Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia

Summary

EudraCT number	2017-003306-40
Trial protocol	GB
Global end of trial date	17 April 2020

Results information

Result version number	v2 (current)
This version publication date	30 April 2021
First version publication date	19 January 2020
Version creation reason	• New data added to full data set Results update at study completion date.

Trial information

Trial identification

Sponsor protocol code	E2006-G000-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03001557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	European Knowledge Centre, Mosquito Way, Hatfield, United Kingdom, AL10 9SN
Public contact	Eisai Medical Information, Eisai Inc., 1-888 274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai 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	17 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2018
Global end of trial reached?	Yes
Global end of trial date	17 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study is to determine the dose response of lemborexant 2.5 milligram (mg), 5 mg, 10 mg, and 15 mg compared to placebo on the change from baseline in actigraphy-derived sleep efficiency (aSE) during the last week of treatment in subjects with irregular sleep-wake rhythm disorder (ISWRD) and Alzheimer's disease dementia , determine the efficacy of lemborexant 2.5 mg, 5 mg, 10 mg, and 15 mg compared to placebo on the change from baseline of aSE during each week of treatment, determine the efficacy of lemborexant 2.5 mg, 5 mg, 10 mg, and 15 mg compared to placebo on the change from baseline on the sleep fragmentation index (SFI) during each week of treatment, and to determine the change from baseline of the mean duration of wake bouts over each week of treatment.

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, 2013) - 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Japan: 11
Worldwide total number of subjects	63
EEA total number of subjects	1

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)	5
From 65 to 84 years	55
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 57 investigative sites in the United States, Japan and United Kingdom from 20 Dec 2016 to 17 Apr 2020.

Pre-assignment

Screening details:

A total of 214 subjects were screened, of which 151 were screen failures and 63 were randomized and enrolled in to the study. Of these 63 subjects, 62 received the study treatment (1 subject was inadvertently randomized but did not receive any study drug).

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lemborexant-matched Placebo

Arm description:

Subjects received two lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

Two lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Arm title	Lemborexant 2.5 mg

Arm description:

Subjects received one lemborexant 2.5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant-matched placebo, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Investigational medicinal product name	Lemborexant 2.5 mg
Investigational medicinal product code	E2006
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One lemborexant 2.5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Arm title	Lemborexant 5 mg

Arm description:

Subjects received one lemborexant 5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant-matched placebo, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant 5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Arm title	Lemborexant 10 mg

Arm description:

Subjects received one lemborexant 10 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant-matched placebo, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant 10 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Arm title	Lemborexant 15 mg

Arm description:

Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week

treatment period.

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

Dosage and administration details:

One lemborexant 5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

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

Dosage and administration details:

One lemborexant 10 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Number of subjects in period 1[1]	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg
Started	12	12	13
Completed	12	12	13

Number of subjects in period 1[1]	Lemborexant 10 mg	Lemborexant 15 mg
Started	13	12
Completed	13	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Eligible subjects who completed the Core Phase and agreed to continue in the Extension Phase.

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Extension Phase: Lemborexant 5 mg

Arm description:

Subject who completed the core study end of study (EOS) visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued or up to 30 months.

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

Dosage and administration details:

lemborexant, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued or up to 30 months.

Arm title	Extension Phase: Lemborexant 10 mg

Arm description:

Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 10 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

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

Dosage and administration details:

Lemborexant 10 mg tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

Arm title	Extension Phase: Lemborexant 15 mg

Arm description:

Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

Arm type	Experimental
Investigational medicinal product name	Lemborexant 15 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

Number of subjects in period 2[2]	Extension Phase: Lemborexant 5 mg	Extension Phase: Lemborexant 10 mg	Extension Phase: Lemborexant 15 mg
Started	5	14	6
Completed	0	0	0
Not completed	5	14	6
Consent withdrawn by subject	1	5	2
Others	1	3	-
Adverse event, non-fatal	2	-	-
Loss of caregiver	-	1	-
Administrative Reason	1	3	3
Lost to follow-up	-	2	1

Notes:

[2] - 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: Eligible subjects who completed the Core Phase and agreed to continue in the Extension Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Lemborexant-matched Placebo
Reporting group description:	
Subjects received two lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 2.5 mg
Reporting group description:	
Subjects received one lemborexant 2.5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 5 mg
Reporting group description:	
Subjects received one lemborexant 5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 10 mg
Reporting group description:	
Subjects received one lemborexant 10 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 15 mg
Reporting group description:	
Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	

Reporting group values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg
Number of subjects	12	12	13
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	75.3	76.5	76.9
standard deviation	± 6.15	± 6.32	± 7.98
Gender categorical Units: Subjects			
Female	7	6	8
Male	5	6	5
Ethnicity Units: Subjects			
Hispanic or Latino	4	2	4
Not Hispanic or Latino	8	10	9
Race Units: Subjects			
Asian	2	2	2
Black or African American	2	1	2
White	8	9	8
Unknown or Not Reported	0	0	1

Reporting group values	Lemborexant 10 mg	Lemborexant 15 mg	Total
Number of subjects	13	12	62
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	71.8	71.9	
standard deviation	± 7.05	± 6.11	-
Gender categorical Units: Subjects			
Female	6	10	37
Male	7	2	25
Ethnicity Units: Subjects			
Hispanic or Latino	6	8	24
Not Hispanic or Latino	7	4	38
Race Units: Subjects			
Asian	3	2	11
Black or African American	1	1	7
White	9	9	43
Unknown or Not Reported	0	0	1

End points

End points reporting groups

Reporting group title	Lemborexant-matched Placebo
Reporting group description:	
Subjects received two lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 2.5 mg
Reporting group description:	
Subjects received one lemborexant 2.5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 5 mg
Reporting group description:	
Subjects received one lemborexant 5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 10 mg
Reporting group description:	
Subjects received one lemborexant 10 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Lemborexant 15 mg
Reporting group description:	
Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.	
Reporting group title	Extension Phase: Lemborexant 5 mg
Reporting group description:	
Subject who completed the core study end of study (EOS) visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued or up to 30 months.	
Reporting group title	Extension Phase: Lemborexant 10 mg
Reporting group description:	
Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 10 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.	
Reporting group title	Extension Phase: Lemborexant 15 mg
Reporting group description:	
Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.	

Primary: Core Phase: Change From Baseline in Mean Actigraphy Sleep Efficiency (aSE) With Lemborexant Compared to Placebo During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean Actigraphy Sleep Efficiency (aSE) With Lemborexant Compared to Placebo During Week 1 of Treatment[1]

End point description:

aSE was defined as the percentage of time spent in bed nocturnal sleeping, as measured by actigraphy. Sleep efficiency was calculated as the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The full analysis set (FAS) included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	76.34 (± 6.559)	77.64 (± 7.883)	78.45 (± 6.844)	76.38 (± 8.037)
Change at Week 1 (n=12, 11, 13, 13, 12)	0.14 (± 5.766)	2.43 (± 3.910)	3.87 (± 4.646)	-0.17 (± 5.861)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	77.35 (± 8.624)			
Change at Week 1 (n=12, 11, 13, 13, 12)	0.05 (± 4.475)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 2 of Treatment[2]

End point description:

aSE was defined as the percentage of time spent in bed nocturnal sleeping, as measured by actigraphy.

Sleep efficiency was calculated as the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	76.34 (± 6.559)	77.64 (± 7.883)	78.45 (± 6.844)	76.38 (± 8.037)
Change at Week 2 (n=12, 10, 13, 13, 12)	-1.31 (± 7.004)	2.17 (± 2.833)	1.65 (± 4.644)	-1.41 (± 5.896)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	77.35 (± 8.624)			
Change at Week 2 (n=12, 10, 13, 13, 12)	-0.07 (± 5.449)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 3 of Treatment[3]

End point description:

aSE was defined as the percentage of time spent in bed nocturnal sleeping, as measured by actigraphy. Sleep efficiency was calculated as the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to

monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	76.34 (± 6.559)	77.64 (± 7.883)	78.45 (± 6.844)	76.38 (± 8.037)
Change at Week 3 (n=11, 11, 12, 12, 12)	-0.30 (± 10.552)	1.68 (± 3.229)	0.91 (± 7.571)	-1.49 (± 4.442)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	77.35 (± 8.624)			
Change at Week 3 (n=11, 11, 12, 12, 12)	1.10 (± 7.112)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean aSE With Lemborexant Compared to Placebo During Week 4 of Treatment

End point description:

aSE was defined as the percentage of time spent in bed nocturnal sleeping, as measured by actigraphy. Sleep efficiency was calculated as the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement.

Here ‘n” are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary
End point timeframe:	
Baseline, Week 4	

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	76.34 (± 6.559)	77.64 (± 7.883)	78.45 (± 6.844)	76.38 (± 8.037)
Change at Week 4 (n=11, 11, 12, 11, 12)	-0.78 (± 9.555)	1.68 (± 4.696)	0.00 (± 5.547)	-1.04 (± 5.920)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of sleep time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	77.35 (± 8.624)			
Change at Week 4 (n=11, 11, 12, 11, 12)	-0.81 (± 7.735)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant 2.5 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1099 [4]
Method	MMRM
Parameter estimate	Least square mean (LSM) difference
Point estimate	3.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.741
upper limit	7.096

Notes:

[4] - Based on a mixed model for repeated measure (MMRM) analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1576 [5]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	2.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.119
upper limit	6.723

Notes:

[5] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616 [6]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.777
upper limit	2.857

Notes:

[6] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7135 [7]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.713

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	4.585

Notes:

[7] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Mean SFI During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean SFI During Week 1 of Treatment[8]

End point description:

The SFI was defined as sum of a movement index (MI) and a fragmentation index (FI) during logged sleep period. The MI was equal to epochs of wake per time in bed (TBI) multiplied by 100. The FI was equal to the number of less than or equal to (<=) 1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). SFI was determined by Actigraphy. Actigraphy was performed with accelerometer that was worn on wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included randomized subjects received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	58.51 (± 12.923)	53.87 (± 17.594)	50.07 (± 12.493)	54.75 (± 16.380)
Change at Week 1 (n=12, 11, 13, 12, 12)	-1.43 (± 9.294)	-5.80 (± 11.388)	-8.16 (± 8.802)	-2.55 (± 11.756)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	54.78 (± 15.338)			
Change at Week 1 (n=12, 11, 13, 12, 12)	-3.52 (± 8.882)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean SFI During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean SFI During Week 2 of Treatment[9]

End point description:

The SFI was defined as sum of a MI and a FI during logged sleep period. The MI was equal to epochs of wake per TBI multiplied by 100. The FI was equal to the number of <=1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). SFI was determined by Actigraphy. Actigraphy was performed with accelerometer that was worn on wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included randomized subjects received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	58.51 (± 12.923)	53.87 (± 17.594)	50.07 (± 12.493)	54.75 (± 16.380)
Change at Week 2 (n=12, 10, 13, 13, 12)	2.52 (± 11.845)	-6.91 (± 5.994)	-4.95 (± 8.399)	0.34 (± 14.194)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	54.78 (± 15.338)			

Change at Week 2 (n=12, 10, 13, 13, 12)	-3.18 (± 8.971)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean SFI During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean SFI During Week 3 of Treatment[10]

End point description:

The SFI was defined as sum of a MI and a FI during logged sleep period. The MI was equal to epochs of wake per TBI multiplied by 100. The FI was equal to the number of <=1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). SFI was determined by Actigraphy. Actigraphy was performed with accelerometer that was worn on wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included randomized subjects received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	58.51 (± 12.923)	53.87 (± 17.594)	50.07 (± 12.493)	54.75 (± 16.380)
Change at Week 3 (n=11, 11, 12, 12, 12)	-3.30 (± 18.512)	-2.79 (± 7.541)	-5.22 (± 11.974)	0.36 (± 9.018)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	54.78 (± 15.338)			

Change at Week 3 (n=11, 11, 12, 12, 12)	-4.92 (± 9.572)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean SFI During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean SFI During Week 4 of Treatment

End point description:

The SFI was defined as sum of a MI and a FI during logged sleep period. The MI was equal to epochs of wake per TBI multiplied by 100. The FI was equal to the number of <=1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). SFI was determined by Actigraphy. Actigraphy was performed with accelerometer that was worn on wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included randomized subjects received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	58.51 (± 12.923)	53.87 (± 17.594)	50.07 (± 12.493)	54.75 (± 16.380)
Change at Week 4 (n=11, 11, 12, 11, 12)	-1.39 (± 19.383)	-1.35 (± 8.821)	-1.96 (± 8.459)	-0.45 (± 13.389)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	54.78 (± 15.338)			
Change at Week 4 (n=11, 11, 12, 11, 12)	-1.68 (± 12.683)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant 2.5 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1582 [11]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-5.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.24
upper limit	2.045

Notes:

[11] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0961 [12]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-6.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.332
upper limit	1.122

Notes:

[12] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8449 [13]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.262
upper limit	7.623

Notes:

[13] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3747 [14]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.178
upper limit	3.897

Notes:

[14] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in the Mean Duration of Wake Bouts (aMeanDurWB) During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in the Mean Duration of Wake Bouts (aMeanDurWB) During Week 1 of Treatment[15]

End point description:

aMeanDurWB was defined as an average duration of all wake bouts that occurred during the defined nocturnal predefined sleep period. The wake bout was defined as continuous wake of 10 minutes or longer. Lower values were better. aMeanDurWB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	20.32 (± 6.625)	20.40 (± 5.140)	20.62 (± 5.898)	21.89 (± 4.885)
Change at Week 1 (n=12, 11, 13, 12, 12)	-1.65 (± 5.078)	-1.99 (± 2.825)	-0.51 (± 6.522)	-0.82 (± 5.722)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	21.94 (± 7.790)			
Change at Week 1 (n=12, 11, 13, 12, 12)	1.54 (± 5.378)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurWB During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurWB During Week 2 of Treatment[16]

End point description:

aMeanDurWB was defined as an average duration of all wake bouts that occurred during the defined nocturnal predefined sleep period. The wake bout was defined as continuous wake of 10 minutes or longer. Lower values were better. aMeanDurWB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	20.32 (± 6.625)	20.40 (± 5.140)	20.62 (± 5.898)	21.89 (± 4.885)
Change at Week 2 (n=12, 10, 13, 12, 12)	-0.32 (± 7.904)	1.79 (± 12.957)	4.71 (± 13.845)	1.54 (± 6.333)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	21.94 (± 7.790)			
Change at Week 2 (n=12, 10, 13, 12, 12)	2.57 (± 6.708)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurWB During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurWB During Week 3 of Treatment[17]

End point description:

aMeanDurWB was defined as an average duration of all wake bouts that occurred during the defined nocturnal predefined sleep period. The wake bout was defined as continuous wake of 10 minutes or longer. Lower values were better. aMeanDurWB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	20.32 (± 6.625)	20.40 (± 5.140)	20.62 (± 5.898)	21.89 (± 4.885)
Change at Week 3 (n=11, 11, 11, 12, 12)	-2.88 (± 7.928)	3.67 (± 7.833)	-0.52 (± 4.595)	-0.64 (± 5.482)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	21.94 (± 7.790)			
Change at Week 3 (n=11, 11, 11, 12, 12)	2.76 (± 7.489)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurWB During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurWB During Week 4 of Treatment

End point description:

aMeanDurWB was defined as an average duration of all wake bouts that occurred during the defined nocturnal predefined sleep period. The wake bout was defined as continuous wake of 10 minutes or longer. Lower values were better. aMeanDurWB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	20.32 (± 6.625)	20.40 (± 5.140)	20.62 (± 5.898)	21.89 (± 4.885)
Change at Week 4 (n=11, 11, 11, 11, 12)	1.26 (± 8.621)	-0.43 (± 8.053)	3.16 (± 8.140)	-2.03 (± 4.947)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	21.94 (± 7.790)			
Change at Week 4 (n=11, 11, 11, 11, 12)	3.38 (± 12.354)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3966 [18]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.932
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.601
upper limit	6.465

Notes:

[18] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1381 [19]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	3.386
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.125
upper limit	7.897

Notes:

[19] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5487 [20]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.104
upper limit	5.778

Notes:

[20] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0581 [21]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	8.793

Notes:

[21] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Mean Actigraphy Wake Efficiency

(aWE) During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean Actigraphy Wake Efficiency (aWE) During Week 1 of Treatment[22]

End point description:

aWE was defined as the percentage of time spent awake in bed during defined wake period, as measured by actigraphy. Wake efficiency was calculated as the total duration of wake epochs during 16 hours outside of the predefined sleep period divided by 16 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	69.74 (± 12.609)	70.57 (± 11.669)	72.53 (± 11.473)	67.19 (± 11.523)
Change at Week 1 (n=12, 11, 13, 12, 12)	0.59 (± 4.177)	-2.41 (± 6.726)	1.09 (± 6.793)	-1.55 (± 9.216)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	70.67 (± 11.221)			
Change at Week 1 (n=12, 11, 13, 12, 12)	-2.37 (± 8.779)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aWE During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean aWE During Week 2 of Treatment[23]

End point description:

aWE was defined as the percentage of time spent awake in bed during defined wake period, as measured by actigraphy. Wake efficiency was calculated as the total duration of wake epochs during 16 hours outside of the predefined sleep period divided by 16 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	69.74 (± 12.609)	70.57 (± 11.669)	72.53 (± 11.473)	67.19 (± 11.523)
Change at Week 2 (n=12, 10, 13, 12, 12)	2.14 (± 2.773)	-1.54 (± 6.550)	1.04 (± 7.511)	-3.16 (± 12.816)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	70.67 (± 11.221)			
Change at Week 2 (n=12, 10, 13, 12, 12)	-0.63 (± 5.617)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aWE During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean aWE During Week 3 of Treatment[24]

End point description:

aWE was defined as the percentage of time spent awake in bed during defined wake period, as measured by actigraphy. Wake efficiency was calculated as the total duration of wake epochs during 16

hours outside of the predefined sleep period divided by 16 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	69.74 (± 12.609)	70.57 (± 11.669)	72.53 (± 11.473)	67.19 (± 11.523)
Change at Week 3 (n=11, 11, 12, 12, 12)	1.64 (± 5.451)	-2.37 (± 6.239)	2.34 (± 8.370)	-4.99 (± 11.479)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	70.67 (± 11.221)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-1.83 (± 5.579)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean aWE During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean aWE During Week 4 of Treatment

End point description:

aWE was defined as the percentage of time spent awake in bed during defined wake period, as measured by actigraphy. Wake efficiency was calculated as the total duration of wake epochs during 16 hours outside of the predefined sleep period divided by 16 hours and multiplied by 100. Higher values were better. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of

randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	69.74 (± 12.609)	70.57 (± 11.669)	72.53 (± 11.473)	67.19 (± 11.523)
Change at Week 4 (n=11, 11, 12, 11, 12)	2.03 (± 6.841)	-2.29 (± 7.724)	3.62 (± 8.586)	-2.65 (± 9.627)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of wake time				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	70.67 (± 11.221)			
Change at Week 4 (n=11, 11, 12, 11, 12)	-0.43 (± 5.848)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1777 [25]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-3.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.481
upper limit	1.608

Notes:

[25] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.563 [26]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	1.458
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.564
upper limit	6.479

Notes:

[26] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0482 [27]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-4.994
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.946
upper limit	-0.041

Notes:

[27] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3036 [28]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-2.593

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.599
upper limit	2.413

Notes:

[28] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Mean Wake Fragmentation Index (WFI) During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean Wake Fragmentation Index (WFI) During Week 1 of Treatment[29]

End point description:

The WFI were calculated as sum of an immobility index (II) and FI during the logged wake period. The II was equal to the epochs of immobility per the 16 hours outside of the defined sleep period multiplied by 100. The FI was equal to the number of <=1-minute periods of mobility/total number of periods of mobility the 16 hours outside of defined sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). The WFI was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	92.43 (± 18.547)	85.72 (± 16.137)	86.53 (± 18.705)	94.76 (± 17.262)
Change at Week 1 (n=12, 11, 13, 12, 12)	-0.14 (± 6.968)	4.22 (± 9.988)	-2.18 (± 10.571)	2.01 (± 13.017)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	87.96 (± 15.928)			
Change at Week 1 (n=12, 11, 13, 12, 12)	3.25 (± 13.006)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean WFI During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean WFI During Week 2 of Treatment[30]

End point description:

The WFI were calculated as the sum of an II and a FI during the logged wake period. The II was equal to the epochs of immobility per the 16 hours outside of the defined sleep period multiplied by 100. The FI was equal to the number of <=1-minute periods of mobility/total number of periods of mobility the 16 hours outside of the defined sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). The WFI was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	92.43 (± 18.547)	85.72 (± 16.137)	86.53 (± 18.705)	94.76 (± 17.262)
Change at Week 2 (n=12, 10, 13, 12, 12)	-3.76 (± 3.940)	4.12 (± 8.671)	-2.36 (± 11.453)	5.09 (± 19.006)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	87.96 (± 15.928)			

Change at Week 2 (n=12, 10, 13, 12, 12)	1.78 (± 9.271)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean WFI During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean WFI During Week 3 of Treatment[31]

End point description:

The WFI were calculated as the sum of an II and a FI during the logged wake period. The II was equal to the epochs of immobility per the 16 hours outside of the defined sleep period multiplied by 100. The FI was equal to the number of <=1-minute periods of mobility/total number of periods of mobility the 16 hours outside of the defined sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). The WFI was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	92.43 (± 18.547)	85.72 (± 16.137)	86.53 (± 94.76)	94.76 (± 17.262)
Change at Week 3 (n=11, 11, 12, 12, 12)	-1.65 (± 7.980)	4.70 (± 9.674)	-3.69 (± 13.236)	6.88 (± 16.704)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	87.96 (± 15.928)			

Change at Week 3 (n=11, 11, 12, 12, 12)	2.10 (± 8.631)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean WFI During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean WFI During Week 4 of Treatment

End point description:

The WFI were calculated as the sum of an II and a FI during the logged wake period. The II was equal to the epochs of immobility per the 16 hours outside of the defined sleep period multiplied by 100. The FI was equal to the number of <=1-minute periods of mobility/total number of periods of mobility the 16 hours outside of the defined sleep period multiplied by 100. Value ranges from 0-100 percent (lower values were better). The WFI was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	92.43 (± 18.547)	85.72 (± 16.137)	86.53 (± 18.705)	94.76 (± 17.262)
Change at Week 4 (n=11, 11, 12, 11, 12)	-3.01 (± 10.620)	4.55 (± 10.930)	-6.93 (± 14.428)	2.77 (± 13.407)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of immobile bouts				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	87.96 (± 15.928)			
Change at Week 4 (n=11, 11, 12, 11, 12)	1.22 (± 8.054)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1991 [32]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	4.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.624
upper limit	12.313

Notes:

[32] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2982 [33]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-3.872
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.263
upper limit	3.518

Notes:

[33] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0664 [34]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	6.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.474
upper limit	14.025

Notes:

[34] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4148 [35]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	3.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.344
upper limit	10.379

Notes:

[35] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in the Mean Duration of Sleep Bouts (aMeanDurSB) During Week 1 of Treatment

End point title	Core Phase: Change From Baseline in the Mean Duration of Sleep Bouts (aMeanDurSB) During Week 1 of Treatment[36]

End point description:

aMeanDurSB was defined as an average duration of all sleep bouts that occurred during the 16 hours outside of the predefined nocturnal sleep period. The sleep bout was defined as the continuous sleep of 10 minutes or longer. Lower values were better. aMeanDurSB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	18.36 (± 4.620)	20.65 (± 3.638)	23.13 (± 5.919)	19.84 (± 3.364)
Change at Week 1 (n=12, 11, 13, 12, 12)	2.15 (± 2.539)	0.09 (± 4.056)	-1.12 (± 5.202)	-0.40 (± 3.394)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	23.30 (± 10.862)			
Change at Week 1 (n=12, 11, 13, 12, 12)	-3.19 (± 10.405)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurSB During Week 2 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurSB During Week 2 of Treatment[37]

End point description:

aMeanDurSB was defined as an average duration of all sleep bouts that occurred during the 16 hours outside of the predefined nocturnal sleep period. The sleep bout was defined as the continuous sleep of 10 minutes or longer. lower values were better. aMeanDurSB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	18.36 (± 4.620)	20.65 (± 3.638)	23.13 (± 5.919)	19.84 (± 3.364)
Change at Week 2 (n=12, 10, 13, 12, 12)	0.25 (± 2.999)	-0.88 (± 4.679)	-2.52 (± 5.965)	-0.80 (± 2.961)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	23.30 (± 10.862)			
Change at Week 2 (n=12, 10, 13, 12, 12)	-3.95 (± 8.980)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurSB During Week 3 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurSB During Week 3 of Treatment[38]

End point description:

aMeanDurSB was defined as an average duration of all sleep bouts that occurred during the 16 hours outside of the predefined nocturnal sleep period. The sleep bout was defined as the continuous sleep of 10 minutes or longer. lower values were better. aMeanDurSB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[38] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	18.36 (± 4.620)	20.65 (± 3.638)	23.13 (± 5.919)	19.84 (± 3.364)
Change at Week 3 (n=11, 11, 12, 12, 12)	-0.14 (± 3.249)	-1.17 (± 4.056)	-3.80 (± 3.701)	-0.68 (± 2.292)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	23.30 (± 10.862)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-4.15 (± 10.264)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the aMeanDurSB During Week 4 of Treatment

End point title	Core Phase: Change From Baseline in the aMeanDurSB During Week 4 of Treatment

End point description:

aMeanDurSB was defined as an average duration of all sleep bouts that occurred during the 16 hours outside of the predefined nocturnal sleep period. The sleep bout was defined as the continuous sleep of 10 minutes or longer. lower values were better. aMeanDurSB was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	18.36 (± 4.620)	20.65 (± 3.638)	23.13 (± 5.919)	19.84 (± 3.364)
Change at Week 4 (n=11, 11, 12, 11, 12)	1.00 (± 4.568)	-1.31 (± 3.639)	-2.80 (± 5.727)	-0.03 (± 2.307)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	23.30 (± 10.862)			
Change at Week 4 (n=11, 11, 12, 11, 12)	-5.30 (± 9.745)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9599 [39]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.452
upper limit	2.579

Notes:

[39] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8541 [40]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.238
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.817
upper limit	2.342

Notes:

[40] - Based on a MMRM analysis adjusted for baseline value, country, Visit and treatment by Visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8117 [41]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.745
upper limit	2.16

Notes:

[41] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2274 [42]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-1.557
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.113
upper limit	1

Notes:

[42] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Mean Intradaily Variability Over

Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 1 of Treatment[43]

End point description:

Intradaily variability gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean(overall variance). The variable has a theoretical range of 0 to 2, with higher values indicating higher fragmentation. Intradaily variability was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.10 (± 0.262)	0.90 (± 0.272)	0.98 (± 0.295)	1.10 (± 0.295)
Change at Week 1 (n=12, 11, 13, 11, 12)	-0.01 (± 0.200)	0.06 (± 0.218)	-0.03 (± 0.237)	0.10 (± 0.271)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.03 (± 0.330)			
Change at Week 1 (n=12, 11, 13, 11, 12)	-0.01 (± 0.278)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 2 of Treatment[44]

End point description:

Intradaily variability gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance). The variable has a theoretical range of 0 to 2, with higher values indicating higher fragmentation. Intradaily variability was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[44] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.10 (± 0.262)	0.90 (± 0.272)	0.98 (± 0.295)	1.10 (± 0.295)
Change at Week 2 (n=12, 9, 12, 12, 11)	-0.05 (± 0.132)	0.14 (± 0.325)	0.02 (± 0.235)	0.07 (± 0.143)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.03 (± 0.330)			
Change at Week 2 (n=12, 9, 12, 12, 11)	0.05 (± 0.234)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 3 of Treatment[45]

End point description:

Intradaily variability gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance). The variable has a theoretical range of 0 to 2, with higher values indicating higher fragmentation. Intradaily

variability was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.10 (± 0.262)	0.90 (± 0.272)	0.98 (± 0.295)	1.10 (± 0.295)
Change at Week 3 (n=11, 11, 12, 12, 12)	-0.06 (± 0.243)	0.07 (± 0.246)	-0.00 (± 0.241)	-0.06 (± 0.311)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.03 (± 0.330)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-0.01 (± 0.219)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean Intradaily Variability Over Week 4 of Treatment

End point description:

Intradaily variability gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance). The variable has a theoretical range of 0 to 2, with higher values indicating higher fragmentation. Intradaily variability was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this

measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.10 (± 0.262)	0.90 (± 0.272)	0.98 (± 0.295)	1.10 (± 0.295)
Change at Week 4 (n=7, 10, 8, 8, 9)	-0.10 (± 0.324)	0.10 (± 0.196)	0.02 (± 0.157)	-0.12 (± 0.274)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1.03 (± 0.330)			
Change at Week 4 (n=7, 10, 8, 8, 9)	-0.10 (± 0.222)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2421 [46]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.232

Notes:

[46] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8661 [47]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	0.131

Notes:

[47] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4251 [48]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.199

Notes:

[48] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7248 [49]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.166

Notes:

[49] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Mean Interdaily Stability (IS) Over Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Mean Interdaily Stability (IS) Over Week 1 of Treatment[50]

End point description:

IS gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability). IS was derived by the ratio between the variance of the average 24-hour pattern around the mean and the overall variance. Higher values indicated stable rhythm. IS was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[50] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.45 (± 0.173)	0.47 (± 0.111)	0.49 (± 0.118)	0.46 (± 0.160)
Change at Week 1 (n=12, 11, 13, 11, 12)	0.04 (± 0.083)	-0.02 (± 0.089)	0.04 (± 0.115)	-0.00 (± 0.155)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.41 (± 0.104)			
Change at Week 1 (n=12, 11, 13, 11, 12)	0.06 (± 0.063)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean IS Over Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Mean IS Over Week 2 of Treatment[51]

End point description:

IS gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability). IS was derived by the ratio between the variance of the average 24-hour pattern around the mean and the overall variance. Higher values indicated stable rhythm. IS was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[51] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.45 (± 0.173)	0.47 (± 0.111)	0.49 (± 0.118)	0.46 (± 0.160)
Change at Week 2 (n=12, 9, 12, 12, 11)	0.06 (± 0.093)	-0.01 (± 0.101)	0.03 (± 0.133)	-0.06 (± 0.091)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.41 (± 0.104)			
Change at Week 2 (n=12, 9, 12, 12, 11)	0.09 (± 0.085)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean IS Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Mean IS Over Week 3 of Treatment[52]

End point description:

IS gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability). IS was derived by the ratio between the variance of the average 24-hour

pattern around the mean and the overall variance. Higher values indicated stable rhythm. IS was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.45 (± 0.173)	0.47 (± 0.111)	0.49 (± 0.118)	0.46 (± 0.160)
Change at Week 3 (n=11, 11, 12, 12, 12)	0.03 (± 0.104)	-0.01 (± 0.107)	0.03 (± 0.115)	-0.04 (± 0.136)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.41 (± 0.104)			
Change at Week 3 (n=11, 11, 12, 12, 12)	0.04 (± 0.075)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Mean IS Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Mean IS Over Week 4 of Treatment

End point description:

IS gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability). IS was derived by the ratio between the variance of the average 24-hour pattern around the mean and the overall variance. Higher values indicated stable rhythm. IS was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:
Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.45 (± 0.173)	0.47 (± 0.111)	0.49 (± 0.118)	0.46 (± 0.160)
Change at Week 4 (n=7, 10, 8, 8, 9)	0.02 (± 0.098)	0.01 (± 0.119)	0.08 (± 0.092)	0.03 (± 0.127)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.41 (± 0.104)			
Change at Week 4 (n=7, 10, 8, 8, 9)	0.00 (± 0.102)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2991 [53]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.029

Notes:
[53] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2861 [54]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.095

Notes:

[54] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0938 [55]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.009

Notes:

[55] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant 15 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8618 [56]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.066

Notes:

[56] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Average Activity Counts Across Least Active 5-hour Period (L5) Per 24-Hour Period Over Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Average Activity Counts Across Least Active 5-hour Period (L5) Per 24-Hour Period Over Week 1 of Treatment[57]

End point description:

L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. This value provides an indication of how restful (inactive) and regular the sleep periods are. L5 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[57] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1163.5 (± 373.3)	1266.4 (± 678.1)	1163.2 (± 591.8)	1257.1 (± 836.6)
Change at Week 1 (n=12, 11, 13, 11, 12)	200.9 (± 633.3)	-259.8 (± 450.3)	-243.2 (± 333.6)	-211.6 (± 378.3)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1490.4 (± 963.1)			
Change at Week 1 (n=12, 11, 13, 11, 12)	-434.2 (± 509.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Average Activity Counts Across L5 Per 24-Hour Period Over Week 2 of Treatment

End point title	Core Phase: Change From Baseline in Average Activity Counts

	Across L5 Per 24-Hour Period Over Week 2 of Treatment[58]

End point description:

L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. This value provides an indication of how restful (inactive) and regular the sleep periods are. L5 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[58] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1163.5 (± 373.3)	1266.4 (± 678.1)	1163.2 (± 591.8)	1257.1 (± 836.6)
Change at Week 2 (n=12, 9, 12, 12, 11)	85.8 (± 525.3)	-259.8 (± 244.9)	-218.7 (± 321.6)	218.5 (± 455.9)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1490.4 (± 963.1)			
Change at Week 2 (n=12, 9, 12, 12, 11)	-246.1 (± 637.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Average Activity Counts Across L5 Per 24-Hour Period Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in Average Activity Counts Across L5 Per 24-Hour Period Over Week 3 of Treatment[59]

End point description:

L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. This value provides an indication of how restful (inactive) and

regular the sleep periods are. L5 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[59] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1163.5 (± 373.3)	1266.4 (± 678.1)	1163.2 (± 591.8)	1257.1 (± 836.6)
Change at Week 3 (n=11, 11, 12, 12, 12)	299.2 (± 1070.2)	-265.3 (± 507.0)	-233.0 (± 369.3)	-114.6 (± 376.6)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1490.4 (± 963.1)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-396.1 (± 543.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in Average Activity Counts Across L5 Per 24-Hour Period Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in Average Activity Counts Across L5 Per 24-Hour Period Over Week 4 of Treatment

End point description:

L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. This value provides an indication of how restful (inactive) and regular the sleep periods are. L5 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects

who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:
Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1163.5 (± 373.3)	1266.4 (± 678.1)	1163.2 (± 591.8)	1257.1 (± 836.6)
Change at Week 4 (n=7, 10, 8, 8, 9)	293.1 (± 662.6)	-334.0 (± 476.4)	-344.5 (± 419.1)	30.5 (± 772.5)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	1490.4 (± 963.1)			
Change at Week 4 (n=7, 10, 8, 8, 9)	-160.7 (± 471.3)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant 2.5 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0294 [60]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-389.873
Confidence interval	
level	95 %
sides	2-sided
lower limit	-739.177
upper limit	-40.569

Notes:

[60] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0243 [61]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-402.994
Confidence interval	
level	95 %
sides	2-sided
lower limit	-751.67
upper limit	-54.319

Notes:

[61] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4209 [62]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-141.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-489.805
upper limit	207.752

Notes:

[62] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0398 [63]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-367.845

Confidence interval	
level	95 %
sides	2-sided
lower limit	-717.87
upper limit	-17.82

Notes:

[63] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in the Average Activity Count During the Most Active 10-hour Period (M10) Per 24-Hour Period Over Week 1 of Treatment

End point title	Core Phase: Change From Baseline in the Average Activity Count During the Most Active 10-hour Period (M10) Per 24-Hour Period Over Week 1 of Treatment[64]

End point description:

M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. M10 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[64] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	8560.4 (± 2631.2)	11567.0 (± 4266.3)	12158.1 (± 3639.9)	10662.1 (± 5023.6)
Change at Week 1 (n=12, 11, 13, 11, 12)	59.7 (± 1832.6)	-731.4 (± 3373.5)	42.5 (± 1789.3)	-334.6 (± 2659.2)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	11460.5 (± 4954.3)			
Change at Week 1 (n=12, 11, 13, 11, 12)	-111.2 (± 2558.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 2 of Treatment

End point title	Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 2 of Treatment[65]

End point description:

M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. M10 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[65] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	8560.4 (± 2631.2)	11567.0 (± 4266.3)	12158.1 (± 3639.9)	10662.1 (± 5023.6)
Change at Week 2 (n=12, 9, 12, 12, 11)	232.7 (± 1829.1)	-968.8 (± 2885.6)	-121.1 (± 2137.3)	-564.2 (± 1975.7)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	11460.5 (± 4954.3)			
Change at Week 2 (n=12, 9, 12, 12, 11)	-325.4 (± 1585.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 3 of Treatment[66]

End point description:

M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. M10 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[66] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	8560.4 (± 2631.2)	11567.0 (± 4266.3)	12158.1 (± 3639.9)	10662.1 (± 5023.6)
Change at Week 3 (n=11, 11, 12, 12, 12)	300.3 (± 2094.9)	-986.2 (± 3502.0)	572.6 (± 2216.0)	-828.3 (± 1970.2)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	11460.5 (± 4954.3)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-635.8 (± 2413.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in the Average Activity Count During the M10 Per 24-Hour Period Over Week 4 of Treatment

End point description:

M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. M10 was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	8560.4 (± 2631.2)	11567.0 (± 4266.3)	12158.1 (± 3639.9)	10662.1 (± 5023.6)
Change at Week 4 (n=7, 10, 8, 8, 9)	1650.4 (± 1815.3)	-1392.1 (± 2249.3)	-477.4 (± 963.2)	279.8 (± 2204.0)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	11460.5 (± 4954.3)			
Change at Week 4 (n=7, 10, 8, 8, 9)	-457.8 (± 1788.7)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant 2.5 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1162 [67]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-1276.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2878.587
upper limit	326.226

Notes:

[67] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7781 [68]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	227.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1382.85
upper limit	1837.777

Notes:

[68] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4255 [69]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-620.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2170.342
upper limit	929.179

Notes:

[69] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4672 [70]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-577.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2160.337
upper limit	1004.697

Notes:

[70] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Amplitude of the Rest-activity Rhythm (AMP) Over Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Amplitude of the Rest-activity Rhythm (AMP) Over Week 1 of Treatment[71]

End point description:

AMP was amplitude of rest-activity rhythm calculated as the difference between M10 and L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. AMP was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[71] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	7396.9 (± 2728.3)	10300.6 (± 4235.8)	10994.8 (± 3601.8)	9405.0 (± 5133.9)
Change at Week 1 (n=12, 11, 13, 11, 12)	-141.1 (± 1583.8)	-471.6 (± 3414.4)	285.8 (± 1788.6)	-123.0 (± 2784.1)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	9970.0 (± 4905.8)			
Change at Week 1 (n=12, 11, 13, 11, 12)	323.0 (± 2436.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in AMP Over Week 2 of Treatment

End point title	Core Phase: Change From Baseline in AMP Over Week 2 of Treatment[72]

End point description:

AMP was amplitude of rest-activity rhythm calculated as the difference between M10 and L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. AMP was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[72] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	7396.9 (± 2728.3)	10300.6 (± 4235.8)	10994.8 (± 3601.8)	9405.0 (± 5133.9)
Change at Week 2 (n=12, 9, 12, 12, 11)	146.8 (± 1603.7)	-708.9 (± 2934.6)	97.6 (± 2105.2)	-782.7 (± 2141.4)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	9970.0 (± 4905.8)			
Change at Week 2 (n=12, 9, 12, 12, 11)	-79.3 (± 1672.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in AMP Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in AMP Over Week 3 of Treatment[73]

End point description:

AMP was amplitude of rest-activity rhythm calculated as the difference between M10 and L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. AMP was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[73] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	7396.9 (± 2728.3)	10300.6 (± 4235.8)	10994.8 (± 3601.8)	9405.0 (± 5133.9)
Change at Week 3 (n=11, 11, 12, 12, 12)	1.1 (± 1862.7)	-721.0 (± 3502.2)	805.6 (± 2195.6)	-713.7 (± 2178.3)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	9970.0 (± 4905.8)			
Change at Week 3 (n=11, 11, 12, 12, 12)	-239.7 (± 2592.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in AMP Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in AMP Over Week 4 of Treatment

End point description:

AMP was amplitude of rest-activity rhythm calculated as the difference between M10 and L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. AMP was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 4

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	7396.9 (± 2728.3)	10300.6 (± 4235.8)	10994.8 (± 3601.8)	9405.0 (± 5133.9)
Change at Week 4 (n=7, 10, 8, 8, 9)	1357.3 (± 1801.9)	-1058.0 (± 2170.9)	-132.9 (± 840.7)	249.4 (± 2694.7)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: activity count				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	9970.0 (± 4905.8)			
Change at Week 4 (n=7, 10, 8, 8, 9)	-297.1 (± 1608.2)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant 2.5 mg v Lemborexant-matched Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2984 [74]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-839.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2440.854
upper limit	762.678

Notes:

[74] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

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

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4218 [75]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	651.922
Confidence interval	
level	95 %
sides	2-sided
lower limit	-962.835
upper limit	2266.678

Notes:

[75] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5655 [76]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-447.245
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1998.44
upper limit	1103.95

Notes:

[76] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8686 [77]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	-130.603
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1706.478
upper limit	1445.272

Notes:

[77] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Primary: Core Phase: Change From Baseline in Relative Amplitude in the Rest-activity Rhythm (RA) Over Week 1 of Treatment

End point title	Core Phase: Change From Baseline in Relative Amplitude in the Rest-activity Rhythm (RA) Over Week 1 of Treatment[78]

End point description:

RA was relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. RA was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average first 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 1

Notes:

[78] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.73 (± 0.136)	0.79 (± 0.141)	0.82 (± 0.089)	0.77 (± 0.165)
Change at Week 1 (n=12, 11, 13, 11, 12)	-0.02 (± 0.101)	0.01 (± 0.080)	0.03 (± 0.067)	0.02 (± 0.096)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.76 (± 0.148)			
Change at Week 1 (n=12, 11, 13, 11, 12)	0.07 (± 0.073)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Core Phase: Change From Baseline in RA Over Week 2 of Treatment

End point title	Core Phase: Core Phase: Change From Baseline in RA Over Week 2 of Treatment[79]

End point description:

RA was relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. RA was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average second 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[79] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.73 (± 0.136)	0.79 (± 0.141)	0.82 (± 0.089)	0.77 (± 0.165)
Change at Week 2 (n=12, 9, 12, 12, 11)	-0.00 (± 0.073)	0.01 (± 0.063)	0.03 (± 0.052)	-0.05 (± 0.112)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.76 (± 0.148)			
Change at Week 2 (n=12, 9, 12, 12, 11)	0.05 (± 0.091)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in RA Over Week 3 of Treatment

End point title	Core Phase: Change From Baseline in RA Over Week 3 of Treatment[80]

End point description:

RA was relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. RA was determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average third 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary

End point timeframe:

Baseline, Week 3

Notes:

[80] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.73 (± 0.136)	0.79 (± 0.141)	0.82 (± 0.089)	0.01 (± 0.090)
Change at Week 3 (n=11, 11, 12, 12, 12)	-0.01 (± 0.143)	0.01 (± 0.088)	0.04 (± 0.063)	0.01 (± 0.090)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.06 (± 0.080)			
Change at Week 3 (n=11, 11, 12, 12, 12)	0.06 (± 0.080)			

Statistical analyses

No statistical analyses for this end point

Primary: Core Phase: Change From Baseline in RA Over Week 4 of Treatment

End point title	Core Phase: Change From Baseline in RA Over Week 4 of Treatment

End point description:

RA was relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5. L5 was defined as the average activity across the least active 5-hour period per 24-hour period, with high values indicating restlessness. M10 was defined as the average activity during the most active 10-hour period per 24-hour period with low levels indicating inactivity. RA was

determined by Actigraphy. Actigraphy was performed with an accelerometer that was worn on the wrist like a watch. It was programmed to monitor degree and intensity of movements while the device was being worn. Change from baseline to average last 7 nights of treatment was reported. The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Primary
End point timeframe:	
Baseline, Week 4	

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.73 (± 0.136)	0.79 (± 0.141)	0.82 (± 0.089)	0.77 (± 0.165)
Change at Week 4 (n=7, 10, 8, 8, 9)	-0.00 (± 0.117)	0.01 (± 0.060)	0.05 (± 0.049)	0.01 (± 0.136)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 13, 13, 12)	0.76 (± 0.148)			
Change at Week 4 (n=7, 10, 8, 8, 9)	0.02 (± 0.069)			

Statistical analyses

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 2.5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 2.5 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4638 [81]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.074

Notes:

[81] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 5 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 5 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0322 [82]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.115

Notes:

[82] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 10 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 10 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9144 [83]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.056

Notes:

[83] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Statistical analysis title	Lemborexant-matched Placebo, Lemborexant 15 mg
Comparison groups	Lemborexant-matched Placebo v Lemborexant 15 mg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0364 [84]
Method	MMRM
Parameter estimate	LSM Difference
Point estimate	0.057

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.11

Notes:

[84] - Based on a MMRM analysis adjusted for baseline value, country, visit and treatment by visit interaction.

Other pre-specified: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

The safety analysis set included the group of randomized subject who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.

End point type	Other pre-specified

End point timeframe:

First dose of study drug (Day 1) to 14 days after last dose of study drug (approximately up to 2 years 7 months)

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: subjects				
TEAEs	4	3	3	4
SAEs	0	0	0	0

End point values	Lemborexant 15 mg	Extension Phase: Lemborexant 5 mg	Extension Phase: Lemborexant 10 mg	Extension Phase: Lemborexant 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	14	6
Units: subjects				
TEAEs	6	4	10	5
SAEs	0	1	2	1

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Core Phase: Number of Subjects in Each Category With Clinician’s Global Impression of Change-Irregular Sleep-Wake Rhythm Disorder (CGIC-ISWRD) Global Score at Day 29

End point title	Core Phase: Number of Subjects in Each Category With Clinician's Global Impression of Change-Irregular Sleep-Wake Rhythm Disorder (CGIC-ISWRD) Global Score at Day 29

End point description:

The CGIC-ISWRD scale is validated categorical measure of change in subject's clinical condition between baseline and follow-up visits. It relies on direct examination of subject and interview of informant. The instrument consisted of 3 parts:a guided baseline interview administered to subject and informant, a follow-up interview administered to subject and informant, clinician's rating review. The baseline interview was reference for future ratings. During baseline interview, the rater evaluated subject regarding domains of(1)sleep and wake symptoms;(2)mood and behavioral symptoms;(3)attention/arousal;and(4)social functioning. In follow-up interview, a 7-pointscale used, from 1=marked improvement,4=no change ,to 7=marked worsening, to score each of the 4 domains and to provide a global score(1[marked improvement] to 7[marked worsening]). The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement.

End point type	Other pre-specified

End point timeframe:

Day 29

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: subjects				
Global score: Marked improvement	1	0	0	0
Global score: Moderate improvement	1	0	2	1
Global score: Minimal improvement	4	4	4	5
Global score: No change	6	5	4	3
Global score: Minimal worsening	0	3	2	3
Global score : Moderate worsening	0	0	0	0
Global score : Marked worsening	0	0	0	0

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
Global score: Marked improvement	0			
Global score: Moderate improvement	0			
Global score: Minimal improvement	3			
Global score: No change	7			
Global score: Minimal worsening	1			
Global score : Moderate worsening	0			
Global score : Marked worsening	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Core Phase: Change From Baseline in the Neuropsychiatric Inventory (NPI-10) Total Score at Day 29

End point title	Core Phase: Change From Baseline in the Neuropsychiatric Inventory (NPI-10) Total Score at Day 29

End point description:

The NPI-10 assessed wide range of behaviors seen in dementia for frequency and severity. It's 10 item questionnaire with domains: delusions,hallucinations,agitation/aggression, depression/dysphoria, anxiety,elation/euphoria,apathy/indifference, disinhibition, irritability/liability and aberrant motor behavior. Total score summarized and analyzed. This scale was administered with caregiver as proxy for subject. The total score was sum of 10 domains, score of each domain calculated as frequency(scale:1=occasionally to 4=very frequently)*Severity(scale:1=Mild to 3=Severe). Each domain has maximum score of 12 and all domains equally weighted for total score,thus range for total score 0 to 120(0=completely healthy and 120=worse score). The FAS included group of randomized subjects received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are subjects who were evaluable for this measure at given time point and were

End point type	Other pre-specified

End point timeframe:

Baseline, Day 29

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 12, 13, 11)	3.8 (± 4.13)	13.1 (± 17.77)	7.7 (± 12.32)	6.4 (± 10.27)
Change at Day 29 (n=12, 12, 12, 13, 10)	-2.8 (± 3.64)	-3.4 (± 9.23)	-0.3 (± 5.85)	-3.4 (± 8.95)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 12, 13, 11)	5.5 (± 5.73)			
Change at Day 29 (n=12, 12, 12, 13, 10)	3.8 (± 13.02)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Core Phase: Change From Baseline in the Sleep Disorders Inventory (SDI) Score at Day 29

End point title	Core Phase: Change From Baseline in the Sleep Disorders Inventory (SDI) Score at Day 29

End point description:

The SDI is an expanded version of one item of the NPI. It described the frequency, severity, and caregiver burden of sleep-disturbed behaviors during a period prior to its administration. The SDI consists of the 7 sub questions relating to sleep from the NPI sleep disturbance item. Each of the sub questions is a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-subject for the 2 weeks prior to the visit. The SDI score is derived as the product of the average of the frequency ratings and the average of the severity ratings (range: 0–12 [worst]). The FAS included group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement. Here 'n" are the subjects who were evaluable for this measure at given time point and were included for the assessment.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 29

End point values	Lemborexant-matched Placebo	Lemborexant 2.5 mg	Lemborexant 5 mg	Lemborexant 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 12, 13, 11)	0.79 (± 0.692)	1.24 (± 1.576)	0.74 (± 0.653)	0.66 (± 0.748)
Change at Day 29 (n=12, 12, 12, 13, 11)	-0.48 (± 1.078)	-0.10 (± 0.616)	-0.33 (± 0.503)	-0.09 (± 0.574)

End point values	Lemborexant 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 12, 13, 11)	1.44 (± 1.708)			
Change at Day 29 (n=12, 12, 12, 13, 11)	-0.49 (± 1.220)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Phase: Change From Baseline in SDI Total Score

End point title	Extension Phase: Change From Baseline in SDI Total Score

End point description:

The SDI is an expanded version of one item of the NPI. It described the frequency, severity, and caregiver burden of sleep-disturbed behaviors during a period prior to its administration. The SDI consists of the 7 sub questions relating to sleep from the NPI sleep disturbance item. Each of the sub questions is a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-subject for the 2 weeks prior to the visit. The SDI score is derived as the

product of the average of the frequency ratings and the average of the severity ratings (range:0–12[worst]). The safety analysis set included the group of extension phase subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment. Number analyzed were the subjects who were evaluable for the measure and "n" were the subjects who were evaluable for the measure for given categories. Here 99999 signifies data not available or no subjects analyzed.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 133, 223, 313, 343, 373, 403, 493, 583, 673, and 763

End point values	Extension Phase: Lemborexant 5 mg	Extension Phase: Lemborexant 10 mg	Extension Phase: Lemborexant 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	12	6	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	1.36 (± 1.948)	0.74 (± 0.728)	1.45 (± 2.331)	
Change at Day 133(Visit 9) (n=1,8,3)	1.40 (± 99999)	-0.45 (± 0.600)	-0.63 (± 0.473)	
Change at Day 223(Visit 12) (n=0,6,3)	99999 (± 99999)	-0.60 (± 0.693)	0.17 (± 0.306)	
Change at Day 313(Visit 15) (n=0,4,3)	99999 (± 99999)	-0.65 (± 0.574)	-0.17 (± 1.266)	
Change at Day 343(Visit 16) (n=1,2,2)	0.60 (± 99999)	0.55 (± 1.061)	0.45 (± 0.919)	
Change at Day 373(Visit 17) (n=0,1,0)	99999 (± 99999)	-0.20 (± 99999)	99999 (± 99999)	
Change at Day 403(Visit 18) (n=0,5,4)	99999 (± 99999)	-0.50 (± 0.539)	-0.55 (± 0.656)	
Change at Day 493(Visit 19) (n=0, 3,1)	99999 (± 99999)	-0.13 (± 0.115)	-0.10 (± 99999)	
Change at Day 583(Visit 20) (n=0,2,2)	99999 (± 99999)	-0.15 (± 0.071)	-0.35 (± 0.354)	
Change at Day 673(Visit 21) (n=0,1,2)	99999 (± 99999)	-0.30 (± 99999)	-0.15 (± 0.071)	
Change at Day 763(Visit 22) (n=0,2,0)	99999 (± 99999)	-0.05 (± 0.354)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug (Day 1) to 14 days after last dose of study drug (approximately up to 2 years 7 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Core Phase: Lemborexant-matched Placebo

Reporting group description:

Subjects received two lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Reporting group title	Core Phase: Lemborexant 2.5 mg

Reporting group description:

Subjects received one lemborexant 2.5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Reporting group title	Core Phase: Lemborexant 5 mg

Reporting group description:

Subjects received one lemborexant 5 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Reporting group title	Core Phase: Lemborexant 10 mg

Reporting group description:

Subjects received one lemborexant 10 mg and one lemborexant-matched placebo, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Reporting group title	Core Phase: Lemborexant 15 mg

Reporting group description:

Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night for 28 consecutive nights in 4-week treatment period.

Reporting group title	Extension Phase: Lemborexant 5 mg

Reporting group description:

Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued or up to 30 months.

Reporting group title	Extension Phase: Lemborexant 10 mg

Reporting group description:

Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 10 mg, tablet, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

Reporting group title	Extension Phase: Lemborexant 15 mg

Reporting group description:

Subject who completed the core study EOS visit within 30 days prior to enrollment in extension phase were eligible to participate in extension phase. Subjects received one lemborexant 5 mg and one lemborexant 10 mg, tablets, orally, once daily, immediately (within 5 minutes) before the bedtime at night until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued or up to 30 months.

Serious adverse events	Core Phase: Lemborexant-matched Placebo	Core Phase: Lemborexant 2.5 mg	Core Phase: Lemborexant 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ilium fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Core Phase: Lemborexant 10 mg	Core Phase: Lemborexant 15 mg	Extension Phase: Lemborexant 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ilium fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
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			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension Phase: Lemborexant 10 mg	Extension Phase: Lemborexant 15 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Ilium fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Core Phase: Lemborexant-matched Placebo	Core Phase: Lemborexant 2.5 mg	Core Phase: Lemborexant 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	3 / 12 (25.00%)	3 / 13 (23.08%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Genital Discharge			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Libido increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Depression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Genital Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Joint Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Limb Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper Limb Fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Palpitations			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Nephrogenic Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Diverticulum			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Acute Kidney Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Chronic Kidney Disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eye infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Otitis Media			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tooth Abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Core Phase: Lemborexant 10 mg	Core Phase: Lemborexant 15 mg	Extension Phase: Lemborexant 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 13 (30.77%)	6 / 12 (50.00%)	4 / 5 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Genital Discharge			

subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Libido increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Genital Injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint Injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Laceration			

subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Limb Injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper Limb Fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Palpitations			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Sedation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	2 / 12 (16.67%)	3 / 5 (60.00%)
occurrences (all)	1	2	4
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Nephrogenic Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Intestinal obstruction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diverticulum			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Acute Kidney Injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Chronic Kidney Disease			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	3	0

Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Osteoporosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Otitis Media			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tooth Abscess			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hypercholesterolaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Extension Phase: Lemborexant 10 mg	Extension Phase: Lemborexant 15 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	5 / 6 (83.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Genital Discharge			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Libido increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nightmare			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Irritability			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Genital Injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Joint Injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Limb Injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Upper Limb Fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Sedation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Nephrogenic Anaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diverticulum			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Acute Kidney Injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Chronic Kidney Disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Osteoporosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	4 / 14 (28.57%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Urinary tract infection			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Otitis Media			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Tooth Abscess			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2017	Amendment 01: The protocol was amended to add allowance for caregiver informants and actigraphy data informants for flexibility in caregiving situations without compromising data collection, add allowance for subjects to attend day care for flexibility regarding daytime activities, add allowance for split baseline visits if necessary for flexibility regarding scheduling, revise minimum age from 65 years to 60 years, revise minimal MMSE score from 18 to 15, revise the requirement to remain in bed for at least 7 hours per night, add allowance for subjects with suicidal behavior in the past, but not within 10 years, add allowance for subjects with bundle branch block, add allowance for participate of subjects who are enrolled in observational studies without treatment components and replace the ADCS-CGIC with the CGIC-ISWRD Scale to focus the clinical rating of improvement on the symptoms related to ISWRD.
01 March 2017	Amendment 02: The protocol was amended to revised minimum criterion for aSE from less than (<) 75% to <85% to be consistent with insomnia program, add potential seizures as AE to be adjudicated as requested by Food and Drug administration (FDA), to include information onpotential seizures for adjudication as potential symptoms of cataplexy and requirement for monitoring of falls per request of FDA and to explicitly evaluate this safety parameter in at-risk population.
05 April 2017	Amendment 03: The protocol was amended to revise inclusion No. 4 MMSE lower end of range from 15 to 10 to allow for subjects with lower MMSE scores within the moderate range, revise the screening and baseline window for flexibility in scheduling, and revise prohibited medications to allow for subjects taking stable doses of medications used to treat ISWRD-related symptoms but who continue to manifest ISWRD symptoms.
10 August 2017	Amendment 04: The protocol was amended to include the conduct of the study in the European Union (EU) to facilitate enrollment and total number of sites from approximately 40 to approximately 60 to facilitate enrollment.
17 November 2017	Amendment 05: The protocol was amended to assess long-term safety and tolerability of lemborexant, added an extension phase of up to 30 months specifying that eligible subjects who elect to receive open- label treatment of lemborexant at 5, 10, or 15 mg per day after completing the end of the study (EOS) Visit and revise inclusion criterion No. 8; updated actigraphy requirement to facilitate enrollment.
20 June 2018	Amendment 06: The protocol was amended to reduce sample size from approximately 125 subjects to approximately 60 subjects and moderate cytochrome P450 (CYP3A) inhibitors were also prohibited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported