Adjunctive treatment with seltorexant improved patient-reported depressive symptoms, insomnia symptoms, and overall health in major depressive disorder with insomnia

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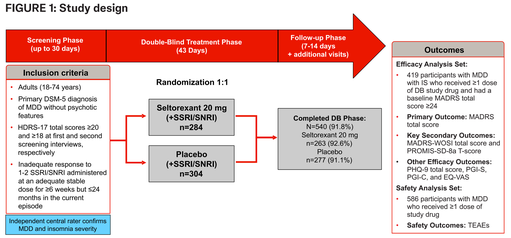
Background

- Most patients with major depressive disorder (MDD) experience insomnia symptoms (IS), which exacerbate the risks associated with MDD.[1,2]
- Seltorexant is a first-in-class, potent, selective orexin-2 receptor antagonist being developed for the adjunctive treatment of MDD with IS.[3]
- In a phase 3 trial comparing the efficacy and safety of adjunctive seltorexant to placebo for the treatment of depressive symptoms in participants with MDD with IS experiencing an inadequate response to selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor (SSRI/SNRI), seltorexant demonstrated statistically and clinically significant improvement in depression, as well as sleep disturbances (poster 124).
  - Here we present secondary and exploratory endpoints assessing patient-reported depressive symptoms, sleep disturbances, and health-related quality of life (HRQoL).

Methods

- NCT04533529 was a phase 3, 6-week, multicenter, international, double-blind (DB), randomized, placebo-controlled trial (**Figure 1**).
- Eligible participants with MDD (with or without IS) were randomized 1:1 to receive seltorexant 20 mg or matching placebo for 6 weeks, while continuing their baseline SSRI/SNRI.
  - MDD with IS was defined as moderate to severe IS by patient and clinician versions of Insomnia Severity Index (ISI) total score ≥15 at the end of screening, and a positive response for IS on the Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials Version (SCID-CT).
- Efficacy analyses were conducted in participants with MDD with IS who received ≥1 dose of DB study drug and had a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥24.
- The following patient-reported measures were used: Patient Health Questionaire-9 (PHQ-9) total score and Patient Global Impression of Change (PGI-C) of Depression assessed depressive symptoms; Patient Reported Outcome Measurement Information System-Sleep Disturbance 8-item short form (PROMIS-SD-8a) and Patient Global Impression of Severity (PGI-S) assessed sleep disturbances; European Quality of Life Group, 5-Dimension, 5-Level EQ visual analog scale (EQ-VAS) assessed HRQoL.
- Analyses used mixed effects models for repeated measures (PHQ-9, PROMIS-SD-8a) or descriptive statistics (PGI-C, PGI-S, EQ-VAS).
  - A least-squares (LS) mean difference 95% confidence interval (CI) that does not include 0 suggests a potential treatment effect.
- Safety analyses were conducted in participants with MDD who received ≥1 dose of study drug and measured via treatment-emergent adverse events (TEAEs).

FIGURE 1: Study design



DB, double-blind; DSM, Diagnostic and Statistical Manual of Mental Disorders; EQ-VAS, European Quality of Life Group, 5-Dimension, 5-Level EQ visual analog scale; HDRS, Hamilton Depression Rating Scale-17; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-WCSI, MADRS without sleep item; MDD, major depressive disorder; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PHQ-9, Patient Health Questionaire-9; PROMIS-SD-8a, Patient Reported Outcome Measurement Information System-Sleep Disturbance 8-item short form; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor; TEAE, treatment-emergent adverse event.

Results

Participants

- 588 participants with MDD were randomized.
  - Seltorexant: n=284 (216 with IS).
  - Placebo: n=304 (228 with IS).
- 586 participants with MDD received ≥1 dose of study drug (**Table 1**).
  - Demographics and baseline characteristics were similar between treatment arms.
  - 77.1% were White, 5.3% Black or African American, 4.8% American Indian or Alaska Native, and 3.8% Asian; 26.8% were Hispanic or Latino.

Efficacy

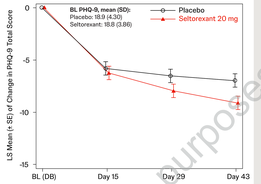
- 419 participants with MDD with IS who received ≥1 dose of DB study drug and had a baseline MADRS total score ≥24 were included in the DB efficacy analysis set.
- There was a greater reduction in patient-reported depression symptoms at Day 43 with seltorexant 20 mg compared to placebo.
  - LS mean difference (95% CI) in PHQ-9 total score change from baseline: -2.1 (-3.30; -0.93) (**Figure 2**).
  - On the PGI-C of Depression, 29.3% on placebo vs. 42.5% on seltorexant 20 mg rated their depression to be "somewhat better" or "much better" at Day 43 (**Figure 3**).
- There was a greater reduction in patient-reported sleep disturbances at Day 43 with seltorexant 20 mg compared to placebo.
  - LS mean difference (95% CI) in PROMIS-SD-8a T-score change from baseline: -3.7 (-5.48, -2.00); 2-sided p<0.001 (**Figure 4**).
  - On the PGI-S Difficulty Falling or Staying Asleep, the percentage of participants with mild or no difficulty at Day 43 was 25.1% on placebo vs. 38.6% on seltorexant 20 mg (**Figure 5**).
  - On the PGI-S Not Feeling Rested the Next Day, the percentage of participants with mild or no problems at Day 43 was 22.1% on placebo vs. 36.0% on seltorexant 20 mg (**Figure 6**).

TABLE 1: Demographics and baseline characteristics (N=586[a])

	Placebo n=303	Seltorexant 20 mg n=283	Total N=586
Age, median (range), years	48.0 (18; 74)	46.0 (18; 74)	47.0 (18; 74)
Female, n (%)	232 (76.6%)	217 (76.7%)	449 (76.6%)
Male, n (%)	71 (23.4%)	66 (23.3%)	137 (23.4%)
HDRS-17 total score, mean (SD)	26.6 (4.17)	26.5 (4.46)	26.5 (4.31)
ISI total score,[b] mean (SD)	20.1 (4.49)	20.0 (4.60)	20.0 (4.54)
Current antidepressant type	n=302	n=282	N=584
SSRI	215 (71.2%)	188 (66.7%)	403 (69.0%)
SNRI	87 (28.8%)	94 (33.3%)	181 (31.0%)
Duration of current depressive episode, mean (SD), weeks	34.9 (20.74)	36.0 (22.53)	35.4 (21.61)

[a]Participants with MDD who received ≥1 dose of study drug. [b]Clinician-reported.
HDRS-17, Hamilton Depression Rating Scale-17; ISI, Insomnia Severity Index; MDD, major depressive disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

FIGURE 2: LS mean (± SE) change from baseline over time[a] in PHQ-9 total score

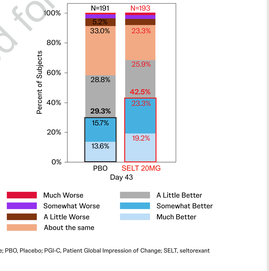


Number of participants:

	BL (DB)	Day 15	Day 29	Day 43
Placebo	210	198	191	195
Seltorexant 20 mg	209	205	199	197

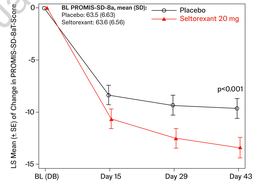
[a]Mixed effects model for repeated measures observed case.
BL, baseline; DB, double-blind; LS, least squares; PHQ-9, Patient Health Questionaire-9; SD, standard deviation; SE, standard error.

FIGURE 3: PGI-C of Depression at Day 43



BL, Baseline; PBO, Placebo; PGI-C, Patient Global Impression of Change; SELT, seltorexant

FIGURE 4: LS mean (± SE) change from baseline over time[a] in PROMIS-SD-8a T-score



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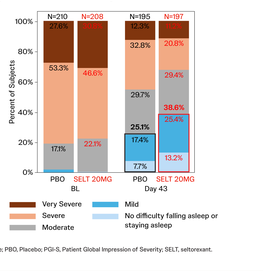
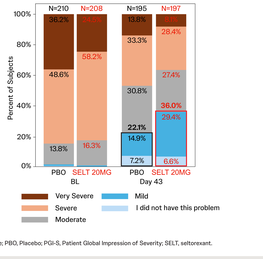
BL, baseline; DB, double-blind; LS, least squares; PROMIS-SD-8a, Patient Reported Outcome Measurement Information System-Sleep Disturbance 8-item short form; SD, standard deviation; SE, standard error.

FIGURE 5: Change in PGI-S Difficulty Falling or Staying Asleep from baseline to Day 43



BL, Baseline; PBO, Placebo; PGI-S, Patient Global Impression of Severity; SELT, seltorexant.

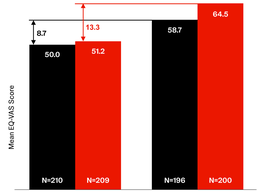
FIGURE 6: Change in PGI-S Not Feeling Rested the Next Day from baseline to Day 43



BL, Baseline; PBO, Placebo; PGI-S, Patient Global Impression of Severity; SELT, seltorexant.

- There was a greater improvement in HRQoL at Day 43 with seltorexant 20 mg compared to placebo.
  - At Day 43, the change in mean EQ-VAS score was 8.7 points with placebo vs. 13.3 points with seltorexant 20 mg (**Figure 7**).
    - 13-point change with seltorexant is above the clinically meaningful threshold of 7-10 points.[4]

FIGURE 7: Change in EQ-VAS from baseline to Day 43



BL, baseline; DB, double-blind; EQ-VAS, European Quality of Life Group, 5-Dimension, 5-Level EQ visual analog scale.

Safety

- 586 participants with MDD who received ≥1 dose of study drug were included in the DB safety analysis set.
- TEAEs were reported for 36.0% of seltorexant and 40.3% of placebo recipients and few participants discontinued study drug due to TEAEs.

Key takeaway

From the patient's perspective, adjunctive treatment with seltorexant improved depressive symptoms, sleep disturbances and overall health, compared to placebo, in adults with MDD with IS and an inadequate response to current antidepressant therapy (SSRI/SNRI).

Conclusion

Seltorexant demonstrated a clinically significant improvement in patient-reported depression, as well as sleep disturbances, in MDD participants experiencing an inadequate response to SSRI/SNRI.

From the patient's viewpoint, seltorexant also improved HRQoL.

Seltorexant demonstrated a safety and tolerability profile similar to placebo, with a high study completion rate.

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Disclosures

Katherine B. Bevans, Joseph M. Trombello, Ryan Kelly, Yun Zhang, Haiyan Xu, John Thipphawong, Yanina Flossbach, Carla M. Canuso, Wayne C. Drevets and **Gahan Pandina** are employees of Janssen Research & Development, LLC and all hold company equity. Joseph M. Trombello is also an unpaid volunteer Clinical Assistant Professor in the Department of Psychiatry at UT Southwestern Medical Center and owns equity in Merck. **Thomas Laughren** is the Director of Laughren Psychopharm Consulting, LLC and in that capacity, he consults for Biohaven, LLC and ANeurotech. He is also a part time employee of the Massachusetts General Hospital Clinical Trials Network and Institute. **Sandra Ruschel** was an investigator and enrolled patients into this study. **Andrew D. Krystal** has received grant support from Janssen Pharmaceuticals; Axsome Pharmaceutics; Neurocrine Biosciences; Reveal Biosensors; The Ray and Dagmar Dolby Family Fund; and the National Institutes of Health. He is a consultant to Adare; Axsome Therapeutics; Big Health; Eisai; Evecxia; Ferring Pharmaceuticals; Galderma; Harmony Biosciences; Idorsia; Janssen Pharmaceuticals; Jazz Pharmaceuticals; Millenium Pharmaceuticals; Merck; Neurocrine Biosciences; Neurawell; Pernix; Otsuka Pharmaceuticals; Sage; Takeda; and Angelini.

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