Clinical trial results:
A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator 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

Summary

EudraCT number	2020-000341-14
Trial protocol	CZ GB LT LV BE BG PL SK
Global end of trial date	03 October 2023

Results information

Result version number	v1 (current)
This version publication date	19 October 2024
First version publication date	19 October 2024

Trial information

Trial identification

Sponsor protocol code	42847922MDD3005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04513912
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	03 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the efficacy of seltorexant compared with quetiapine extended-release (XR) as adjunctive therapy to an antidepressant drug in treatment response in subjects with major depressive disorder with insomnia symptoms (MDDIS), who have had an inadequate response to current antidepressant therapy with a serotonin-norepinephrine reuptake inhibitor or selective serotonin reuptake inhibitor (SSRI/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: -

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	Argentina: 88
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 95
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Malaysia: 22
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Serbia: 111
Country: Number of subjects enrolled	Slovakia: 57
Country: Number of subjects enrolled	Ukraine: 23
Country: Number of subjects enrolled	United States: 223
Worldwide total number of subjects	756
EEA total number of subjects	253

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)	686
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 757 subjects were randomised in this study, out of which 756 were treated with either seltorexant 20 milligrams (mg) tablet once daily (OD) or quetiapine XR 50 mg or 150 mg or 300 mg tablet. One subject randomised to seltorexant 20 mg treatment group did not receive treatment as enrollment criteria was not met.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Quetiapine extended release (XR)

Arm description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For the first 2 days (Day 1 to 2), adult subjects received one over-encapsulated tablet of quetiapine XR 50 milligrams (mg) daily at bedtime, followed by 1 over-encapsulated tablet of 150 mg tablet daily (lower dose) from Day 3 to 7. Elderly subjects on quetiapine XR started treatment with one over-encapsulated 50 mg tablet daily at bedtime from Day 1 to 3 and took a second over-encapsulated 50 mg tablet from Day 4-7 according to the local prescribing label and investigator's judgement. From the second week, subjects on the quetiapine XR lower dose received 1 over-encapsulated tablet of quetiapine XR 150 mg and 1 capsule of placebo daily at bedtime. Subjects on the quetiapine XR higher dose received two over encapsulated tablets of 150 mg quetiapine XR daily at bedtime from Day 14 onwards till Day 182.

Arm type	Active comparator
Investigational medicinal product name	Quetiapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received over encapsulated tablets of either quetiapine 50 mg, or 150 mg or 300 mg once daily dose at bedtime from Day 1 to Day 182.

Arm title	Arm 2: Seltorexant

Arm description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For first week (from Day 1 to 7), adult subjects received one over encapsulated tablet of seltorexant 20 mg daily at bedtime. During the second week adult subjects received 2 capsules (1 over encapsulated tablet of seltorexant 20 mg and placebo) at bedtime from Day 8 to 182. Elderly patients on seltorexant will start with 1 over-encapsulated tablet of 20 mg on Day 1 and a second capsule of placebo to match the blinded dose titration schedule of quetiapine XR from Day 4 till Day 182. Matching placebo dosing for elderly subjects were flexible for Days 4 to 7 alone.

Arm type	Experimental

Investigational medicinal product name	Seltorexant 20 mg
Investigational medicinal product code	JNJ-42847922
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received over encapsulated tablets of seltorexant 20 mg once daily dose at bedtime from Day 1 to Day 182.

Number of subjects in period 1	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant
Started	390	366
Completed	304	300
Not completed	86	66
Adverse event, non-fatal	16	9
Unspecified	13	16
Lost to follow-up	8	10
Withdrawal by subject	49	31

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Quetiapine extended release (XR)

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For the first 2 days (Day 1 to 2), adult subjects received one over-encapsulated tablet of quetiapine XR 50 milligrams (mg) daily at bedtime, followed by 1 over-encapsulated tablet of 150 mg tablet daily (lower dose) from Day 3 to 7. Elderly subjects on quetiapine XR started treatment with one over-encapsulated 50 mg tablet daily at bedtime from Day 1 to 3 and took a second over-encapsulated 50 mg tablet from Day 4-7 according to the local prescribing label and investigator's judgement. From the second week, subjects on the quetiapine XR lower dose received 1 over-encapsulated tablet of quetiapine XR 150 mg and 1 capsule of placebo daily at bedtime. Subjects on the quetiapine XR higher dose received two over encapsulated tablets of 150 mg quetiapine XR daily at bedtime from Day 14 onwards till Day 182.

Reporting group title	Arm 2: Seltorexant

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For first week (from Day 1 to 7), adult subjects received one over encapsulated tablet of seltorexant 20 mg daily at bedtime. During the second week adult subjects received 2 capsules (1 over encapsulated tablet of seltorexant 20 mg and placebo) at bedtime from Day 8 to 182. Elderly patients on seltorexant will start with 1 over-encapsulated tablet of 20 mg on Day 1 and a second capsule of placebo to match the blinded dose titration schedule of quetiapine XR from Day 4 till Day 182. Matching placebo dosing for elderly subjects were flexible for Days 4 to 7 alone.

Reporting group values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant	Total
Number of subjects	390	366	756
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	349	337	686
From 65 to 84 years	41	29	70
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	47.9	47.8	
standard deviation	± 13.64	± 13.15	-
Title for Gender Units: subjects			
Female	277	281	558
Male	113	85	198

End points

End points reporting groups

Reporting group title	Arm 1: Quetiapine extended release (XR)

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For the first 2 days (Day 1 to 2), adult subjects received one over-encapsulated tablet of quetiapine XR 50 milligrams (mg) daily at bedtime, followed by 1 over-encapsulated tablet of 150 mg tablet daily (lower dose) from Day 3 to 7. Elderly subjects on quetiapine XR started treatment with one over-encapsulated 50 mg tablet daily at bedtime from Day 1 to 3 and took a second over-encapsulated 50 mg tablet from Day 4-7 according to the local prescribing label and investigator's judgement. From the second week, subjects on the quetiapine XR lower dose received 1 over-encapsulated tablet of quetiapine XR 150 mg and 1 capsule of placebo daily at bedtime. Subjects on the quetiapine XR higher dose received two over encapsulated tablets of 150 mg quetiapine XR daily at bedtime from Day 14 onwards till Day 182.

Reporting group title	Arm 2: Seltorexant

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For first week (from Day 1 to 7), adult subjects received one over encapsulated tablet of seltorexant 20 mg daily at bedtime. During the second week adult subjects received 2 capsules (1 over encapsulated tablet of seltorexant 20 mg and placebo) at bedtime from Day 8 to 182. Elderly patients on seltorexant will start with 1 over-encapsulated tablet of 20 mg on Day 1 and a second capsule of placebo to match the blinded dose titration schedule of quetiapine XR from Day 4 till Day 182. Matching placebo dosing for elderly subjects were flexible for Days 4 to 7 alone.

Primary: Percentage of Subjects with Response (Greater than or Equal to [>=] 50 Percent [%] Improvement from Baseline in Montgomery-Asberg Depression Rating Scale [MADRS] Total Score) at Week 26

End point title	Percentage of Subjects with Response (Greater than or Equal to [>=] 50 Percent [%] Improvement from Baseline in Montgomery-Asberg Depression Rating Scale [MADRS] Total Score) at Week 26

End point description:

The 10-item clinician-administered MADRS scale score was designed to measure depression severity and to detect changes due to antidepressant treatment using the 10 items followed: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, & suicidal thoughts. Each item scored from 0 (no item/normal) to 6 (severe/continuous presence of symptoms), & sum of scores of individual questions at a given time point ranged from 0 to 60. Higher scores indicated more severe condition. Responders were defined as subjects with >=50% improvement in MADRS total score from baseline & those with missing values were imputed as non-responders. Full analysis set 2 without Ukraine subjects involved in conflict (FAS2CON) included all randomised subjects who received at least 1 dose of study drug but excluded Ukraine subjects who were ongoing in double-blind phase at time of Ukraine-Russian war in 2022.

End point type	Primary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	361		
Units: percentage of subjects				

number (not applicable)	53.7	57.9		

Statistical analyses

Statistical analysis title	Seltorexant vs Quetiapine XR
Comparison groups	Arm 1: Quetiapine extended release (XR) v Arm 2: Seltorexant
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	11.4

Secondary: Change from Baseline in Body Weight (in Kilograms) up to Week 26

End point title	Change from Baseline in Body Weight (in Kilograms) up to Week 26
End point description:	
Change from baseline in body weight (in kilograms) up to Week 26 were reported. The full analysis set 2 (FAS2) included all randomised subjects who received at least 1 dose of study intervention.	
End point type	Secondary
End point timeframe:	
From baseline (Day 1) up to Week 26	

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	366		
Units: Kilograms (Kg)				
arithmetic mean (standard deviation)	2.0 (± 3.81)	0.5 (± 2.96)		

Statistical analyses

Statistical analysis title	Seltorexant vs Quetiapine XR
Comparison groups	Arm 1: Quetiapine extended release (XR) v Arm 2: Seltorexant

Number of subjects included in analysis	756
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	-0.93
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: Time to Study Drug Discontinuation for Potentially Treatment Related Reasons

End point title	Time to Study Drug Discontinuation for Potentially Treatment Related Reasons

End point description:

Time to study drug discontinuation for potentially treatment related reasons were reported. Time to discontinuation of study drug: the number of days from first dose up to last dose of study drug. Potentially treatment related reasons were all study drug discontinuations excluding potentially non-treatment related discontinuations (for example, loss of insurance for antidepressant therapy, movement/travel out of area, change of work-schedule being unable to accommodate visit schedule, family circumstances). Subjects who complete double-blind treatment were not considered as discontinued. Discontinuations due to AE or lack of efficacy or product quality complaints were considered potentially treatment related. FAS2 analysis set were analysed. Here, "99999" signifies that data were not estimable due to low number of subjects with events. Here "N" (Number of subjects analysed) signifies the number of subjects that were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	44		
Units: days				
median (full range (min-max))	206 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in MADRS Total Score

End point title	Change from Baseline to Week 26 in MADRS Total Score

End point description:

Change from baseline to Week 26 in MADRS total score were reported. The MADRS scale score was a 10-item clinician-administered scale designed to measure depression severity and to detect changes due to antidepressant treatment using the 10 items followed: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item scored from 0 (no item or normal) to 6 (severe or continuous presence of symptoms), and the sum of scores of individual question items at a given time point ranged from 0 to 60. Higher scores indicated more severe condition. FAS2 analysis set included all randomised subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	366		
Units: score on a scale				
arithmetic mean (standard deviation)	-22.5 (± 9.42)	-22.8 (± 10.08)		

Statistical analyses

Statistical analysis title	Seltorexant Vs Quetiapine XR
Comparison groups	Arm 1: Quetiapine extended release (XR) v Arm 2: Seltorexant
Number of subjects included in analysis	756
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of LS Means
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	1.37
Variability estimate	Standard error of the mean
Dispersion value	0.77

Secondary: Change from Baseline to Week 26 in MADRS-6 Total Score

End point title	Change from Baseline to Week 26 in MADRS-6 Total Score

End point description:

Change from baseline to Week 26 in MADRS-6 total score were reported. The MADRS-6 scale was a subset of the MADRS-10 scale, the clinician-administered questionnaire used to measure the core symptoms of depression severity and to detect changes due to antidepressant intervention using the 7 core symptoms from the MADRS-10 scale as followed: Apparent Sadness, Reported Sadness, Inner Tension, Lassitude, Inability to Feel, and Pessimistic Thoughts. MADRS-6 scale was the sum of the

scores from individual question items at a given time point and ranged from 0 (no apparent symptoms) to 36 (most severe symptoms). Higher scores represent a more severe condition. FAS2 analysis set included all randomised subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	366		
Units: score on a scale				
arithmetic mean (standard deviation)	-14.4 (± 6.56)	-14.7 (± 6.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score

End point title	Change from Baseline to Week 26 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score

End point description:

Change from baseline to Week 26 in MADRS-WOSI were reported. MADRS-WOSI was defined as full MADRS total score without sleep item. The MADRS was a 10-item clinician-administered scale designed to measure depression severity and to detect changes due to antidepressant treatment using items on a scale scored from 0 (no item or normal) to 6 (severe or continuous presence of symptoms), & higher scores indicated greater symptom severity. MADRS-WOSI included 9 items (apparent sadness, reported sadness, inner tension, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, & suicidal thoughts) of 10 MADRS total score items, excluding "reduced sleep" item. The total score ranged from 0 to 54. Higher scores indicated a more severe condition. FAS2 analysis set included all randomised subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	366		
Units: score on a scale				
arithmetic mean (standard deviation)	-19.3 (± 8.55)	-19.6 (± 9.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Patient Health Questionnaire, 9-Item (PHQ-9) Scale Total Score

End point title	Change from Baseline to Week 26 in Patient Health Questionnaire, 9-Item (PHQ-9) Scale Total Score

End point description:

Change from baseline to Week 26 in PHQ-9 scale total score were reported. The PHQ-9 scale was a 9-item, patient-reported outcome measure used to assess depressive symptoms. PHQ-9 scale scored 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 on the 4-point score scale ranged from 0 to 4 with 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 achieve the total score (ranged from 0 to 27), where the higher score indicated greater severity of depressive symptoms. FAS2 analysis set included all randomised subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	366		
Units: score on a scale				
arithmetic mean (standard deviation)	-12.4 (± 5.94)	-12.0 (± 6.34)		

Statistical analyses

Statistical analysis title	Seltorexant vs Quetiapine XR
Comparison groups	Arm 1: Quetiapine extended release (XR) v Arm 2: Seltorexant
Number of subjects included in analysis	756
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of LS means
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	0.47

Secondary: Percentage of Subjects with Remission (MADRS Total Score less than or equal to (<=) 12) at Week 26

End point title	Percentage of Subjects with Remission (MADRS Total Score less than or equal to (<=) 12) at Week 26

End point description:

The MADRS scale score was a 10-item clinician-administered scale designed to measure depression severity and to detect changes due to antidepressant treatment using 10 items followed: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item scored from 0 (no item or normal) to 6 (severe or continuous presence of symptoms), and sum of scores of individual question items at a given time point ranged from 0 to 60. Higher scores indicated more severe condition. A subject was considered a remitter at time if MADRS total score <=12 at that time. Subjects who did not meet criterion were non-remitters. Subjects with missing values at a given time point were imputed as non-remitters. FAS2CON analysis set was analysed. Here "N" (Number of subjects analysed) signifies the number of subjects that were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	361		
Units: percentage of subjects				
number (not applicable)	44.2	47.6		

Statistical analyses

Statistical analysis title	Seltorexant vs Quetiapine XR
Comparison groups	Arm 1: Quetiapine extended release (XR) v Arm 2: Seltorexant
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage difference
Point estimate	3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	10.6

Secondary: Percentage of Subjects with a >=50 Percent Improvement in MADRS Total Score and a MADRS Total Score <=18 at Week 26

End point title	Percentage of Subjects with a >=50 Percent Improvement in MADRS Total Score and a MADRS Total Score <=18 at Week 26

End point description:

Percentage of subjects with a >=50% improvement in MADRS total score & MADRS total score <=18 at Week 26 were reported. The 10-item clinician-administered MADRS score measured depression severity & changes by antidepressant treatment from 10 items followed: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, & suicidal thoughts. Scale scored from 0 (no item/normal) to 6 (severe/continuous presence of symptoms),& summed scores of each item at a given time point ranged from 0 to 60. Higher scores indicated more severe condition. A >=50% improvement from baseline in MADRS total score & MADRS total score <=18 at assessed time point indicated a responder with mild symptoms & those did not meet both criteria were considered non-responders. FAS2CON analysis set was analysed. Here "N" (Number of subjects analysed) signifies number of subjects that were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	361		
Units: percentage of subjects				
number (not applicable)	52.4	57.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Body Weight Increase >=7% from Baseline at Week 26

End point title	Percentage of Subjects with Body Weight Increase >=7% from Baseline at Week 26

End point description:

Percentage of subjects with body weight increase >=7% from baseline was reported. FAS2 analysis set included all randomised subjects who received at least 1 dose of study intervention. Here "N" (Number of subjects analysed) signifies the number of subjects that were evaluable for this endpoint and "n"(number of subjects analysed) signifies number of subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to Week 26

End point values	Arm 1: Quetiapine extended release (XR)	Arm 2: Seltorexant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	279		
Units: percentage of subjects				
number (not applicable)	18.6	4.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 1) up to Week 28 (Day 196)

Adverse event reporting additional description:

Safety analysis set included all randomised subjects who received at least 1 dose of study intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Arm 2: Seltorexant

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For first week (from Day 1 to 7), adult subjects received one over encapsulated tablet of seltorexant 20 mg daily at bedtime. During the second week adult subjects received 2 capsules (1 over encapsulated tablet of seltorexant 20 mg and placebo) at bedtime from Day 8 to 182. Elderly patients on seltorexant will start with 1 over-encapsulated tablet of 20 mg on Day 1 and a second capsule of placebo to match the blinded dose titration schedule of quetiapine XR from Day 4 till Day 182. Matching placebo dosing for elderly subjects were flexible for Days 4 to 7 alone.

Reporting group title	Arm 1: Quetiapine extended release (XR)

Reporting group description:

Adult subjects received 1 capsule daily during the first week and 2 capsules daily from the second week onwards. For the first 2 days (Day 1 to 2), adult subjects received one over-encapsulated tablet of quetiapine XR 50 milligrams (mg) daily at bedtime, followed by 1 over-encapsulated tablet of 150 mg tablet daily (lower dose) from Day 3 to 7. Elderly subjects on quetiapine XR started treatment with one over-encapsulated 50 mg tablet daily at bedtime from Day 1 to 3 and took a second over-encapsulated 50 mg tablet from Day 4-7 according to the local prescribing label and investigator's judgement. From the second week, subjects on the quetiapine XR lower dose received 1 over-encapsulated tablet of quetiapine XR 150 mg and 1 capsule of placebo daily at bedtime. Subjects on the quetiapine XR higher dose received two over encapsulated tablets of 150 mg quetiapine XR daily at bedtime from Day 14 onwards till Day 182.

Serious adverse events	Arm 2: Seltorexant	Arm 1: Quetiapine extended release (XR)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 366 (1.37%)	6 / 390 (1.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Burns Second Degree			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 366 (0.27%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 366 (0.27%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Intervertebral Disc Disorder			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Burn Infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	1 / 366 (0.27%)	0 / 390 (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: 5 %

Non-serious adverse events	Arm 2: Seltorexant	Arm 1: Quetiapine extended release (XR)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 366 (27.05%)	200 / 390 (51.28%)	
Investigations			
Weight Increased			
subjects affected / exposed	20 / 366 (5.46%)	54 / 390 (13.85%)	
occurrences (all)	20	54	
Nervous system disorders			
Headache			

subjects affected / exposed	42 / 366 (11.48%)	43 / 390 (11.03%)	
occurrences (all)	56	53	
Somnolence			
subjects affected / exposed	23 / 366 (6.28%)	94 / 390 (24.10%)	
occurrences (all)	30	120	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 366 (3.55%)	23 / 390 (5.90%)	
occurrences (all)	13	29	
Gastrointestinal disorders			
Dry Mouth			
subjects affected / exposed	10 / 366 (2.73%)	38 / 390 (9.74%)	
occurrences (all)	10	39	
Nausea			
subjects affected / exposed	11 / 366 (3.01%)	20 / 390 (5.13%)	
occurrences (all)	11	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2020	The first amendment addressed health authority feedback concerning neurologic examinations, restrictions on driving, operating machinery or engaging in hazardous activity, European Union (EU)-specific statistical analyses, and concomitant therapy following study drug stoppage, study discontinuation for subjects. No subjects had been enrolled in the study at that point.
09 July 2020	The second amendment addressed health authority feedback concerning for 26-week response rate estimates for the seltorexant and quetiapine group sample size estimates and analysis sets to be used for the primary and sensitivity analyses. No subjects had been enrolled in the study at that point.
13 January 2021	The third amendment incorporated recommendations and suggestions from world-wide health authorities and ethics committees, as well as changes made to the 2020-000337-40 and 2020-000338-16 study protocols. The estimand definitions and corresponding analyses for the key secondary endpoint (weight change) were clarified. 5 subjects had been enrolled in the study at that point.
25 June 2021	The purpose of the fourth amendment was to modify eligibility criteria, based on early enrollment experiences.
15 September 2022	The purpose of the fifth amendment was to remove the interim analysis from this protocol along with amendment in the schedule of activities to clarify how the consensus sleep diary (CSD) would be collected and to mention how to perform additional follow-up for early withdrawal of study drug and correction of typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The primary & endpoints related to response and remission analysis were based on FAS1CON & FAS2CON sets that excluded 13 ongoing Ukraine subjects at time of Ukraine-Russian war 2022, with which subjects did not complete DB phase or provide results.

Notes: