Seltorexant, adjunctive to antidepressants, in adults with MDD with insomnia symptoms: results of a double-blind, randomized, placebo-controlled study

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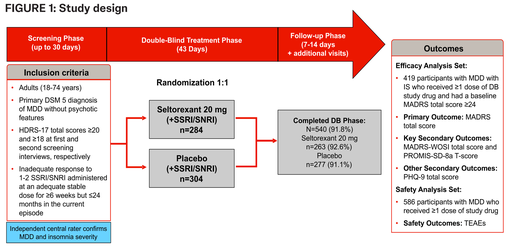
Background

- Insomnia symptoms are common in patients with major depressive disorder (MDD), exacerbating the risks associated with MDD.[1,2]
- Seltorexant is a first-in-class, potent, selective orexin-2 receptor antagonist that normalizes manifestation of hyperarousal and enhances physiological sleep.[3]
- A phase 2 study demonstrated the antidepressant effects of seltorexant versus placebo in participants with MDD, particularly in those with insomnia symptoms (IS).[4]
- Here we present primary and secondary results from 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 SSRI/SNRI.

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).
  - MDD without IS was defined as MDD with either the patient ISI or clinician ISI total score <15 or a negative response for IS on the SCID-CT.
- Efficacy analyses were conducted via mixed effects models for repeated measures 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 primary efficacy outcome was change from baseline to day 43 in MADRS total score.
  - Key secondary efficacy outcomes were changes from baseline to day 43 in MADRS without sleep item (MADRS-WOSI) total score and Patient Reported Outcome Measurement Information System-Sleep Disturbance 8-item short form (PROMIS-SD-8a) T-score.
  - Self-reported depression symptoms were measured via Patient Health Questionaire-9 (PHQ-9) total score.
- Safety analyses were conducted in participants with MDD who received ≥1 dose of study drug.

FIGURE 1: Study design



DB, double-blind; DSM, Diagnostic and Statistics Manual; HDRS-17, Hamilton Depression Rating Scale-17; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-WOSI, MADRS without sleep item; MDD, major depressive disorder; PROMIS-SD-8a, Patient Reported Outcome Measurement Information System-Sleep Disturbance 8-item short form; PHQ-9, Patient Health Questionaire-9; 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.

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

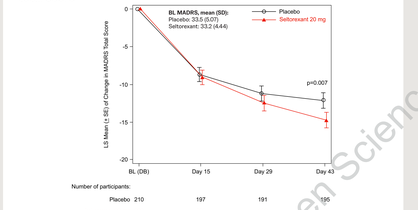
	Placebo n=303	Seltorexant 20 mg n=283	Total N=586
Age, median (range), years	48.0 (18; 74)	46.0 (18; 74)	47.0 (18; 74)
Female, n (%)	232 (76.6%)	217 (76.7%)	449 (76.6%)
Male, n (%)	71 (23.4%)	66 (23.3%)	137 (23.4%)
HDRS-17 total score, mean (SD)	26.6 (4.17)	26.5 (4.46)	26.5 (4.31)
ISI total score,[b] 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

Efficacy

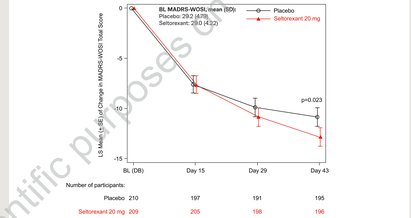
- 419 participants with MDD with IS who received ≥1 dose of DB study drug and had a baseline MADRS total score ≥24 were included in the DB efficacy analysis set.
- The primary efficacy outcome significantly improved with seltorexant versus placebo at day 43 (**Figure 2**).
  - Least squares (LS) mean difference (95% CI) in MADRS total score change from baseline: -2.6 (-4.53, -0.74); 2-sided p=0.007.
- Secondary outcomes also significantly improved with seltorexant at day 43.
  - LS mean difference (95% CI) in MADRS-WOSI total score change from baseline: -2.0 (-3.75, -0.28); 2-sided p=0.023 (**Figure 3**).
  - 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**).
  - LS mean difference (95% CI) in PHQ-9 total score change from baseline: -2.1 (-3.30; -0.93) (**Figure 5**).
    - 95% CI for LS mean difference that does not include 0 is suggestive of a potential treatment effect that needs to be confirmed in other studies.

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



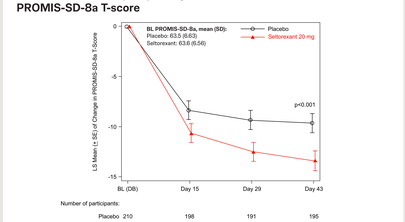
[a]Mixed effects model for repeated measures observed case.
BL, baseline; DB, double-blind; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SE, standard error

FIGURE 3: LS mean (± SE) change from baseline over time[a] in MADRS-WOSI total score



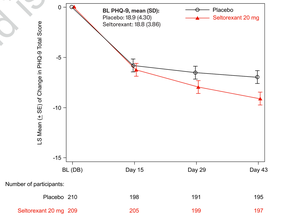
[a]Mixed effects model for repeated measures observed case.
BL, baseline; DB, double-blind; LS, least squares; MADRS-WOSI, Montgomery-Åsberg Depression Rating Scale without sleep item; SD, standard deviation; SE, standard error

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



[a]Mixed effects model for repeated measures observed case.
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: LS mean (± SE) change from baseline over time[a] in PHQ-9 total score



[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

Safety

- 586 participants with MDD who received ≥1 dose of study drug were included in the DB safety analysis set.
- Treatment-emergent adverse events (TEAEs) were reported for 36.0% of seltorexant and 40.3% of placebo recipients (**Table 2**).
- Few participants discontinued study drug due to TEAEs.
- TEAEs of special interest were uncommon.
  - Seltorexant: confusional arousal (n=1; related), fall (n=2; not related), motor vehicle accident (n=2; not related).
  - Placebo: bruxism aggravated (n=1; not related), fall (n=4; not related), sleep terror (n=1; related), sleep paralysis (n=1; related, occurred on the day of DB end-of-treatment [placebo] visit, but after first dose of open-label seltorexant).
- There were no deaths in this study.
- One participant in each group experienced a serious TEAE(s) in the DB phase, all deemed unrelated to study drug.
  - Seltorexant: iron deficiency anemia.
  - Placebo: fall, lumbar spine compression fracture, and spinal canal stenosis.

TABLE 2: Safety summary (N=586[a])

TEAEs, n (%)	Placebo (n=303)	Seltorexant 20 mg (n=283)
Participants with ≥1 TEAE	122 (40.3%)	102 (36.0%)
TEAEs occurring in ≥5% of participants		
Headache	27 (8.9%)	24 (8.5%)
Related TEAEs[b]	51 (16.8%)	34 (12.0%)
TEAEs leading to discontinuation of study drug	7 (2.3%)	6 (2.1%)
Related TEAEs leading to discontinuation of study drug[b]	5 (1.7%)	3 (1.1%)
TEAEs of special interest	7 (2.3%)	5 (1.8%)
Serious TEAEs	1 (0.3%)	1 (0.4%)
Related serious TEAEs[b]	0	0

[a]Participants with MDD who received ≥1 dose of study drug. [b]TEAEs are assessed by the investigator as related to study drug.
TEAE, treatment-emergent adverse event

Key takeaway

Seltorexant improved depressive symptoms in participants with MDD with IS experiencing an inadequate response to current antidepressant therapy (SSRI/SNRI).

Conclusion

- Seltorexant demonstrated statistically and clinically significant improvement in depression, as well as insomnia symptoms, in MDD participants experiencing an inadequate response to SSRI/SNRI.
- Seltorexant improved a broad range of the psychic symptoms of depression, apart from its effects on sleep.
- Seltorexant demonstrated a safety and tolerability profile similar to placebo, with a high study completion rate.

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Disclosures

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