SYNOPSIS

Study Title: 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

Study Number: 42847922MDD3002

Study Phase: Phase 3

Name of Study Intervention: JNJ-42847922 (seltorexant)

Name of Sponsor/Company: Janssen Research & Development*

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Status: Approved

Date: 27 March 2023

Prepared by: Janssen Research and Development, LLC

Regulatory Agency Identifier Number:

EudraCT	2020-000338-16
NCT	NCT04532749

Number of Study Center(s) and Countries:

This study was conducted at 56 centers that enrolled participants in 10 countries (Argentina, Chile, Denmark, Finland, Malaysia, Poland, Slovakia, South Korea, Ukraine, and the USA).

Publications (if any):

None

Study Period:

17 September 2020 to 14 July 2022

Rationale:

This study was intended to confirm the AD efficacy and safety of 20 mg seltorexant versus placebo, as adjunctive treatment to an SSRI or SNRI in adult (18 to 64 years, inclusive) and elderly (65 to 74 years, inclusive) participants with MDDIS, who had an inadequate response to treatment with a SSRI/SNRI. The primary efficacy endpoint of the study was the change in the MADRS total score from baseline to Day 43.

Objectives and Endpoints

Objectives	Endpoints
Efficacy	
Primary	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an AD in improving depressive symptoms in participants with MDDIS who have had an inadequate response to current ADT with a SSRI or SNRI.	Change from baseline to Day 43 in the MADRS total score.
Key Secondary	
To assess the efficacy of seltorexant compared with placebo as an adjunctive therapy to an AD in participants with MDDIS on the following:	
MDD symptoms other than insomnia symptoms,	Change from baseline to Day 43 in the MADRS-WOSI total score.
Patient-reported assessment of sleep outcomes.	Change from baseline to Day 43 in sleep disturbance using the PROMIS-SD Short Form (8a) T-score.
Secondary	
To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an AD in participants with MDDIS on the following:	
Core symptoms of depression,	Change from baseline to Day 43 in the MADRS-6 total score.
Response of depressive symptoms,	Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in the MADRS total score, from baseline to Day 43.
Patient-reported symptoms of depression.	Change from baseline to Day 43 in the PHQ-9 total score.
Exploratory	
To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an AD on the following:	
Patient-reported sleep diary,	Change from baseline to Day 43 in subjective sleep parameters as measured by the CSD.
Remission of depressive symptoms,	Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤12 at Day 43.
Patient-reported health-related quality of life,	Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the EQ-5D-5L questionnaire.
Patient-reported global functioning (work/school, social and family life),	Change from baseline to Day 43 in the SDS total score.
Patient-reported insomnia symptoms,	Change from baseline to Day 43 in the patient-reported ISI total score.

Patient-reported assessment of sleep outcomes,	Change from baseline over time in sleep symptoms using the PGI-S score.
Patient-reported assessment of change in depressive symptoms,	Change from baseline over time in depressive symptoms using the PGI-C score.
Clinical symptom severity,	Change from baseline over time in the CGI-S score.
Patient-reported rumination symptoms.	Change from baseline to Day 43 in the RRS total score.
Safety	
To assess the safety and tolerability of seltorexant as adjunctive therapy to an AD in participants with MDDIS in the short-term compared with placebo.	AEs including AESI. Vital signs. Suicidality assessment using the C-SSRS. Withdrawal symptoms assessment using PWC-20. Laboratory values and ECGs. Patient-reported sexual functioning using the ASEX.
Additional Exploratory Objectives	
• To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers (eg, HPA axis, metabolic function and, biomarkers of immune system activation) in relation to clinical response on depression symptoms and IS upon adjunctive treatment with seltorexant. • To identify genetic (eg, CYP genes) and other factors that may influence the PK, safety, or tolerability of seltorexant. • To assess the plasma exposure of seltorexant and its M12 metabolite along with alpha-1-acid glycoprotein levels in participants with MDDIS when used as adjunctive treatment.	

Methodology:

This was a randomized, DB, placebo-controlled, parallel-group 6-week study conducted at multiple sites in the United States, Europe, Asia, and South America that evaluated adjunctive seltorexant 20 mg versus placebo in adult men and women with MDDIS and who had an inadequate response (<50% reduction in depressive symptom severity) to current antidepressant therapy with an SSRI/SNRI.

The participants were randomized in a 1:1 ratio to receive DB seltorexant 20 mg or placebo once daily and continued to take their baseline SSRI/SNRI AD throughout the study.

The primary analysis endpoint was the change in MADRS total score from baseline to Day 43. Key secondary analysis endpoints were the changes in MADRS-WOSI total score and PROMIS-SD T score from baseline to Day 43. Other secondary analysis endpoints were changes in MADRS-6 (core symptoms of depression), number of responders (≥50% improvement in the MADRS total score), and PHQ-9 total scores (participant reported depressive symptoms) from baseline to Day 43. Exploratory endpoints were remission of depressive symptoms (MADRS total score ≤12 at Day 43), clinician-reported depression disease severity (CGI-S), and the following participant-reported assessments: quality of life (EQ-5D-5L), global disability (SDS), insomnia symptoms (ISI), sleep outcomes (PGI-S), depressive symptoms (PGI-C), rumination symptoms (RRS), and sleep diary (CSD – to be reported separately). Safety evaluations included adverse event monitoring (including AESIs), concomitant medications, physical examinations (including a brief neurological examination,) urine drug and alcohol breath tests, clinical laboratory tests (hematology, serum chemistry panel, lipid panel, insulin, hemoglobin A1c, thyroid-stimulating hormone, free thyroxine, and urinalysis) including serum or urine pregnancy tests for women of childbearing potential, vital signs (blood pressures, pulse rate, and body temperature), body weight

and BMI, ECG monitoring, suicidality (C-SSRS), post-treatment withdrawal symptoms (PWC-20), and sexual functioning (ASEX). Menstrual cycle tracking was also performed in premenopausal women who were still having their menses.

Blood samples were also obtained for pharmacokinetic, pharmacogenomic, and biomarker analyses that will be reported separately.

Number of Participants (planned and analyzed):

The planned total sample size was approximately 386 participants (193 per group). A total of 212 participants had been randomized when the study was terminated early for meeting futility criteria; the number of participants included in each analysis set is provided in the table below. The analyses of primary and key secondary endpoints (and other efficacy analyses) were based on the FAS1 and FAS2 (identical to the safety analysis set). The FAS1 was used for all submissions, except for the EU dossier, whereas the FAS2 was used for the EU dossier.

Number of Subjects in Each Analysis Set; All Randomized Analysis Set (Study 42847922MDD3002)

	Placebo	Seltorexant 20 mg	Total
All randomized	105	107	212
FAS1 analysis set [a]	102 (97.1%)	105 (98.1%)	207 (97.6%)
FAS2 analysis set [b]	105 (100.0%)	107 (100.0%)	212 (100.0%)
Safety (DB) analysis set [c]	105 (100.0%)	107 (100.0%)	212 (100.0%)
Follow-up (DB) analysis set [d]	98 (93.3%)	103 (96.3%)	201 (94.8%)

[a] FAS1 analysis set includes all randomized participants with MDDIS who received at least 1 dose of study intervention in the DB phase and had baseline MADRS total score ≥ 24 (per IWRS).
[b] FAS2 analysis set includes all randomized participants with MDDIS who received at least 1 dose of study intervention in the DB phase.
[c] Safety analysis set includes all participants who received at least 1 dose of study intervention in the DB phase.
[d] The follow-up analysis set includes all randomized participants who entered the follow-up phase.

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Diagnosis and Main Criteria for Inclusion and Exclusion:

The study population included adult and elderly men and women (aged 18 to 74 years, inclusive) who met DSM-5 diagnostic criteria for MDD without psychotic features (confirmed by the SCID-CT) with insomnia symptoms (MDDIS) and who had an inadequate response to at least 1 but no more than 2 antidepressant therapies with an SSRI or SNRI, including current treatment, administered at an adequate stable dose and duration in the current episode, indicating that the participant required additional treatment but does not have TRD. A participant was not eligible for study participation if they had an adequate response to the current antidepressant or were treatment resistant.

Eligible participants had an HDRS-17 total score ≥20 at the first screening interview with no greater than 20% improvement at the second screening interview and total score ≥18 at the end of screening. The sleep item of the MDD symptoms (Item 4 [Insomnia Symptoms] of the SCID-CT) must have been positive for IS and ISI total scores (patient and clinician versions) must have been ≥15 at the second screening visit. The HDRS-17 and ISI (clinician version) were administered by independent central raters.

Medical history of insomnia disorder, according to the DSM-5, was reported at screening, based on the SCID-CT and participants were asked to complete the CSD for 7 days prior to the baseline visit to characterize baseline sleep status.

Prohibited medications were tapered and discontinued prior to the start of the DB treatment phase. Safety evaluations (eg, physical examination, including a brief neurological examination, vital signs, ECG, C-SSRS to assess current and recent suicidal ideation and behaviors, urine drug screen, alcohol breath test, and clinical laboratory tests) were performed to assess eligibility.

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

Oral seltorexant supplied for this study was formulated as 20-mg tablets. The oral placebo film-coated tablets had the same appearance as the 20-mg seltorexant tablets. Oral seltorexant 20 mg lot numbers were: 20A31/G018, 20F29/G018, 21A18/G018, and 21F11/G018. Oral placebo lot numbers were: 20B07/G028, 20J26/G028, and 21F10/G028.

Duration of Study Intervention:

The planned duration of study treatment was 42 days (6 weeks) for each participant.

Statistical Methods:

Approximately 386 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg) were planned to be enrolled in the DB treatment phase. The enrollment was targeted to achieve approximately 374 participants eligible to be included in the FAS1. Assuming a treatment difference of 4.4 points in change from baseline in MADRS total score between seltorexant and placebo, standard deviation of 12, and a 1-sided significance level of 0.025 (equivalent, 2-sided 0.05), this sample size provided approximately 90% power in a comparison between seltorexant and placebo in the primary efficacy analysis, accounting for a discontinuation rate of approximately 15%. The assumed treatment difference and standard deviation used in this calculation were based on Phase 2 (42847922MDD2001) study results, as well as on clinical judgment.

For the primary and key secondary endpoints, a fixed sequence testing procedure was applied to control the familywise error rate at 2-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and key secondary efficacy endpoints (MADRS-WOSI and PROMIS-SD). The first test in the fixed sequence testing procedure was the primary endpoint at the 2-sided 0.05 level. If the hypothesis corresponding to the primary endpoint was rejected, then the first key secondary endpoint (MADRS-WOSI) was tested at the 2-sided 0.05 level; if the hypothesis corresponding to the primary endpoint was not rejected, then the testing procedure was stopped. If the hypothesis corresponding to MADRS-WOSI was rejected, then the second key secondary endpoint (PROMIS-SD) was tested at the 2-sided 0.05 level; if the hypothesis corresponding to MADRS-WOSI was not rejected, then the testing procedure was stopped.

A preplanned, unblinded IA for futility was performed for pooled and individual data from Studies 42847922MDD3001 (another seltorexant Phase 3 study) and 42847922MDD3002 once 276 participants in the pooled FAS1 had completed double-blind treatment phase. This study was stopped due to futility at the IA. In the final analysis, the primary endpoint was not significant, and the testing procedure ended at that point. As a result, the key secondary endpoints were not formally evaluated.

For the non-EU dossier, the comparison between seltorexant and placebo for the primary and key secondary endpoints was performed using the appropriate contrasts in a MMRM with main comparison at Day 43. The MMRM included country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level (RRS total score <54, ≥54), time, treatment (placebo and seltorexant), and treatment by time interaction as factors, baseline endpoint total score as a covariate. Because the primary endpoint was not significant, a sensitivity analysis (delta adjustment with a tipping point) was not performed.

For the EU dossier, the CR MI method was performed for the primary and key secondary endpoints. Five hundred imputations were performed using the MCMC method to create 500 unique datasets which then had a monotone missing (ie, missing data after the participant experienced an intercurrent event) data pattern. The monotone missing data were imputed using the copy reference method. A mixed model that included country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level [RRS total score <54, ≥54], time, treatment [placebo and seltorexant], and treatment by time interaction as factors, and baseline endpoint total score as a covariate was applied to each imputed dataset (with the CR MI method). Rubin's rule was used to compile results from each imputed dataset. The CIR MI method was performed as a sensitivity analysis.

The other secondary endpoints and exploratory endpoints were analyzed without the use of estimands or evaluation for statistical significance.

All safety analyses were based on the safety analysis set and were analyzed descriptively. TEAEs, clinical laboratory tests, ECG data, vital signs, and physical examination CCI [redacted]. Adverse events of special interest were cataplexy, sleep paralysis, and complex, sleep-related behaviors (parasomnias), falls, and motor vehicle accidents.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Baseline Characteristics:

Of the 455 participants screened for the study, 212 (46.6%) were enrolled/randomized and treated with either seltorexant 20 mg (107 [50.5%]) or placebo (105 [49.5%]).

The demographic characteristics were comparable across treatment groups in the FAS1. Most participants were female (75.9%) and white (83.5%). The mean (SD) age was 49.5 (14.12) years

(range 18 to 74 years). The countries with the most (≥10%) enrolled participants were the United States (34.9%), Ukraine (22.6%), and Argentina (12.7%). The mean (SD) baseline MADRS total score was 32.6 (5.01) which is a score related to moderate depression, most participants (67.0%) were at least "markedly ill" based on CGI-S scores, and the mean (SD) clinician-rated baseline ISI score was 22.6 (3.59). The mean (SD) duration of the current episode of depression was 32.5 (19.59) weeks, and the majority (71.7%) had a lifetime history of ≥3 major depressive episodes including the current episode. Most participants (82.5%) were taking only 1 AD of sufficient dose (based on MGH-ATRQ) and duration (≥6 weeks) during this episode and the majority (73.1%) were currently taking an SSRI. Similar results were obtained in the FAS2 (identical to the safety analysis set).

Exposure:

All participants received at least 1 dose of study drug in the DB phase. The mean [SD] duration of study drug exposure in the FAS1 was similar for seltorexant 20 mg (42 [5.14] days) and placebo (39.5 [8.65] days). Results were similar in the FAS2 (identical to the safety analysis set). Compliance with study drug was at least 98.7% across treatment groups in both FAS1 and FAS2.

Efficacy Results:

Primary Efficacy Results

Under Estimand 1, no statistically significant difference in improvement for MADRS total score was observed between the groups at Day 43 (2-sided p-value 0.411; LS mean difference [95% CI]: -1.2 [-4.00, 1.64]) although seltorexant 20 mg showed a numerically greater improvement in MADRS total score over placebo. The arithmetic mean (SD) change from baseline to Day 43 in MADRS total score was -14.0 (10.46) for seltorexant 20 mg and -13.1 (9.51) for placebo.

Under Estimand 2, consistent with the results of Estimand 1, no statistically significant difference in improvement was observed between the groups at Day 43 (2-sided p-value 0.219; LS mean difference [95% CI]: -1.7 [-4.47, 1.03]). Seltorexant 20 mg showed a numerically greater improvement in MADRS total score over placebo with an arithmetic mean change from baseline (SD) to Day 43 in MADRS total score of -14.1 (10.36) for seltorexant 20 mg and -12.6 (9.51) for placebo.

Key Secondary Efficacy Results

A numerically greater improvement in MADRS–WOSI total score was observed in favor of seltorexant 20 mg over placebo at Day 43 (LS mean difference [95% CI]: -0.9 [-3.41; 1.59]) under Estimand 1, for which the arithmetic mean (SD) changes from baseline to Day 43 were -12.0 (9.27) for seltorexant 20 mg and -11.3 (8.44) for placebo. Consistent with the results of Estimand 1, a numerically greater improvement for MADRS–WOSI total score was observed in favor of seltorexant 20 mg over placebo at Day 43 (LS mean difference [95% CI]: -1.4 [-3.79; 1.08]) under Estimand 2, for which the arithmetic mean (SD) changes from baseline to Day 43 were -12.1 (9.20) for seltorexant 20 mg and -10.9 (8.42) for placebo.

A numerically greater improvement in PROMIS-SD T score was observed in favor of seltorexant 20 mg over placebo at Day 43 (LS mean difference [95% CI]: -2.0 [-4.87; 0.85]) under Estimand 1, for which the arithmetic mean (SD) change from baseline to Day 43 were -13.7 (11.06) for seltorexant 20 mg and -11.9 (11.83) for placebo. Consistent with the results of Estimand 1, a numerically greater improvement for PROMIS-SD T was observed in favor of seltorexant 20 mg over placebo at Day 43 (LS mean difference [95% CI]: -2.2 [-4.94; 0.61]) under Estimand 2, for which the arithmetic mean (SD) changes from baseline to Day 43 were -13.6 (10.93) for seltorexant 20 mg and -11.9 (11.72) for placebo.

Other Secondary Efficacy Results

Seltorexant 20 mg achieved a numerically greater rate of response (≥50% improvement from baseline in MADRS total score) over placebo. The number of participants in the FAS1 who were considered responders by Day 43 was 42.9% for seltorexant 20 mg and 36.3% for placebo. Similar results were observed for the FAS2 (43.9% and 35.2%, respectively).

Seltorexant 20 mg provided a numerically greater improvement in MADRS-6 total score over placebo. For the FAS1, the arithmetic mean change from baseline (SD) to Day 43 in MADRS-6 total score was -9.1 (6.86) for seltorexant 20 mg and -8.1 (6.37) for placebo. The LS mean difference [95% CI] was -1.2 (-3.10; 0.63). Similar results were seen for the FAS2: LS mean difference [95% CI] -1.4 (-3.25; 0.42).

Seltorexant 20 mg provided a numerically greater improvement in PHQ-9 total score over placebo. For the FAS1, the arithmetic mean change from baseline (SD) to Day 43 in PHQ-9 total score was -8.8 (6.44) for seltorexant 20 mg and -8.1 (6.27) for placebo. The LS mean difference [95% CI] was -0.8 (-2.39; 0.76). Similar results were seen for the FAS2: LS mean difference [95% CI] -1.0 (-2.52; 0.57).

Exploratory Efficacy Results

Exploratory analyses showed a consistent numerically greater improvement in treatment effect (MADRS, MADRS-WOSI, PROMIS-SD, MADRS-6, and PHQ-9) for the seltorexant-treated participants. CCI [redacted] Scores for other illness severity parameters (SDS, PGI-C, CGI-C, and RRS) also showed a numerically greater improvement for seltorexant over placebo.

Safety Results:

The incidence of all TEAEs reported during the study was similar between the study intervention groups. The most common TEAE (reported by ≥5% of participants) in either treatment group during the DB phase was headache, which was experienced by 11 (10.5%) participants in the placebo group and 14 (13.1%) participants in the seltorexant 20 mg group. All other TEAEs had an incidence of <5% and were comparable between the treatment groups. Overall, the mean changes in clinical laboratory values, vital signs, and other safety measures were similar across the

study intervention groups. No deaths or serious adverse events were reported in the seltorexant group. In the placebo group, 6 (5.7%) participants discontinued study treatment due to adverse events, compared with 1 (0.9%) participant in the seltorexant 20 mg group (ligament sprain secondary to a fall, considered not related to study treatment). Among adverse events of special interest, 3 falls were observed in the seltorexant group and none in the placebo group. None of the falls had precipitating events (eg, syncope, drowsiness, dizziness, or cataplexy-like events) at the time of the fall or were deemed related to study drug administration by the investigator. No body collapse was reported. In the post-treatment FU phase, 2 participants who had previously received seltorexant 20 mg experienced self-limiting, nonserious sleep paralysis deemed related to seltorexant by the investigators. No adverse events related to suicidality were reported. CCI [redacted] The PWC-20 by item results were generally similar between the seltorexant 20 mg and placebo groups.

Summary of Treatment-emergent Adverse Events (Double-Blind Phase)

	Placebo	Seltorexant 20 mg
Analysis set: Safety (DB)	105	107
Subjects with 1 or more:		
AEs	40 (38.1%)	38 (35.5%)
Related AEs [a]	19 (18.1%)	23 (21.5%)
Related non-serious AEs [a]	19 (18.1%)	23 (21.5%)
AEs leading to death [b]	0	0
Related AEs leading to death [a,b]	0	0
Serious AEs	2 (1.9%)	0
Related serious AEs [a]	0	0
AEs leading to discontinuation of study treatment	6 (5.7%)	1 (0.9%)
Related AEs leading to discontinuation of study treatment [a]	2 (1.9%)	0

Key: AE = adverse event
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: Safety analysis set includes all participants who received at least 1 dose of study intervention in the DB phase.
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Conclusions:

- No statistically significant difference in MADRS total score at Day 43 was observed between the seltorexant 20 mg and placebo groups at the time of the IA or at the final analysis for this study.
- Numerically greater improvements in MADRS total score for seltorexant 20 mg daily over placebo support a treatment effect for seltorexant in participants with MDDIS. The magnitude of the effect for seltorexant in this study is consistent with that observed in previous studies; however, the placebo effect observed in this study was greater than that observed in previous studies.

- The key secondary analysis results for MADRS-WOSI total scores and PROMIS-SD T scores as well as other secondary and exploratory analysis results supported the primary analysis results with numerically greater improvement for seltorexant 20 mg over placebo. In comparison with placebo, participants receiving seltorexant 20 mg were less likely to discontinue study treatment due to adverse events or lack of efficacy.
- A high placebo response with regional, country, and participant subgroup variations, the COVID-19 pandemic, and operational issues affecting participant selection likely impacted the study results resulting in study failure.
- Overall, seltorexant 20 mg was well tolerated with a safety profile similar to that observed in previous studies of seltorexant. No new clinically important safety signals were observed for seltorexant 20 mg compared with placebo.

Note from the Sponsor: Cancelled (or early terminated) trial

Sponsor name:	Janssen Research & Development
EudraCT number:	2020-000338-16
Protocol number:	42847922MDD3002
Clinical trial title:	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
Reasons for the Cancellation (or early termination):	42847922MDD3002 was stopped based on the interim analysis (IA) results as recommended by the Independent Data Monitoring Committee (IDMC).

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