5 milligram (mg) or lemborexant 10 mg up to Month 12 .

Arm type	Placebo
Investigational medicinal product name	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 for up to Month 6 in the placebo-controlled treatment period.

Arm title	Lemborexant 5 mg
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Arm description:

Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).

Arm type	Experimental
Investigational medicinal product name	Lemborexant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 6-12 (in Period 2).

Arm title	Lemborexant 10 mg
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Arm description:

Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).

Arm type	Experimental
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Investigational medicinal product name	Lemborexant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 6-12 (in Period 2).

Number of subjects in period 1	Placebo	Lemborexant 5 mg	Lemborexant 10 mg
Started	325	323	323
Treated	321	319	319
Safety Analysis Set	319	314	314
Completed	261	254	235
Not completed	64	69	88
Adverse event, non-fatal	8	9	16
Other than specified	-	14	13
Withdrawal of consent	13	11	21
Lost to follow-up	7	7	6
Inadequate therapeutic effect	17	12	11
Subject choice	15	12	17
Not treated	4	4	4

Period 2

Period 2 title	Active Treatment Period (6 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Lemborexant 5 mg

Arm description:

Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).

Arm type	Experimental
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Investigational medicinal product name	Lemborexant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 12.	
Arm title	Lemborexant 10 mg

Arm description:

Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).

Arm type	Experimental
Investigational medicinal product name	Lemborexant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 12.

Number of subjects in period 2^[1]	Lemborexant 5 mg	Lemborexant 10 mg
Started	384	352
Completed	346	321
Not completed	38	31
Adverse event, non-fatal	6	5
Other than specified	6	2
Withdrawal of consent	6	8
Lost to follow-up	4	6
Inadequate therapeutic effect	6	2
Subject choice	10	7
Not treated	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects from Placebo were re-randomized to Lemborexant 5 mg and Lemborexant 10 mg.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received lemborexant-matched placebo, tablet, orally, once daily for up to Month 6 in the placebo-controlled treatment period. Then they were re-randomized to lemborexant 5 milligram (mg) or lemborexant 10 mg up to Month 12 .	
Reporting group title	Lemborexant 5 mg
Reporting group description: Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	
Reporting group title	Lemborexant 10 mg
Reporting group description: Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	

Reporting group values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg
Number of subjects	325	323	323
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	54.262	54.087	54.715
standard deviation	± 14.017	± 13.656	± 13.59
Gender categorical Units: Subjects			
Female	220	213	225
Male	105	110	98

Reporting group values	Total		
Number of subjects	971		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)	0 0 0 0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	658		
Male	313		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received lemborexant-matched placebo, tablet, orally, once daily for up to Month 6 in the placebo-controlled treatment period. Then they were re-randomized to lemborexant 5 milligram (mg) or lemborexant 10 mg up to Month 12 .	
Reporting group title	Lemborexant 5 mg
Reporting group description: Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	
Reporting group title	Lemborexant 10 mg
Reporting group description: Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	
Reporting group title	Lemborexant 5 mg
Reporting group description: Subjects received lemborexant 5 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	
Reporting group title	Lemborexant 10 mg
Reporting group description: Subjects received lemborexant 10 mg, tablets, orally, once daily through Month 1-6 (in Period 1) and Month 7-12 (in Period 2).	
Subject analysis set title	Lemborexant 5 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received lemborexant 5 mg/placebo, tablets, orally, once daily through Month 1-6 (in Period 1) and lemborexant 5 mg, tablets, orally, once daily through Month 7-12 (in Period 2)	
Subject analysis set title	Lemborexant 10 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received lemborexant 10 mg/placebo, tablets, orally, once daily through Month 1-6 (in Period 1) and lemborexant 10 mg, tablets, orally, once daily through Month 7-12 (in Period 2).	

Primary: Change From Baseline in Subjective Sleep Onset Latency (sSOL) at Month 6

End point title	Change From Baseline in Subjective Sleep Onset Latency (sSOL) at Month 6
End point description: sSOL was defined as estimated minutes from the time that the subject attempted to sleep until sleep onset. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.	
End point type	Primary
End point timeframe: Baseline and Month 6	

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=316, 314, 312)	64.03 (± 45.209)	62.19 (± 45.674)	64.97 (± 44.020)	
Change at Month 6 (249, 245, 229)	-16.57 (± 35.313)	-29.39 (± 33.261)	-32.49 (± 35.962)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was based on mixed effect model repeated measurement analysis (MMRM) model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be missing not at random (missing not at random/complete case missing value [MNAR/CCMV]).	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	least squares geometric mean (LSGM)ratio
Point estimate	0.732
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	0.843

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.701

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.607
upper limit	0.81

Secondary: Change From Baseline in sSOL at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1 and 3

End point title	Change From Baseline in sSOL at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1 and 3
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End point description:

sSOL was defined as estimated minutes from time attempted to sleep to sleep onset. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, (mean of 7 nights [approximately Week 1]), Months 1 and 3

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=316, 314, 312)	64.03 (± 45.209)	62.19 (± 45.674)	64.97 (± 44.020)	
Change at 1st 7 nights (n= 314, 310, 310)	-4.11 (± 27.671)	-16.86 (± 27.784)	-18.89 (± 31.003)	
Change at Month 1 (n=299, 298, 297)	-11.48 (± 32.726)	-19.41 (± 32.221)	-24.06 (± 35.234)	
Change at Month 3 (n=279, 268, 264)	-13.84 (± 35.277)	-25.08 (± 34.081)	-27.94 (± 39.192)	

Statistical analyses

Statistical analysis title	First 7 nights (Statistical Analysis 1)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
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Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.781
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.725
upper limit	0.842

Statistical analysis title	First 7 nights (Statistical Analysis 2)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	0.811

Statistical analysis title	Month 1 (Statistical analysis 3)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	0.893

Statistical analysis title	Month 1 (Statistical analysis 4)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	0.848

Statistical analysis title	Month 3 (Statistical Analysis 5)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.778
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.878

Statistical analysis title	Month 3 (Statistical Analysis 6)
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Statistical analysis description:

Based on MMRM model with log transformation of sSOL and factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and the study baseline sSOL as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSGM ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.681
upper limit	0.869

Secondary: Change From Baseline in Subjective Sleep Efficiency (sSE) at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6

End point title	Change From Baseline in Subjective Sleep Efficiency (sSE) at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6
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End point description:

sSE was defined as percentage of subjective total sleep time (sTST) divided by subjective time spent in bed, calculated as the interval from the time the subject reported attempting to sleep until the time subject stopped trying to sleep for the night (operationalized as the time the subject got out of bed for the day), and time spent asleep derived from subjective time spent in bed minus sWASO. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, (mean of 7 nights [approximately Week 1]), Months 1, 3 and 6

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: percentage of sTST				
arithmetic mean (standard deviation)				
Baseline (n=307, 302, 299)	61.34 (± 17.836)	63.14 (± 18.231)	62.03 (± 17.248)	
Change at 1st 7 nights (n=303, 295, 296)	2.68 (± 10.765)	6.61 (± 10.386)	8.27 (± 10.566)	
Change at Month 1 (n= 291, 284, 282)	6.11 (± 12.876)	7.87 (± 12.263)	9.92 (± 12.922)	
Change at Month 3 (n= 269, 256, 251)	9.16 (± 13.644)	13.03 (± 13.522)	13.61 (± 14.035)	

Change at Month 6 (n= 242, 235, 220)	10.36 (\pm 13.799)	15.34 (\pm 14.613)	15.55 (\pm 15.617)	
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Statistical analyses

Statistical analysis title	First 7 nights (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	4.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.638
upper limit	5.961
Variability estimate	Standard error of the mean
Dispersion value	0.848

Statistical analysis title	First 7 nights (Statistical Analysis 2)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	5.793
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.133
upper limit	7.452
Variability estimate	Standard error of the mean
Dispersion value	0.846

Statistical analysis title	Month 1 (Statistical Analysis 3)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	2.227
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.307
upper limit	4.146
Variability estimate	Standard error of the mean
Dispersion value	0.979

Statistical analysis title	Month 1 (Statistical Analysis 4)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	3.615
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.635
upper limit	5.595
Variability estimate	Standard error of the mean
Dispersion value	1.01

Statistical analysis title	Month 3 (Statistical Analysis 5)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.068
upper limit	6.377
Variability estimate	Standard error of the mean
Dispersion value	1.099

Statistical analysis title	Month 3 (Statistical Analysis 6)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	4.361
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	6.501
Variability estimate	Standard error of the mean
Dispersion value	1.092

Statistical analysis title	Month 6 (Statistical Analysis 7)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
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Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	4.549
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.236
upper limit	6.861
Variability estimate	Standard error of the mean
Dispersion value	1.179

Statistical analysis title	Month 6 (Statistical Analysis 8)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sSE as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	4.667
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.373
upper limit	6.96
Variability estimate	Standard error of the mean
Dispersion value	1.17

Secondary: Change From Baseline in Subjective Wake After Sleep Onset (sWASO) at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6

End point title	Change From Baseline in Subjective Wake After Sleep Onset (sWASO) at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6
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End point description:

sWASO was defined as sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night, operationalized as the time the subject got out of bed for the day. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
End point timeframe:	
Baseline, (mean of 7 nights [approximately Week 1]), Months 1, 3 and 6	

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=314, 313, 311)	132.49 (± 80.198)	132.77 (± 82.518)	136.83 (± 87.391)	
Change at first 7 nights (n= 312, 308, 309)	-6.12 (± 45.893)	-20.21 (± 46.015)	-23.30 (± 47.700)	
Change at Month 1 (n=297, 297, 293)	-19.01 (± 50.279)	-23.42 (± 56.251)	-26.82 (± 56.989)	
Change at Month 3 (n=278, 267, 262)	-27.08 (± 54.408)	-42.98 (± 60.064)	-39.42 (± 62.783)	
Change at Month 6 (n=248, 244, 227)	-32.14 (± 55.279)	-51.45 (± 67.295)	-48.12 (± 68.550)	

Statistical analyses

Statistical analysis title	First 7 nights (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-14.328
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.411
upper limit	-7.245
Variability estimate	Standard error of the mean
Dispersion value	3.614

Statistical analysis title	First 7 nights (Statistical Analysis 2)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-16.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.813
upper limit	-9.626
Variability estimate	Standard error of the mean
Dispersion value	3.619

Statistical analysis title

Month 1 (Statistical Analysis 3)

Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1796
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-5.514
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.568
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	4.109

Statistical analysis title

Month 1 (Statistical Analysis 4)

Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
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Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0898
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-7.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.098
upper limit	1.088
Variability estimate	Standard error of the mean
Dispersion value	4.129

Statistical analysis title	Month 3 (Statistical Analysis 5)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-13.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.218
upper limit	-4.631
Variability estimate	Standard error of the mean
Dispersion value	4.486

Statistical analysis title	Month 3 (Statistical Analysis 6)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
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Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0277
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-10.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.053
upper limit	-1.104
Variability estimate	Standard error of the mean
Dispersion value	4.578

Statistical analysis title	Month 6 (Statistical Analysis 7)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-17.474
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.306
upper limit	-7.643
Variability estimate	Standard error of the mean
Dispersion value	5.014

Statistical analysis title	Month 6 (Statistical Analysis 8)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sWASO as a covariate. Missing values are imputed using multiple imputation and assumed to be MNAR/CCMV.

Comparison groups	Placebo v Lemborexant 10 mg
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Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0105
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-12.671
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.378
upper limit	-2.964
Variability estimate	Standard error of the mean
Dispersion value	4.951

Secondary: Change From Baseline in sTST at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6

End point title	Change From Baseline in sTST at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), and at Months 1, 3 and 6
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End point description:

sTST was defined as minutes of sleep from sleep onset to time stopped trying to sleep for the night. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, (mean of 7 nights [approximately Week 1]), Months 1, 3 and 6

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=307, 302, 299)	304.25 (± 91.459)	315.52 (± 93.498)	306.89 (± 88.031)	
Change at first 7 nights (n=303, 295, 296)	14.78 (± 54.995)	34.29 (± 54.142)	46.01 (± 55.110)	
Change at Month 1 (n=291, 284, 282)	30.74 (± 70.687)	39.32 (± 63.548)	53.22 (± 67.910)	
Change at Month 3 (n= 269, 256, 251)	48.16 (± 75.859)	65.82 (± 71.331)	70.95 (± 70.913)	
Change at Month 6 (n=242, 235, 220)	53.53 (± 74.539)	76.21 (± 77.714)	78.32 (± 80.741)	

Statistical analyses

Statistical analysis title	First 7 Nights (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be missing at random (MAR).	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	22.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.488
upper limit	30.579
Variability estimate	Standard error of the mean
Dispersion value	4.354

Statistical analysis title	First 7 nights (Statistical Analysis 2)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	31.796
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.258
upper limit	40.334
Variability estimate	Standard error of the mean
Dispersion value	4.35

Statistical analysis title	Month 1 (Statistical analysis 3)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not	

imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0259
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	11.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.418
upper limit	22.102
Variability estimate	Standard error of the mean
Dispersion value	5.269

Statistical analysis title	Month 1 (Statistical Analysis 4)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	22.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.757
upper limit	32.505
Variability estimate	Standard error of the mean
Dispersion value	5.286

Statistical analysis title	Month 3 (Statistical Analysis 5)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
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Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	17.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.781
upper limit	28.968
Variability estimate	Standard error of the mean
Dispersion value	5.906

Statistical analysis title	Month 3 (Statistical Analysis 6)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	21.686
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.014
upper limit	33.359
Variability estimate	Standard error of the mean
Dispersion value	5.946

Statistical analysis title	Month 6 (Statistical Analysis 7)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
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Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	18.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.14
upper limit	30.969
Variability estimate	Standard error of the mean
Dispersion value	6.324

Statistical analysis title	Month 6 (Statistical Analysis 8)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline sTST as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	22.686
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.137
upper limit	35.234
Variability estimate	Standard error of the mean
Dispersion value	6.392

Secondary: Percentage of Sleep Onset Responders and Sleep Maintenance Responders at Month 6

End point title	Percentage of Sleep Onset Responders and Sleep Maintenance Responders at Month 6
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End point description:

Sleep onset responder was defined as follows: sSOL at study Baseline was greater than or equal to (\geq) 30 minutes and mean sSOL at 6 months was less than or equal to (\leq) 20 minutes. Sleep maintenance responder was defined as follows: sWASO at study Baseline was \geq 60 minutes and mean sWASO at 6 months was \leq 60 minutes and showed a reduction of greater than ($>$) 10 minutes compared to Study Baseline. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to number of subjects evaluable for specified category.

End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: percentage of responders				
number (not applicable)				
Sleep Onset Responders (n= 254, 250, 249)	17.7	31.2	30.1	
Sleep Maintenance Responders (n=250, 263, 257)	20.4	35.0	30.0	

Statistical analyses

Statistical analysis title	Sleep Onset Responders: Statistical Analysis 1
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentage
Point estimate	13.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.24
upper limit	21.1

Statistical analysis title	Sleep Onset Responders: Statistical Analysis 2
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentage
Point estimate	12.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	19.86

Statistical analysis title	Sleep Maintenance Responders
Statistical analysis description:	
Statistical Analysis 3	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentage
Point estimate	14.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.97
upper limit	22.33

Statistical analysis title	Sleep Maintenance Responders
Statistical analysis description:	
Statistical Analysis 4	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentage
Point estimate	9.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.29
upper limit	17.35

Secondary: Percentage of Sleep Onset Responders and Sleep Maintenance Responders at Month 12

End point title	Percentage of Sleep Onset Responders and Sleep Maintenance Responders at Month 12
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End point description:

Sleep onset responder was defined as follows: sSOL at study Baseline was ≥ 30 minutes and mean sSOL at 6 months was ≤ 20 minutes. Sleep maintenance responder was defined as follows: sWASO at study Baseline was ≥ 60 minutes and mean sWASO at 6 months was ≤ 60 minutes and showed a reduction of > 10 minutes compared to study Baseline. On-treatment FAS was the group of subjects who received at least 1 dose of lemborexant and had at least 1 post dose primary efficacy measurement. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

Month 12

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of subjects				
number (not applicable)				
Sleep Onset Responders (n= 310, 285)	34.2	37.2		
Sleep Maintenance Responders (n= 317, 280)	35.0	39.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insomnia Severity Index (ISI) Daytime Functioning Score at Months 1, 3, and 6

End point title	Change From Baseline in Insomnia Severity Index (ISI) Daytime Functioning Score at Months 1, 3, and 6
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End point description:

The ISI is a 4-7 item, self-report questionnaire assessing the nature, severity, and impact of insomnia. The dimensions evaluated were: 1. severity of sleep onset; 2. sleep maintenance; 3. early morning awakening problems; 4. sleep dissatisfaction; 5. interference of sleep difficulties with daytime functioning; 6. noticeability of the sleep problems by others; and 7. 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). Daytime functioning score (sum of items 4 to 7) were analyzed. Higher score indicated severe insomnia problem. The total score range for sum of items is 0-16. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Months 1, 3, and 6

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=318, 316, 315)	11.0 (± 2.10)	11.4 (± 2.02)	11.0 (± 2.15)	
Change at Month 1 (n= 296, 300, 286)	-3.1 (± 3.41)	-4.1 (± 3.66)	-4.2 (± 4.01)	
Change at Month 3 (n=283, 274, 259)	-3.7 (± 3.55)	-5.2 (± 3.88)	-5.2 (± 4.05)	
Change at Month 6 (n= 257, 258, 234)	-4.3 (± 3.66)	-6.0 (± 3.76)	-5.7 (± 4.00)	

Statistical analyses

Statistical analysis title	Month 1 (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0137
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.287

Statistical analysis title	Month 1 (Statistical Analysis 2)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.38
Variability estimate	Standard error of the mean
Dispersion value	0.289

Statistical analysis title	Month 3 (Statistical Analysis 3)
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Statistical analysis description:

Based on MMRM model with factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	-0.57
Variability estimate	Standard error of the mean
Dispersion value	0.302

Statistical analysis title	Month 3 (Statistical Analysis 4)
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Statistical analysis description:

Based on MMRM model with factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	-0.76
Variability estimate	Standard error of the mean
Dispersion value	0.305

Statistical analysis title	Month 6 (Statistical Analysis 5)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.71
Variability estimate	Standard error of the mean
Dispersion value	0.302

Statistical analysis title	Month 6 (Statistical Analysis 8)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and study baseline ISI score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	-0.71
Variability estimate	Standard error of the mean
Dispersion value	0.307

Secondary: Change From Baseline in Fatigue Severity Scale (FSS) Total Score at Months 1, 3 and

End point title	Change From Baseline in Fatigue Severity Scale (FSS) Total Score at Months 1, 3 and
End point description:	
The FSS is a self-reported scale on which subjects were instructed to choose a number from 1 to 7 that indicated their degree of agreement with 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS total score was the sum of all responses to the 9 questions. Higher total scores and average item scores indicated greater fatigue. Total score range is 9 to 63. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.	
End point type	Secondary
End point timeframe:	
Baseline, Months 1, 3 and 6	

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=318, 316, 315)	35.2 (± 13.55)	37.4 (± 12.74)	36.0 (± 13.01)	
Change at Month 1 (n= 296, 300, 286)	-3.9 (± 11.62)	-6.6 (± 11.83)	-6.4 (± 13.68)	
Change at Month 3 (n= 283, 274, 259)	-4.3 (± 11.37)	-7.7 (± 12.97)	-7.9 (± 13.56)	
Change at Month 6 (n= 257, 258, 234)	-6.3 (± 12.07)	-10.1 (± 13.56)	-8.9 (± 14.91)	

Statistical analyses

Statistical analysis title	Month 1 (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.905

Statistical analysis title	Month 1 (Statistical Analysis 2)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0257
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.83
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.913

Statistical analysis title	Month 3 (Statistical Analysis 3)
Statistical analysis description:	
Based on MMRM model with factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.02
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.939

Statistical analysis title	Month 3 (Statistical Analysis 4)
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Statistical analysis description:

Based on MMRM model with factors for age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.91
upper limit	-1.18
Variability estimate	Standard error of the mean
Dispersion value	0.95

Statistical analysis title

Month 6 (Statistical Analysis 5)

Statistical analysis description:

Based on MMRM model with factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.48
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.112

Statistical analysis title

Month 6 (Statistical Analysis 6)

Statistical analysis description:

Based on MMRM model with factors for age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effects, and study baseline FSS score as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
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Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0128
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.57
upper limit	-0.54
Variability estimate	Standard error of the mean
Dispersion value	1.026

Secondary: Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), Month 1, 3 and 6

End point title	Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Placebo-Controlled Period), Month 1, 3 and 6
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End point description:

The Sleep Diary was used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" subjects rated their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely poor (sleepy) and 9 being extremely good (alert). Higher score indicated better outcome. The FAS was the group of randomized subjects who received at least one dose of randomized study drug and had at least one postdose primary efficacy measurement. Number analyzed refers to subjects evaluable for this outcome measure at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, (mean of 7 nights [approximately Week 1]) in placebo-controlled period, Month 1, 3, 6

End point values	Placebo	Lemborexant 5 mg	Lemborexant 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	316	315	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=316, 314, 312)	3.94 (± 1.558)	3.93 (± 1.349)	3.93 (± 1.324)	
Change at First 7 nights (n= 314, 310, 310)	0.15 (± 0.991)	0.36 (± 0.964)	0.33 (± 1.018)	
Change at Month 1 (n= 300, 298, 297)	0.44 (± 1.233)	0.53 (± 1.172)	0.55 (± 1.298)	
Change at Month 3 (n= 280, 268, 264)	0.62 (± 1.366)	0.74 (± 1.325)	0.90 (± 1.452)	
Change at Month 6 (n=249, 245, 229)	0.79 (± 1.392)	0.98 (± 1.463)	1.05 (± 1.524)	

Statistical analyses

Statistical analysis title	First 7 nights (Statistical Analysis 1)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.353
Variability estimate	Standard error of the mean
Dispersion value	0.076

Statistical analysis title	First 7 nights (Statistical Analysis 2)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (First 7 nights), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.	
Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0237
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.076

Statistical analysis title	Month 1 (Statistical analysis 3)
Statistical analysis description:	
Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a	

covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.107
upper limit	0.261
Variability estimate	Standard error of the mean
Dispersion value	0.094

Statistical analysis title	Month 1 (Statistical Analysis 4)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 1), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4347
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.258
Variability estimate	Standard error of the mean
Dispersion value	0.094

Statistical analysis title	Month 3 (Statistical Analysis 5)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
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Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4992
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.141
upper limit	0.289
Variability estimate	Standard error of the mean
Dispersion value	0.109

Statistical analysis title	Month 3 (Statistical Analysis 6)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 3), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0208
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.255
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.471
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Month 6 (Statistical Analysis 7)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 5 mg
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Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2248
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.089
upper limit	0.378
Variability estimate	Standard error of the mean
Dispersion value	0.119

Statistical analysis title	Month 6 (Statistical Analysis 8)
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Statistical analysis description:

Based on MMRM model with factors of age group, region, treatment, visit (Month 6), and treatment-by-visit interaction as fixed effect, and the study baseline Mean Rating on Morning Sleepiness as a covariate. Missing values are not imputed and assumed to be MAR.

Comparison groups	Placebo v Lemborexant 10 mg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0298
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.261
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.497
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Active Treatment Period)

End point title	Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the Beginning of Treatment (Mean of the 7 Nights After the First Dose in Active Treatment Period)
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End point description:

Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, First 7 nights (approximately Week 1) in active treatment period

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: score on scale				
arithmetic mean (standard deviation)				
Baseline (n=442, 434)	4.15 (± 1.526)	4.16 (± 1.428)		
Change at First 7 nights (n=310, 310)	0.36 (± 0.964)	0.33 (± 1.018)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Screening in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the First and Second 7 Mornings of the Follow-up Period

End point title	Change From Screening in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at the First and Second 7 Mornings of the Follow-up Period
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End point description:

The Sleep Diary was used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" Subjects rated their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely poor (sleepy) and 9 being extremely good (alert). Higher score indicated better outcome. On-treatment FAS was the group of subjects who received at least 1 dose of lemborexant and had at least 1 post dose primary efficacy measurement. Overall subjects analyzed here is based on the number in the "On-Treatment FAS". Hence these numbers include the lemborexant data from the subjects re-randomized from placebo in Period 1.

End point type	Secondary
End point timeframe:	
Screening, First and second 7 mornings in follow-up period (Week 52 to 54)	

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: score on a scale				
arithmetic mean (standard deviation)				
Screening (n=440, 436)	3.63 (± 1.393)	3.54 (± 1.197)		
Change at First 7 mornings (n=335, 328)	1.03 (± 1.615)	1.32 (± 1.611)		
Change at Second 7 mornings (n=327, 313)	0.98 (± 1.699)	1.22 (± 1.635)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at Months 1, 3, 6, 9 and 12

End point title	Change From Baseline in Mean Rating on the Morning Sleepiness Item of the Sleep Diary at Months 1, 3, 6, 9 and 12
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End point description:

The Sleep Diary was used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" Subjects rated their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely poor (sleepy) and 9 being extremely good (alert). Higher score indicated better outcome. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
End point timeframe:	
Baseline, Months 1, 3, 6, 9 and 12	

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=442, 434)	4.15 (± 1.516)	4.16 (± 1.428)		
Change at Month 1 of exposure (n=415, 412)	0.46 (± 1.082)	0.42 (± 1.223)		
Change at Month 3 of exposure (n=386, 375)	0.60 (± 1.264)	0.70 (± 1.356)		
Change at Month 6 of exposure (n=352, 331)	0.78 (± 1.424)	0.86 (± 1.461)		
Change at Month 9 of exposure (n=233, 213)	1.00 (± 1.512)	1.08 (± 1.489)		
Change at Month 12 of exposure (216, 204)	1.11 (± 1.499)	1.31 (± 1.604)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rebound Insomnia: Mean sSOL on Each of the First 3 Nights, First 7

Nights, and Last 7 Nights of the Follow-up Period

End point title	Rebound Insomnia: Mean sSOL on Each of the First 3 Nights, First 7 Nights, and Last 7 Nights of the Follow-up Period
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End point description:

Rebound Insomnia: Rebound insomnia was defined as insomnia that occurred following discontinuation of a sedative substance taken to relieve primary insomnia. sSOL was defined as estimated minutes from the time that the subject attempted to sleep until sleep onset. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

First 3 nights, first and last 7 nights of the follow up period (Week 52 to 54)

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: minutes				
arithmetic mean (standard deviation)				
Mean of first 3 nights (n=287, 284)	40.35 (± 48.661)	41.73 (± 55.694)		
Mean sSOL of the first 7 nights (n=337, 328)	41.35 (± 38.967)	41.90 (± 47.826)		
Mean sSOL of the second 7 nights (329, 312)	44.10 (± 38.030)	41.30 (± 47.471)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rebound Insomnia: Mean sWASO on Each of the First 3 Nights, First 7 Nights, and Last 7 Nights of the Follow-up Period

End point title	Rebound Insomnia: Mean sWASO on Each of the First 3 Nights, First 7 Nights, and Last 7 Nights of the Follow-up Period
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End point description:

Rebound Insomnia: Rebound insomnia was defined as insomnia that occurred following discontinuation of a sedative substance taken to relieve primary insomnia. sWASO was defined as sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night, operationalized as the time the subject got out of bed for the day. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

First 3 nights, first and last 7 nights of the follow up period (Week 52 to 54)

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: minutes				
arithmetic mean (standard deviation)				
Mean of first 3 nights (n=282, 282)	86.66 (± 80.038)	97.88 (± 83.302)		
Mean of the first 7 nights (337, 326)	91.56 (± 81.738)	95.79 (± 79.784)		
Mean of the Last 7 nights (329, 312)	92.62 (± 82.672)	98.19 (± 80.668)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rebound Insomnia: Percentage of Subjects Whose sSOL Was Longer Than at Screening for First 3 Nights of the Follow-up Period, or Whom Mean sSOL Was Longer Than at Screening for First 7 Nights or Last 7 Nights of the Follow-up Period

End point title	Rebound Insomnia: Percentage of Subjects Whose sSOL Was Longer Than at Screening for First 3 Nights of the Follow-up Period, or Whom Mean sSOL Was Longer Than at Screening for First 7 Nights or Last 7 Nights of the Follow-up Period
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End point description:

Rebound Insomnia: Rebound insomnia was defined as insomnia that occurred following discontinuation of a sedative substance taken to relieve primary insomnia. sSOL was defined as estimated minutes from the time that the subject attempted to sleep until sleep onset. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

First 3 nights, first and last 7 nights of the follow up period (Week 52 to 54)

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of subjects				
number (not applicable)				
Average of first 3 nights (285, 284)	9.46	9.38		
Average of first 7 nights (n=335, 328)	11.94	10.53		
Average of second 7 nights (327, 312)	11.71	9.38		

Statistical analyses

No statistical analyses for this end point

Secondary: Rebound Insomnia: Percentage of Subjects Whose sWASO is Higher Than at Screening for First 3 Nights of the Follow-up Period, or Whose Mean sWASO is Higher Than at Screening for the First 7 Nights or Last 7 Nights of the Follow-up Period

End point title	Rebound Insomnia: Percentage of Subjects Whose sWASO is Higher Than at Screening for First 3 Nights of the Follow-up Period, or Whose Mean sWASO is Higher Than at Screening for the First 7 Nights or Last 7 Nights of the Follow-up Period
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End point description:

Rebound Insomnia: Rebound insomnia was defined as insomnia that occurred following discontinuation of a sedative substance taken to relieve primary insomnia. sWASO was defined as sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night, operationalized as the time the subject got out of bed for the day. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

First 3 nights, First and Last 7 nights of the follow up period (Week 52 to 54)

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of subjects				
number (not applicable)				
Average of first 3 nights (n=280, 282)	11.26	12.59		
Average of first 7 nights (n= 335, 325)	12.39	14.19		
Average of second 7 nights (n= 327, 311)	13.51	11.90		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of Effect: Mean Change From Baseline in sSOL, sWASO, and sTST at Months 3, 6, 9, and 12 Compared to Month 1

End point title	Persistence of Effect: Mean Change From Baseline in sSOL, sWASO, and sTST at Months 3, 6, 9, and 12 Compared to
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End point description:

At each month beyond Month 1, the change from Baseline was compared to either the lower bound of the 95% CI (for sTST) or the upper bound of the 95% CI (for sSOL and sWASO) at Month 1. Persistence of efficacy was defined as present if the mean change from Baseline at Month 6 was above the lower bound of the 95% CI at Month 1 for sTST and below the upper bound of the 95% CI at Month 1 for sSOL and sWASO. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, 3, 6, 9, 12

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: minutes				
least squares mean (confidence interval 95%)				
sSOL: Change at Month 1 of exposure (n=415, 412)	-17.17 (-19.76 to -14.58)	-18.64 (-21.26 to -16.02)		
sSOL: Change at Month 3 of exposure (n=386, 375)	-21.47 (-24.46 to -18.48)	-21.58 (-24.61 to -18.54)		
sSOL: Change at Month 6 of exposure (n=352, 331)	-24.13 (-27.22 to -21.04)	-22.99 (-26.14 to -19.83)		
sSOL: Change at Month 9 of exposure (n=233, 213)	-26.00 (-29.25 to -22.75)	-27.36 (-30.70 to -24.01)		
sSOL: Change at Month 12 of exposure (n=216, 214)	-25.83 (-29.44 to -22.22)	-26.32 (-30.03 to -22.61)		
sWASO: Change at Month 1 of exposure (n=414, 408)	-17.26 (-22.54 to -11.97)	-18.69 (-24.05 to -13.33)		
sWASO: Change at Month 3 of exposure (n=385, 373)	-31.34 (-37.12 to -25.57)	-28.97 (-34.86 to -23.09)		
sWASO: Change at Month 6 of exposure (n=351, 329)	-36.10 (-42.57 to -29.63)	-31.54 (-38.16 to -24.91)		
sWASO: Change at Month 9 of exposure (n=232, 212)	-39.28 (-46.74 to -31.83)	-40.39 (-48.08 to -32.71)		
sWASO: Change at Month 12 of exposure (n=215, 203)	-42.87 (-50.13 to -35.61)	-43.76 (-51.21 to -36.31)		
sTST: Change at Month 1 of exposure (n=400, 396)	31.98 (25.54 to 38.42)	38.04 (31.51 to 44.57)		
sTST: Change at Month 3 of exposure (n=373, 361)	49.27 (42.33 to 56.22)	53.51 (46.42 to 60.61)		
sTST: Change at Month 6 of exposure (n=342, 321)	54.99 (47.18 to 62.80)	56.36 (48.35 to 64.36)		
sTST: Change at Month 9 of exposure (n=222, 205)	55.41 (46.49 to 64.33)	61.13 (51.93 to 70.32)		
sTST: Change at Month 12 of exposure (n=207, 196)	58.15 (49.29 to 67.01)	66.50 (57.41 to 75.60)		

Statistical analyses

Secondary: Persistence of Effect: Mean Change From Baseline in sSE at Months 3, 6, 9, and 12 Compared to Month 1

End point title	Persistence of Effect: Mean Change From Baseline in sSE at Months 3, 6, 9, and 12 Compared to Month 1
End point description:	
sSE was defined as percentage of sTST per subjective time spent in bed, calculated as the interval from the time the subject reports attempting to sleep until the time the subject stopped trying to sleep for the night (operationalized as the time the participant got out of bed for the day), and time spent asleep derived from subjective time spent in bed minus sWASO. At each month beyond Month 1, the change from Baseline was compared to the lower bound of the 95% CI at Month 1. Persistence of efficacy was defined as present if the mean change from Baseline at Month 6 was above the lower bound of the 95% CI at Month 1 for sSE. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.	
End point type	Secondary
End point timeframe:	
Baseline, Months 1, 3, 6, 9, and 12	

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of sTST				
least squares mean (confidence interval 95%)				
Change at Month 1 of exposure (n=400, 396)	6.35 (5.13 to 7.57)	7.32 (6.09 to 8.56)		
Change at Month 3 of exposure (n=373, 361)	10.01 (8.69 to 11.34)	10.25 (8.90 to 11.60)		
Change at Month 6 of exposure (n=342, 321)	11.10 (9.61 to 12.58)	11.08 (9.56 to 12.60)		
Change at Month 9 of exposure (n=222, 205)	11.85 (10.13 to 13.56)	12.84 (11.08 to 14.61)		
Change at Month 12 of exposure (n=207, 196)	12.61 (10.92 to 14.31)	13.66 (11.92 to 15.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of Effect: Mean Change From Period 2 Baseline (Month 6) in sSOL, sWASO, and sTST at Months 9 and 12 Compared to Month 7

End point title	Persistence of Effect: Mean Change From Period 2 Baseline (Month 6) in sSOL, sWASO, and sTST at Months 9 and 12 Compared to Month 7
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End point description:

At each month beyond Month 7, the change from Baseline was compared to either the lower bound of the 95% CI for sTST or the upper bound of the 95% CI (for sSOL and sWASO) at Month 7. Persistence of effect was defined as present if the mean change from Baseline at Month 12 was above the lower bound of the 95% CI at Month 7 for sTST and below the upper bound of the 95% CI at Month 7 for sSOL

and sWASO. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
End point timeframe:	
Baseline, Month 7, 9, 12	

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: minutes				
least squares mean (confidence interval 95%)				
sSOL: Change at Month 7 of exposure (n=355, 334)	-28.55 (-32.39 to -24.70)	-29.46 (-33.42 to -25.50)		
sSOL: Change at Month 9 of exposure (n=349, 324)	-32.10 (-35.39 to -28.80)	-30.91 (-34.31 to -27.52)		
sSOL: Change at Month 12 of exposure (n=323, 306)	-31.40 (-34.85 to -27.96)	-31.33 (-34.88 to -27.78)		
sWASO: Change at Month 7 of exposure (n=355, 304)	-45.62 (-52.53 to -38.70)	-43.09 (-50.20 to -35.99)		
sWASO: Change at Month 9 of exposure (n=349, 324)	-47.70 (-54.54 to -40.86)	-48.87 (-55.92 to -41.82)		
sWASO: Change at Month 12 of exposure (n=323, 306)	-48.46 (-55.35 to -41.57)	-49.28 (-56.36 to -42.19)		
sTST: Change at Month 7 of exposure (n=355, 334)	75.00 (65.30 to 84.71)	76.95 (66.97 to 86.92)		
sTST: Change at Month 9 of exposure (n=349, 324)	78.69 (68.99 to 88.39)	81.24 (71.26 to 91.23)		
sTST: Change at Month 12 of exposure (n=323, 306)	78.61 (68.61 to 88.61)	83.61 (73.33 to 93.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of Effect: Mean Change From Period 2 Baseline (Month 6) in sSE at Months 9 and 12 Compared to Month 7

End point title	Persistence of Effect: Mean Change From Period 2 Baseline (Month 6) in sSE at Months 9 and 12 Compared to Month 7
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End point description:

sSE: percentage of sTST per subjective time spent in bed, calculated as the interval from the time the subject reports attempting to sleep until the time the subject stopped trying to sleep for the night (operationalized as the time the subject got out of bed for the day), and time spent asleep derived from subjective time spent in bed minus sWASO. At each month beyond Month 7, the change from Baseline was compared to the lower bound of the 95% CI for sSE at Month 7. Persistence of effect was defined as present if the mean change from Baseline at Month 12 was above the lower bound of the 95% CI at Month 7 for sSE. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:
Baseline, Month 7, 9, 12

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of sTST				
least squares mean (confidence interval 95%)				
Change at Month 7 of exposure (n=354, 334)	12.88 (9.01 to 16.75)	15.12 (11.13 to 19.10)		
Change at Month 9 of exposure (n=349, 324)	16.54 (14.88 to 18.20)	16.49 (14.78 to 18.20)		
Change at Month 12 of exposure (n=323, 306)	16.34 (14.70 to 17.98)	16.82 (15.13 to 18.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of Effect: Mean Change From Study Baseline and Period 2 Baseline (Month 6) in sSOL, sWASO, and sTST at Months 3 and 6 Exposure Compared to Month 1

End point title	Persistence of Effect: Mean Change From Study Baseline and Period 2 Baseline (Month 6) in sSOL, sWASO, and sTST at Months 3 and 6 Exposure Compared to Month 1
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End point description:

At 3 and 6 months of exposure, the change from Baseline was compared to either the lower bound of the 95% CI for sTST or the upper bound of the 95% CI (for sSOL and sWASO) at 1 month of exposure. Persistence of effect was defined as present if the mean change from Baseline at 6 months of exposure was above the lower bound of the 95% CI at 1 month of exposure for sTST and below the upper bound of the 95% CI at 1 month of exposure for sSOL and sWASO. On-treatment FAS was the group of subjects who received at least 1 dose of lemborexant and had at least 1 post dose primary efficacy measurement. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, 3, 6

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: minutes				
least squares mean (confidence interval 95%)				

sSOL: Change at Month 1 of exposure (n=415, 412)	-17.17 (-19.76 to -14.58)	-18.64 (-21.26 to -16.02)		
sSOL: Change at Month 3 of exposure (n=386, 375)	-21.47 (-24.46 to -18.48)	-21.58 (-24.61 to -18.54)		
sSOL: Change at Month 6 of exposure (n=352, 331)	-24.13 (-27.22 to -21.04)	-22.99 (-26.14 to -19.83)		
sWASO: Change at Month 1 of exposure (n=414, 408)	-17.26 (-22.54 to -11.97)	-18.69 (-24.05 to -13.33)		
sWASO: Change at Month 3 of exposure (n=385, 373)	-31.34 (-37.12 to 25.57)	-28.97 (-34.86 to -23.09)		
sWASO: Change at Month 6 of exposure (n=351, 329)	-36.10 (-42.57 to -29.63)	-31.54 (-38.16 to -24.91)		
sTST: Change at Month 1 of exposure (n=400, 396)	31.98 (25.54 to 38.42)	38.04 (31.51 to 44.57)		
sTST: Change at Month 3 of exposure (n=373, 361)	49.27 (42.33 to 56.22)	53.51 (46.42 to 60.61)		
sTST: Change at Month 6 of exposure (n=342, 321)	54.99 (47.18 to 62.80)	56.36 (48.35 to 64.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of Effect: Mean Change From Study Baseline and Period 2 Baseline (Month 6) in sSE at Months 3 and 6 Exposure Compared to Month 1

End point title	Persistence of Effect: Mean Change From Study Baseline and Period 2 Baseline (Month 6) in sSE at Months 3 and 6 Exposure Compared to Month 1
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End point description:

At 3 and 6 months of exposure, the change from Baseline was compared to the lower bound of the 95% CI for sSE at 1 month of exposure. Persistence of effect was defined as present if the mean change from Baseline at 6 months of exposure was above the lower bound of the 95% CI at 1 month of exposure for sSE. Overall subjects analyzed based on number in "On-Treatment FAS (subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement)". Hence, these numbers include lemborexant data from subjects re-randomized from placebo in Period 1. Number analyzed=subjects analyzed at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 1, 3, 6

End point values	Lemborexant 5 mg	Lemborexant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	437		
Units: percentage of sTST				
least squares mean (confidence interval 95%)				
Change at Month 1 of exposure (n=400, 396)	6.35 (5.13 to 7.57)	7.32 (6.09 to 8.56)		
Change at Month 3 of exposure (n=373, 361)	10.01 (8.69 to 11.34)	10.25 (8.90 to 11.60)		
Change at Month 6 of exposure (n=342, 321)	11.10 (9.61 to 12.58)	11.08 (9.56 to 12.60)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to Week 54

Adverse event reporting additional description:

Placebo arm included AE data for subjects who received placebo in Period 1. Lemborexant 5 mg and 10 mg arms included AE data of subjects who received either lemborexant 5 mg or 10 mg throughout the study (Period 1 and 2 both) and subjects re-randomized from placebo (in Period 1) to either lemborexant 5 mg or lemborexant 10 mg in Period

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received lemborexant-matched placebo, tablet, orally, once daily for up to Month 6 in the placebo-controlled treatment period. Then they were re-randomized to lemborexant 5 mg or lemborexant 10 mg up to Month 12 .

Reporting group title	Lemborexant 5 mg
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Reporting group description:

Subjects received lemborexant 5 mg/placebo, tablets, orally, once daily through Month 1-6 (in Period 1) and lemborexant 5 mg, tablets, orally, once daily through Month 7-12 (in Period 2)

Reporting group title	Lemborexant 10 mg
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Reporting group description:

Subjects received lemborexant 10 mg/placebo, tablets, orally, once daily through Month 1-6 (in Period 1) and lemborexant 10 mg, tablets, orally, once daily through Month 7-12 (in Period 2).

Serious adverse events	Placebo	Lemborexant 5 mg	Lemborexant 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 319 (1.57%)	18 / 447 (4.03%)	16 / 437 (3.66%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Deep Vein Thrombosis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Chest Pain			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Cyst			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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
Reproductive system and breast disorders			
Hydrosalpinx			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			

subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Inflammation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand Fracture			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Lower Limb Fracture			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Intentional Overdose			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus Injury			

subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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
Tibia fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Extrasystoles			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Neuropathy			

subjects affected / exposed	0 / 319 (0.00%)	2 / 447 (0.45%)	0 / 437 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance In Attention			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diabetic Retinopathy			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Floppy Eyelid Syndrome			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Gastrointestinal disorders			
Alcoholic Pancreatitis			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Inflammation			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Hiatus Hernia			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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			
Osteoarthritis			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	3 / 437 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw Fistula			
subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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
Jaw Cyst			

subjects affected / exposed	1 / 319 (0.31%)	0 / 447 (0.00%)	0 / 437 (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			
Erysipelas			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Cystitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 319 (0.31%)	1 / 447 (0.22%)	0 / 437 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Wound Infection			
subjects affected / exposed	0 / 319 (0.00%)	1 / 447 (0.22%)	0 / 437 (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
Metabolism and nutrition disorders			
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 319 (0.00%)	0 / 447 (0.00%)	1 / 437 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Lemborexant 5 mg	Lemborexant 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 319 (23.51%)	129 / 447 (28.86%)	140 / 437 (32.04%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	5 / 319 (1.57%)	38 / 447 (8.50%)	60 / 437 (13.73%)
occurrences (all)	5	44	64

Headache subjects affected / exposed occurrences (all)	21 / 319 (6.58%) 33	43 / 447 (9.62%) 76	32 / 437 (7.32%) 41
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	15 / 319 (4.70%) 15	22 / 447 (4.92%) 22	26 / 437 (5.95%) 29
Nasopharyngitis subjects affected / exposed occurrences (all)	40 / 319 (12.54%) 43	51 / 447 (11.41%) 67	48 / 437 (10.98%) 56

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2016	The purpose of this amendment is 1. Stated that enrollment of subjects <65 years would be limited if the percentage of enrolled subjects >65 years was below expectations toward the end of the study. 2. Clarified that subjects who discontinued study medication but did not agree to return for study visits underwent an EOS visit. 3. Clarified the term abstinence. 4. Clarified excessive caffeine use. 5. Clarified that subjects who lacked capacity and/or whose cognitive decline indicated disorientation to person/place/time and/or situation are excluded. 6. Specified that the statistical model included region if necessary, that countries with small numbers of subjects would be pooled by region, and that regions were grouped in consideration of the number and homogeneity of subjects from each region. 7. Specified that informed consent was taken by personnel in accordance with national legislation. 8. Clarified the reason why subjects should not eat a meal within 3 hours before taking the study drug. 9. Specified that the neurological examination was conducted by a clinician whose clinical experience ensured that an adequate assessment of domains underlying the exclusion criteria could be performed. 10. Specified that the investigator agreed to allow direct access to source documents and study facilities to sponsor representative(s), monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative.
28 June 2018	Amendment 4: 1. Added analysis of Treatment Period 1. Because based on the results of pivotal Study 304 and special safety studies, the sponsor decided to include a database lock with interim analysis to assess efficacy in the double-blind placebo-controlled treatment period. All available safety data were assessed. 2. In the event of an interim analysis, Sponsor staff will be unblinded; however, site personnel, investigator, and subjects will remain blinded 3. To align with Regulatory Authority provision ICH-E9 addendum, analysis sets and analysis plan were updated
03 August 2018	Amendment 5: Updated interim analysis description (to clarify that no interim analysis was being performed and that when all subjects had completed Period 1, all data were unblinded to the sponsor and that study sites and subjects would remain blinded until the study had been completed.)
13 August 2018	Amendment 6: 1. Added results from Study E2006-A001-012 2. Updated list of prohibited concomitant medications to prohibit moderate cytochrome P450 3A (CYP3A) inhibitors 3. Revised other secondary endpoint analyses for FSS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported