Clinical trial results:
A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy and an Open-labeled Long-term Safety Extension Treatment with Seltorexant.

Summary

EudraCT number	2020-000337-40
Trial protocol	CZ BG
Global end of trial date	30 April 2024

Results information

Result version number	v1 (current)
This version publication date	16 May 2025
First version publication date	16 May 2025

Trial information

Trial identification

Sponsor protocol code	CR108804

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04533529
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202 South, Raritan, New Jersey, United States, 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	30 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the efficacy of seltorexant 20 milligrams compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in subjects with major depressive disorder with insomnia symptoms (MDDIS) who had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy:

Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI)

Evidence for comparator: -

Actual start date of recruitment	18 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 77
Country: Number of subjects enrolled	Czechia: 78
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 70
Country: Number of subjects enrolled	Brazil: 89
Country: Number of subjects enrolled	Colombia: 41
Country: Number of subjects enrolled	Mexico: 30
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	United States: 117
Worldwide total number of subjects	586
EEA total number of subjects	251

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)	535
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 588 subjects were enrolled and randomised, 586 were treated with either seltorexant or matching placebo (2 randomised subjects didn't meet enrollment criteria and were withdrawn before treatment).

Pre-assignment

Screening details:

Out of 586 treated subjects, 540 completed the double-blind (DB) phase, 522 entered the open-label (OL) phase, and 360 completed OL phase.

Period 1

Period 1 title	DB Treatment phase (Day 1 to Day 43)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Double -blind Phase (DB): Placebo

Arm description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

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

Dosage and administration details:

Subjects received placebo matching to seltorexant tablet orally once daily from Day 1 to Day 42.

Arm title	DB: Seltorexant 20 mg

Arm description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

Arm type	Experimental
Investigational medicinal product name	Seltorexant
Investigational medicinal product code	JNJ-42847922
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received seltorexant 20 mg tablet orally once daily from Day 1 to Day 42.

Number of subjects in period 1	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg
Started	303	283
Completed	277	263
Not completed	26	20
Consent withdrawn by subject	11	6
Physician decision	-	2
Adverse event, non-fatal	5	5
Initiated prohibited medication	1	-
Non-Compliance with primary antidepressant	2	-
Pregnancy	-	1
Non-Compliance with study drug	3	3
Lost to follow-up	2	1
Protocol deviation	1	2
Lack of efficacy	1	-

Period 2

Period 2 title	OL Treatment Phase (Day 43 to 1 year)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OL Treatment Phase: Seltorexant 20 mg

Arm description:

Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase and received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.

Arm type	Experimental
Investigational medicinal product name	Seltorexant
Investigational medicinal product code	JNJ-42847922
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year.

Number of subjects in period 2[1]	OL Treatment Phase: Seltorexant 20 mg
Started	522
Completed	360
Not completed	162
Adverse event, serious fatal	1
Consent withdrawn by subject	64
Physician decision	1
Adverse event, non-fatal	33
Initiated prohibited medication	6
Non-Compliance with primary antidepressant	3
Site terminated by sponsor	3
Non-Compliance with study drug	11
Unspecified	2
Lost to follow-up	13
Lack of efficacy	22
Protocol deviation	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only reported subjects were eligible to include in the current period.

Period 3

Period 3 title	DB FU (Day 44 to Day 57)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DB Follow-up (FU) Phase: Placebo

Arm description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	DB FU Phase: Seltorexant 20 mg

Arm description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3[2]	DB Follow-up (FU) Phase: Placebo	DB FU Phase: Seltorexant 20 mg
Started	22	22
Completed	18	15
Not completed	4	7
Consent withdrawn by subject	2	4
Adverse event, non-fatal	-	2
Unspecified	1	1
Lost to follow-up	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: Only reported subjects were eligible to include in the current period.

Period 4

Period 4 title	OL FU (1 year to 1 year, 2 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OL FU Phase: Seltorexant 20 mg

Arm description:

After completion of OL treatment phase, subjects were followed up for safety up to 7 to14 days from 1 year up to 1 year 2 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	OL FU Phase: Seltorexant 20 mg
Started	453
Completed	425
Not completed	28
Consent withdrawn by subject	16
Adverse event, non-fatal	4
Site terminated by sponsor	1
Unspecified	2
Lost to follow-up	5

Baseline characteristics

Reporting groups	
Reporting group title	Double -blind Phase (DB): Placebo
Reporting group description:	
During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.	
Reporting group title	DB: Seltorexant 20 mg
Reporting group description:	
During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.	

Reporting group values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg	Total
Number of subjects	303	283	586
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	45.9	44.3	
standard deviation	± 14.28	± 13.99	-
Gender categorical			
Units: Subjects			
Male	71	66	137
Female	232	217	449

End points

End points reporting groups

Reporting group title	Double -blind Phase (DB): Placebo

Reporting group description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

Reporting group title	DB: Seltorexant 20 mg

Reporting group description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

Reporting group title	OL Treatment Phase: Seltorexant 20 mg

Reporting group description:

Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase and received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.

Reporting group title	DB Follow-up (FU) Phase: Placebo

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Reporting group title	DB FU Phase: Seltorexant 20 mg

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Reporting group title	OL FU Phase: Seltorexant 20 mg

Reporting group description:

After completion of OL treatment phase, subjects were followed up for safety up to 7 to14 days from 1 year up to 1 year 2 weeks.

Primary: Double-blind (DB) Phase: Change From Baseline to Day 43 in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score : Estimand 2

End point title	Double-blind (DB) Phase: Change From Baseline to Day 43 in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score : Estimand 2

End point description:

MADRS, clinician-rated scale designed to measure depression severity and detected changes due to antidepressant intervention. Scale consisted of 10 items, each of which was scored from 0 (not present or normal) to 6 (severe or continuous presence of symptoms). MADRS evaluated reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. MADRS total score was sum of scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative changes in MADRS total score indicated improvement. Full analysis set 2 (FAS2) included all randomised subjects with major depressive disorder with insomnia symptoms (MDDIS) per interactive web response system (IWRS) who received at least 1 dose of study intervention in DB phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

DB: Baseline (Day 1), Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	201		
Units: Units on a scale				
arithmetic mean (standard deviation)	-10.2 (± 10.20)	-12.9 (± 9.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis set -1
Comparison groups	DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	mixed model repeated measures (MMRM)
Parameter estimate	Least square (LS) difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	-0.68
Variability estimate	Standard error of the mean
Dispersion value	0.94

Primary: Open Label (OL) Treatment Phase: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point title	Open Label (OL) Treatment Phase: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study drug. Treatment emergent AEs was defined as any AE occurred at or after the initial administration of study intervention through the day of last dose plus 2 days. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase.

End point type	Primary

End point timeframe:

From start of the treatment in OL phase (Day 1 [Day 43 from study baseline]) up to 2 days after last dose (up to 52 weeks of the OL phase)

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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	522			
Units: Subjects	330			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Blood Pressure

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Blood Pressure[2]

End point description:

Change from baseline in vital signs of systolic/diastolic blood pressure (SBP/DBP) were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	359			
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
DBP: Week 52	0.5 (± 8.30)			
SBP: Week 52	0.0 (± 10.85)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI)

End point title	OL Treatment Phase: Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI)[3]

End point description:

The AEs considered to be of special interest: cataplexy, sleep paralysis, complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism, sleep terrors, bruxism, sleep sex, sleep-related eating disorder, and catathrenia, fall, motor vehicle accident. Treatment emergent AEs was defined as any AE occurred at or after the initial administration of study intervention through the day of last dose plus 2 days. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase.

End point type	Primary

End point timeframe:

From start of the treatment in OL phase (Day 1 [Day 43 from study baseline]) up to 2 days after last dose (up to 52 weeks of the OL phase)

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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	522			
Units: Subjects	18			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Pulse Rate

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Pulse Rate[4]

End point description:

Change from baseline in vital signs of pulse rate were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[4] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	359			
Units: Beats per minute				
arithmetic mean (standard deviation)	0.3 (± 8.81)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Body Mass Index (BMI)

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Body Mass Index (BMI)[5]

End point description:

Change from baseline in vital signs of BMI were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[5] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	365			
Units: Kilograms per square meter (kg/m^2)				
arithmetic mean (standard deviation)	0.55 (± 1.634)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Waist Circumference

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Waist Circumference[6]

End point description:

Change from baseline in vital signs of waist circumference were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[6] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	362			
Units: Centimeters				
arithmetic mean (standard deviation)	0.6 (± 5.94)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Temperature

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Temperature[7]

End point description:

Change from baseline in vital signs of temperature were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[7] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	359			
Units: Centigrade				
arithmetic mean (standard deviation)	-0.01 (± 0.306)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Weight

End point title	OL Treatment Phase: Change From Baseline in Vital Signs: Weight[8]

End point description:

Change from baseline in vital signs of weight were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	365			
Units: Kilograms				
arithmetic mean (standard deviation)	1.54 (± 4.442)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Number of Subjects with New Suicidal Ideation and Behavior Using the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	OL Treatment Phase: Number of Subjects with New Suicidal Ideation and Behavior Using the Columbia Suicide Severity Rating Scale (C-SSRS)[9]

End point description:

C-SSRS is a clinician-rated instrument that reports severity and frequency of suicide-related ideation and behaviors. Suicidal ideation was classified on a 5-item scale: 1 (wish to be dead), 2 (non-specific active suicidal thoughts), 3 (suicidal ideation without plan and intent), 4 (suicidal ideation intent to act without plan), and 5 (suicidal ideation with plan and intent), Suicidal behavior is classified on a 5-item scale: 6 (preparatory acts or behavior), 7 (aborted attempt), 8 (interrupted attempt), 9 (actual attempt), and 10 (suicide). Minimum total score 0, maximum total score 10; higher total scores indicate more suicidal ideation and/or suicidal behavior. If no events qualify for scores of 1 to 10, score of 0 was assigned (0= "no event that can be assessed on the basis of C-SSRS"). The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Higher scores indicated greater severity.

End point type	Primary

End point timeframe:

From DB Baseline up to week 52 of OL phase

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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	522			
Units: Subjects				
Suicidal ideation	87			
Suicidal behavior	7			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Physician Withdrawal Checklist (PWC-20) Total Scores

End point title	OL Treatment Phase: Physician Withdrawal Checklist (PWC-20) Total Scores[10]

End point description:

Potential withdrawal effects were assessed by the clinician using the PWC-20. The PWC-20 was a reliable and sensitive instrument for the assessment of discontinuation symptoms. The assessment has 20 items evaluated to detect withdrawal symptoms. Symptoms are rated on a scale of 0-3. Symptoms rated on a scale of 0 =not present, 1=mild, 2 =moderate, and 3 =severe. The total PWC-20 score was the sum of 20 item scores and ranged between 0 and 60. The higher score indicates more frequent/severe symptoms. Follow-up analysis set included all randomised subjects who entered the follow-up phase after OL. Here, "N" (overall number of subjects analysed): subjects who were evaluable and "n" (number analysed): number of subjects evaluable for each arm at specified time points.

End point type	Primary

End point timeframe:

End of OL (Week 52 of OL phase), follow-up 1 (1 day after end of OL phase), and follow-up 2 (2 weeks after end of OL phase)

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 reported for this endpoint.

End point values	OL FU Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	443			
Units: Units on a scale				
arithmetic mean (standard deviation)				
End of OL (Week 59) (n=443)	7.6 (± 8.37)			
followup 1 (n=435)	5.8 (± 7.34)			
followup 2 (n=401)	6.7 (± 7.42)			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Number of Subjects with Clinical Laboratory Abnormalities

End point title	OL Treatment Phase: Number of Subjects with Clinical Laboratory Abnormalities[11]

End point description:

Laboratory parameters: hematology (platelet count, red blood cell [RBC] count, hemoglobin, hematocrit, neutrophils (Segmented/Leukocytes), lymphocytes, monocytes, eosinophils/leukocytes [Eos/Leu], basophils, Reticulocytes/ Erythrocytes [Reti/Ery]); chemistry (sodium, potassium, chloride, bicarbonate, creatinine, glucose, aspartate transaminase [AST], alanine transaminase [ALT], gamma-glutamyl transferase [GGT], alkaline phosphatase, total, bilirubin, phosphate, albumin, total protein, total cholesterol); urine (specific gravity, pH, glucose, blood, bilirubin, urobilinogen, RBC). Clinically significant abnormalities (low/high) were determined at the investigator's discretion. Only those categories in which at least one subject had data were reported in this endpoint. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, n (number analysed) signifies number of subjects evaluable for specified categories.

End point type	Primary

End point timeframe:

From OL Baseline (Day 1 [Day 43 from study baseline]) to Week 52 of OL phase

Notes:

[11] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	522			
Units: Subjects				
ALT High (n=516)	3			
AST High (n=519)	1			
Bicarbonate Low (n=507)	1			
Chloride Low (n=520)	1			
Cholesterol High (n=520)	18			
Creatine Kinase High (n=519)	10			
GGT High (n=516)	1			
Glucose High (n=518)	1			
HDL Cholesterol low (n=520)	43			
Hemoglobin A1C/ Hemoglobin High (n=518)	5			
LDL Cholesterol Low (n=520)	85			
LDL Cholesterol High (n=520)	90			
Phosphate low (n=520)	8			
Potassium Low (n=517)	2			
Potassium High (n=517)	3			
Triglycerides High (n=520)	1			
Eos/Leu High (n=518)	5			
Erythrocytes High(n=516)	5			
Hematocrit High (n=514)	8			
Leukocytes Low (n=516)	1			
Leukocytes High (n=516)	4			
Lymphocytes/Leukocytes High (n=518)	2			
Lymphocytes/Leukocytes Low (n=518)	6			
Neutrophils low (n=518)	5			
Neutrophils High (n=518)	1			

Platelets Low (n=516)	1			
Platelets High (n=516)	2			
Reti/Ery Low (n=518)	6			
Reti/Ery High (n=518)	136			
Specific Gravity High (n=522)	47			
Urine pH High (n=522)	56			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Number of Subjects with Electrocardiogram (ECG) Abnormalities

End point title	OL Treatment Phase: Number of Subjects with Electrocardiogram (ECG) Abnormalities[12]

End point description:

The ECG parameters that were analysed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazetts formula (QTcB), Fridericias formula (QTcF). The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Only those categories in which at least one subject had data were reported in this endpoint. Here, n (number analysed) signifies number of subjects evaluable for specified time points. Here B: denotes baseline.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[12] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	522			
Units: Subjects				
B: ECG Mean Heart Rate <=50 (n=522)	11			
B: ECG Mean Heart Rate >=100 (n=522)	4			
B: PR Interval <=120 (n=522)	10			
B: PR Interval >=200 (n=522)	6			
B: RR Interval <=600 (n=522)	4			
B: RR Interval >=1200 (n=522)	10			
B: QRS Duration >=120 (n=522)	3			
B: QT Interval >= 500 (n=522)	1			
W52: ECG Mean Heart Rate <=50 (n=358)	3			
W52:ECG Mean Heart Rate >=100 (n=358)	4			
W52:PR Interval <=120 (n=358)	6			
W52: PR Interval >=200 (n=358)	5			
W52: RR Interval <=600 (n=358)	4			

W52: RR Interval >=1200 (n=358)	3			
W52: QRS Duration >=120 (n=358)	4			

Statistical analyses

No statistical analyses for this end point

Primary: OL Treatment Phase: Number of Subjects With Sexual Dysfunction as Determined by Arizona Sexual Experiences Scale (ASEX) Score

End point title	OL Treatment Phase: Number of Subjects With Sexual Dysfunction as Determined by Arizona Sexual Experiences Scale (ASEX) Score[13]

End point description:

ASEX is a five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each of the 5 items is rated on a 6-point Likert scale, ranging from 1 to 6. The 5 items are summed to create a total score, ranging from 5 to 30, with the higher scores indicating more sexual dysfunction. Sexual dysfunction is defined as an ASEX total score of 19 or greater, or a score of 5 or greater on any item, or a score of 4 or greater on any 3 items. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. . Here, "N" (overall number of subjects analysed): subjects who were evaluable and "n" (number analysed): number of subjects evaluable for each arm at specified time points.

End point type	Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[13] - 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 reported for this endpoint.

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	512			
Units: Subjects				
Baseline (OL) (n=512)	391			
Week 52 (n=365)	235			

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Change from Baseline to Day 43 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score- Estimand 2

End point title	DB Phase: Change from Baseline to Day 43 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score- Estimand 2

End point description:

The MADRS was a clinician-rated scale designed to measure depression severity and detected changes due to antidepressant treatment. MADRS-WOSI was defined as the full MADRS without the sleep item.

The MADRS-WOSI scale consisted of 9 items, each of which was scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS-WOSI total score was the sum of scores from individual question items, which ranged from 0 to 54, higher scores represented a more severe condition. The MADRS-WOSI evaluated apparent sadness, reported sadness, inner tension, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Negative change in MADRS total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

DB: Baseline (Day 1), Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	201		
Units: Units on a scale				
arithmetic mean (standard deviation)	-9.2 (± 9.31)	-11.3 (± 8.68)		

Statistical analyses

Statistical analysis title	Statistical Analysis set -2

Statistical analysis description:

In accordance with protocol predefined testing sequence, statistical significance of the primary endpoint and first key secondary endpoint was required before testing the secondary endpoint (MADRS-WOSI) and thus, a formal statistical testing was performed.

Comparison groups	DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.85

Secondary: DB Phase: Change from Baseline to Day 43 in Sleep Disturbance Using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score: Estimand 2

End point title	DB Phase: Change from Baseline to Day 43 in Sleep Disturbance Using the Patient Reported Outcome Measurement

	Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score: Estimand 2

End point description:

PROMIS-SD Short Form 8a: static 8-item questionnaire, assessed self-perceptions of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items), worrying about sleep (1 item). Each question, 5 options ranged 1 to 5. Direction of responses was not same, sometimes "not at all" =more sleep disturbance; "not at all" =less sleep disturbance. Total raw score for short form with all questions answered was sum of values of response to each question, total score ranged 8 - 40. Lower scores=less sleep disturbance. Total raw score converted into T-score. T-score rescaled the raw score into standardized score with mean-50; SD-10. Negative changes in scores=improvement. Higher values represent more severe sleep disturbance. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. N (number of subjects analysed) signifies subjects evaluable.

End point type	Secondary

End point timeframe:

DB: Baseline (Day 1), Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	201		
Units: T-score				
arithmetic mean (standard deviation)	-7.1 (± 10.44)	-10.9 (± 9.10)		

Statistical analyses

Statistical analysis title	Statistical analysis set -3

Statistical analysis description:

In accordance with protocol predefined testing sequence, statistical significance of the primary endpoint was required before testing the secondary endpoint (PROMIS-SD; Short Form 8a) and thus, a formal statistical testing was performed.

Comparison groups	DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.25
upper limit	-1.85
Variability estimate	Standard error of the mean
Dispersion value	0.87

Secondary: DB Phase: Change from Baseline to Day 43 in the MADRS-6 Total Score

End point title	DB Phase: Change from Baseline to Day 43 in the MADRS-6 Total Score

End point description:

The 6-item MADRS was a clinician-administered scale designed to measure the core symptoms of depression severity and detected changes due to antidepressant intervention. It is a subset of MADRS (10-item). The MADRS-6 subscale score was the sum of scores for the following MADRS items: apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. Each item is scored from 0 (item not present or normal) to 6 (most severe or continuous presence of symptoms); the overall score ranges from 0 to 36, higher scores represented a more severe condition. Negative change in score indicates improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

DB: Baseline (Day 1), Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	201		
Units: Units on a scale				
arithmetic mean (standard deviation)	-6.9 (± 7.02)	-8.4 (± 6.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Percentage of Subjects with Response on Depressive Symptoms Scale Based on MADRS at Day 43

End point title	DB Phase: Percentage of Subjects with Response on Depressive Symptoms Scale Based on MADRS at Day 43

End point description:

Responders, defined as subjects with a >=50 percent (%) improvement in the MADRS total score from baseline to a given timepoint. The MADRS was a clinician-rated scale designed to measure depression severity and detected changes due to antidepressant treatment. Scale consisted of 10 items, each of which was scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score was sum of scores from individual question items, which ranged from 0 to 60, higher scores represented a more severe condition. The MADRS evaluated apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts. Negative change in MADRS total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase.

End point type	Secondary

End point timeframe:

At Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	213		
Units: Percentage of subjects				
number (not applicable)	22.9	36.2		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Change From Baseline to Day 43 in Patient Health Questionnaire 9-item (PHQ-9) Total Score

End point title	DB Phase: Change From Baseline to Day 43 in Patient Health Questionnaire 9-item (PHQ-9) Total Score

End point description:

The PHQ-9 was a 9-item, subject reported endpoint to assess depressive symptoms. The scale scores each of the 9 symptom domains of the diagnostic and statistical manual of mental disorders-5th edition (DSM-5) major depressive disorder (MDD) criteria. Each item was rated on a 4 points scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses were summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately Severe (15-19) and severe (20-27). Negative changes in PHQ-9 total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

DB: Baseline (Day 1), Day 43

End point values	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	201		
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.5 (± 6.63)	-7.6 (± 5.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: OL Treatment Phase: Change From Baseline Over Time in MADRS Total Score

End point title	OL Treatment Phase: Change From Baseline Over Time in MADRS Total Score

End point description:

MADRS was a clinician-administered scale designed to measure depression severity and detected changes due to antidepressant treatment. The MADRS evaluates the following 10 items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), total score was sum of scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative change in MADRS total score indicated improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and n (number analysed) signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	381			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=381)	-5.0 (± 8.27)			
Week 8 (n=366)	-6.2 (± 9.53)			
Week 12 (n=345)	-6.8 (± 9.88)			
Week 16 (n=339)	-7.7 (± 10.41)			
Week 20 (n=327)	-8.6 (± 10.53)			
Week 24 (n=311)	-8.0 (± 10.93)			
Week 28 (n=296)	-8.8 (± 11.03)			
Week 32 (n=291)	-9.5 (± 11.20)			
Week 36 (n=289)	-9.3 (± 11.32)			
Week 40 (n=280)	-10.2 (± 11.45)			
Week 44 (n=274)	-11.0 (± 10.93)			
Week 48 (n=274)	-11.2 (± 10.62)			
Week 52 (n=273)	-11.4 (± 10.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: OL Treatment Phase: Change From Baseline Over Time in the Clinical Global Impression-Severity (CGI S) Score

End point title	OL Treatment Phase: Change From Baseline Over Time in the Clinical Global Impression-Severity (CGI S) Score

End point description:

The CGI-S (depression) provided an overall clinician-determined summary measure of severity of the subject's illness that considers all available information, included knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on subject's ability to function. CGI-S evaluated severity of psychopathology on a scale of 1 to 7. The CGI-S was 7-point global assessment scale that measures clinician's impression of severity of illness, rating: 1=normal (not at all ill), 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill subjects, with higher scores indicate worsening. Negative changes in CGI-S score indicate improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable, n signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	381			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=381)	-0.6 (± 0.99)			
Week 8 (n=366)	-0.8 (± 1.12)			
Week 12 (n=345)	-0.8 (± 1.21)			
Week 16 (n=339)	-1.0 (± 1.34)			
Week 20 (n=327)	-1.0 (± 1.35)			
Week 24 (n=311)	-1.1 (± 1.39)			
Week 28 (n=296)	-1.1 (± 1.40)			
Week 32 (n=291)	-1.3 (± 1.35)			
Week 36 (n=289)	-1.2 (± 1.47)			
Week 40 (n=280)	-1.3 (± 1.45)			
Week 44 (n=274)	-1.5 (± 1.42)			
Week 48 (n=274)	-1.5 (± 1.39)			
Week 52 (n=273)	-1.6 (± 1.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: OL Treatment Phase: Change from Baseline Over Time in the MADRS-WOSI Total Score

End point title	OL Treatment Phase: Change from Baseline Over Time in the MADRS-WOSI Total Score

End point description:

MADRS was a clinician-administered scale designed to measure depression severity and detected changes due to antidepressant treatment. The MADRS evaluates the following 10 items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), total score was sum of

scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative change in MADRS total score indicated improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and n (number analysed) signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	381			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=381)	-4.2 (± 7.47)			
Week 8 (n=366)	-5.3 (± 8.56)			
Week 12 (n=345)	-5.9 (± 8.91)			
Week 16 (n= 339)	-6.7 (± 9.41)			
Week 20 (n=327)	-7.5 (± 9.50)			
Week 24 (n= 311)	-7.0 (± 9.95)			
Week 28 (n=296)	-7.7 (± 10.03)			
Week 32 (n= 291)	-8.3 (± 10.25)			
Week 36 (n=289)	-8.1 (± 10.19)			
Week 40 (n=280)	-8.8 (± 10.44)			
Week 44 (n= 274)	-9.6 (± 9.87)			
Week 48 (n= 274)	-9.9 (± 9.62)			
Week 52 (n= 273)	-9.8 (± 9.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: OL Treatment Phase: Change From Baseline Over Time in Sleep Disturbance Using the PROMIS SD Short Form 8a T-score

End point title	OL Treatment Phase: Change From Baseline Over Time in Sleep Disturbance Using the PROMIS SD Short Form 8a T-score

End point description:

PROMIS-SD Short Form 8a: static 8-item questionnaire, assessed self-perceptions of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items), worrying about sleep (1item). Each question, 5 options ranged 1- 5. Direction of responses was not same, sometimes "not at all" =more sleep disturbance; "not at all" =less sleep disturbance. Total raw score for short form with all questions answered was sum of values of response to each question, total score ranged 8 - 40. Lower scores=less sleep disturbance. Total raw score converted into T-score. T-score rescaled raw score into standardized score with mean-50; SD-10. Negative changes in scores=improvement. Higher values represent more severe sleep disturbance. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in OL phase. Here, N (number of subjects analysed) signifies subjects evaluable, n (number analysed) signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	OL Treatment Phase: Seltorexant 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	380			
Units: T-score				
arithmetic mean (standard deviation)				
Week 4 (n=380)	-4.9 (± 8.57)			
Week 8 (n=366)	-5.3 (± 9.21)			
Week 12 (n=344)	-6.3 (± 9.48)			
Week 16 (n=339)	-6.4 (± 10.24)			
Week 20 (n=326)	-6.8 (± 10.29)			
Week 24 (n=311)	-6.7 (± 9.99)			
Week 28 (n=296)	-7.1 (± 10.09)			
Week 32 (n=291)	-7.2 (± 10.32)			
Week 36 (n= 289)	-7.6 (± 10.66)			
Week 40 (n=280)	-8.2 (± 10.46)			
Week 44 (n=274)	-9.1 (± 10.56)			
Week 48 (n=274)	-8.6 (± 10.42)			
Week 52 (n=273)	-9.6 (± 10.44)			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

SAEs/other AEs: DB: Day (D) 1 to 2 days after last dose (D44); DB FU: D44 to D57; OL: D1 [D43 study BL] to 2 days after last dose (Week [W] 52); OL FU: W 52 to 2 Weeks after end of OL phase (W61); Death: DB: D1 to D43, OL: D43 to 1 year 2 weeks

Adverse event reporting additional description:

DB phase: The safety analysis included all randomised subjects who received at least 1 dose of study intervention in the DB phase. OL Phase: The safety analysis included all randomised subjects who received at least 1 dose of study intervention in the OL phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Double -blind Phase (DB): Placebo

Reporting group description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

Reporting group title	DB: Seltorexant 20 mg

Reporting group description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoingantidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tabletorally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

Reporting group title	OL Treatment Phase: Seltorexant 20 mg

Reporting group description:

Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase andreceived seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.

Reporting group title	DB Follow-up (FU) Phase: Placebo

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Reporting group title	DB FU Phase: Seltorexant 20 mg

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

Reporting group title	OL FU Phase: Seltorexant 20 mg

Reporting group description:

After completion of OL treatment phase, subjects were followed up for safety up to 7 to14 days from 1 year up to 1 year 2 weeks.

Serious adverse events	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg	OL Treatment Phase: Seltorexant 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 303 (0.33%)	1 / 283 (0.35%)	29 / 522 (5.56%)

number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurogenic Tumour			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid Tumour Benign			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypertension			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
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			
Chest Pain			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	2 / 522 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Suicidal Ideation			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	2 / 522 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	7 / 522 (1.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Increased			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 303 (0.33%)	0 / 283 (0.00%)	0 / 522 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Laceration			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 283 (0.00%)	0 / 522 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Infarction			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 283 (0.35%)	0 / 522 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic Nerve Sheath Haemorrhage			

subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Stenosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 283 (0.00%)	0 / 522 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Septic Shock			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urosepsis			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular Neuronitis			
subjects affected / exposed	0 / 303 (0.00%)	0 / 283 (0.00%)	1 / 522 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB Follow-up (FU) Phase: Placebo	DB FU Phase: Seltorexant 20 mg	OL FU Phase: Seltorexant 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurogenic Tumour			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Parathyroid Tumour Benign			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Hypertension			

subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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			
Chest Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Suicidal Ideation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Suicide Attempt			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Weight Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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

Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Fall			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Skin Laceration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Spinal Compression Fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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			
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Cerebral Infarction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Ischaemic Stroke			

subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Syncope			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Transient Ischaemic Attack			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Eye disorders			
Optic Nerve Sheath Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Gastrointestinal disorders			
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Spinal Stenosis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Pneumonia Aspiration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Sepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Septic Shock			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Urosepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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
Vestibular Neuronitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (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

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

Non-serious adverse events	Double -blind Phase (DB): Placebo	DB: Seltorexant 20 mg	OL Treatment Phase: Seltorexant 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 303 (11.55%)	41 / 283 (14.49%)	162 / 522 (31.03%)
Investigations			
Weight Increased			
subjects affected / exposed	4 / 303 (1.32%)	5 / 283 (1.77%)	34 / 522 (6.51%)
occurrences (all)	4	5	34
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 303 (8.91%)	25 / 283 (8.83%)	62 / 522 (11.88%)
occurrences (all)	33	38	117
Infections and infestations			
Covid-19			
subjects affected / exposed	5 / 303 (1.65%)	9 / 283 (3.18%)	46 / 522 (8.81%)
occurrences (all)	5	10	47
Nasopharyngitis			
subjects affected / exposed	4 / 303 (1.32%)	4 / 283 (1.41%)	44 / 522 (8.43%)
occurrences (all)	4	4	56

Non-serious adverse events	DB Follow-up (FU) Phase: Placebo	DB FU Phase: Seltorexant 20 mg	OL FU Phase: Seltorexant 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	10 / 453 (2.21%)
Investigations			
Weight Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 453 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	6 / 453 (1.32%)
occurrences (all)	0	0	6
Infections and infestations			
Covid-19			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	3 / 453 (0.66%)
occurrences (all)	1	0	3
Nasopharyngitis			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 22 (0.00%) 0	1 / 453 (0.22%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2020	The purpose of this amendment was to address health authority feedback in regards to the assumption of treatment difference and increase in sample size determination, the addition of the Montgomery-Asberg Depression Rating Scale without Sleep Item (MADRS-WOSI) as a key secondary endpoint, European Union (EU)-specific statistical analyses, use of approved selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) as a background antidepressant in the participating country, language of restrictions on driving and alcohol use, disallowed concomitant medications, addition of brief neurological examinations, and adjustment of concomitant therapy following study drug stoppage, and study discontinuation for subjects.
25 June 2021	The purpose of this amendment was to clarify and modify eligibility criteria based on early enrolment experiences and made the following changes at screening: lower the initial screening assessment of the Hamilton Depression Rating Scale (HDRS), 17 items total score from 22 to 20 and greater than or equal to (>=)18 at end of screening; increase the maximum duration of stable antidepressant therapy from 12 months to 18 months; increase the length of the current depressive episode to less than or equal to (<=)24 months (<=18 months); revise the upper limit of body mass index (BMI) eligibility range to kilogram per square meter (kg/m2) 40 kg/m2 (from 37 kg/m2); extend the screening period for up to 2 weeks if approved by the medical monitor and clarify use of concomitant medications in the OL phase. This amendment also included changes to laboratory tests to remove evaluation of prothrombin time (PT) and clarify follicle stimulating hormone (FSH) testing; added text to specify that locally approved (including under emergency use authorization Coronavirus disease 2019 (COVID-19) vaccination may be used during the trial with the recommendation that vaccination occurs at least 5 days prior to the start of dosing, or once randomized, at least 5 days prior to the next scheduled visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported