Seltorexant Versus Quetiapine Extended Release as Adjunctive Treatment in Major Depressive Disorder with Insomnia Symptoms: Phase 3 Trial

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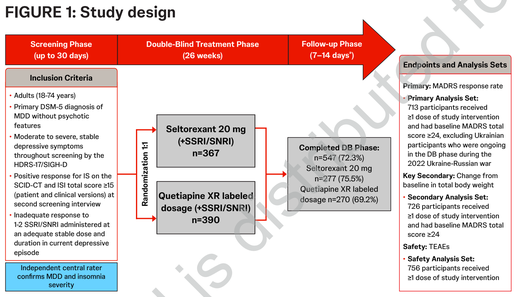
Background

- Inadequate antidepressant response to first-line pharmacologic treatment for major depressive disorder (MDD) remains a significant challenge.
  - Insomnia symptoms (IS) are a common problem among depressed patients, with approximately two-thirds experiencing this sleep disturbance.
  - Use of quetiapine extended release (XR) or other atypical antipsychotics as adjunctive therapy is common not only in case of an inadequate improvement in depressive symptoms but also in the presence of clinically relevant IS in MDD patients.
- Seltorexant is a first-in-class, selective, high-affinity, orexin-2 receptor antagonist that treats depression symptoms by normalizing manifestations of hyperarousal and promoting physiological sleep.
  - A phase 2 study demonstrated the antidepressant effects of adjunctive seltorexant versus placebo in participants with MDD, particularly in those with IS.[1]
  - Primary findings from a phase 3, 6-week study (NCT04533529) in participants with MDD with IS who were on standard antidepressants revealed statistically significant and clinically relevant antidepressant effects, beyond sleep disturbance improvements, with a safety profile comparable to that of a placebo.
- Here we present phase 3 trial (NCT04513912) results of adjunctive seltorexant, with adjunctive quetiapine XR as a comparator, in MDD with IS.

Methods

- NCT04513912 was an international, double-blind (DB), active-controlled trial in participants with MDD with IS and inadequate response to 1–2 antidepressants (**Figure 1**).
- Participants (18–74 years old) were randomized (1:1) to seltorexant 20 mg or quetiapine XR (labeled dosage) once daily for 26 weeks, while continuing their background SSRI/SNRI.
- The primary endpoint was response rate defined as ≥50% improvement from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 26 (those who discontinued early were counted as non-responders); comparison between treatment groups was based on stratified Cochran–Mantel–Haenszel test adjusted for region, age group, and baseline rumination level.
  - Primary analysis set consists of all randomized participants who received ≥1 dose of study intervention and had baseline MADRS total score ≥24, excluding Ukrainian participants who were ongoing in the DB phase at the time of the Ukraine-Russian war in 2022.
- Other endpoints included change from baseline to Week 26 in total body weight (key secondary), in MADRS total score (secondary), in Patient Health Questionnaire-9 (PHQ-9) total score (secondary), and in Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) T- score (exploratory); comparison between treatment groups was based on mixed model for repeated measures with treatment, country, age group, baseline rumination level, time, and time-by-intervention interaction as factors and baseline weight, MADRS total score, PHQ-9 total score, or PROMIS–SD T-score as a covariate.
  - Secondary analysis set consists of all randomized participants who received ≥1 dose of study intervention and had baseline MADRS total score ≥24.
- A fixed sequence testing procedure was applied, accounting for multiplicity in the primary and key secondary endpoints.
- Treatment-emergent adverse events (TEAEs) are summarized in all randomized participants who received ≥1 dose of study intervention (safety analysis set).

FIGURE 1: Study design



*Up to 196 days from baseline for participants who stopped study treatment early. DB, double-blind; DSM, The Diagnostic and Statistical Manual of Mental Illnesses; HDRS-17, Hamilton Depression Rating Scale-17; IS, insomnia symptoms; ISI, Insomnia Severity Index; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SCID-CT, Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials Version; SIGH-D, Structured Interview Guide for the Hamilton Depression Rating Scale; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor; TEAE, treatment-emergent adverse event; XR, extended release.

Results

Participants

- Of 757 participants randomized, 756 received ≥1 dose of study intervention (seltorexant: 366; quetiapine XR: 390).
  - 89.7% were White, 5.0% Black or African American, 3.4% Asian, 0.3% Native Hawaiian or other Pacific Islander, and 0.1% American Indian or Alaska Native; 21.4% were Hispanic or Latino.
- Demographics and baseline characteristics were similar between treatment arms (**Table 1**).

TABLE 1: Demographics and baseline characteristics (safety analysis set)

	Seltorexant 20 mg n=366	Quetiapine XR n=390	Total N=756
Age, years, median (range)	49.0 (19, 74)	49.0 (18, 72)	49.0 (18, 74)
Female, n (%)	281 (76.8)	277 (71.0)	558 (73.8)
Male, n (%)	85 (23.2)	113 (29.0)	198 (26.2)
HDRS-17 total score, mean (SD)	28.1 (4.22)	27.8 (4.21)	27.9 (4.22)
ISI total score,[a] mean (SD)	23.0 (3.03)	22.9 (2.89)	22.9 (2.95)
Current antidepressant type, n (%)			
SSRI	257 (70.2)	262 (67.2)	519 (68.7)
SNRI	109 (29.8)	128 (32.8)	237 (31.3)
Duration of current depressive episode, weeks, mean (SD)	30.3 (20.11)	29.9 (18.91)	30.1 (19.49)

[a]Clinician-rated. HDRS-17, Hamilton Depression Rating Scale-17; ISI, Insomnia Severity Index; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; XR, extended release.

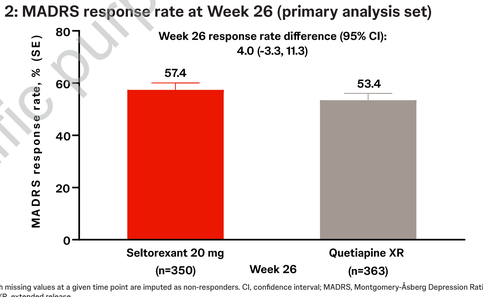
Efficacy

- Seltorexant showed a numerically greater response rate at Week 26 (57.4% [201/350]) than quetiapine XR (53.4% [194/363]) (**Figure 2**), although this difference was not statistically significant (4.0% [95% CI: −3.3, 11.3]).
- Mean (SD) change from baseline to Week 26 in total body weight (kg) was 0.5 (2.89) for seltorexant and 2.1 (3.93) for quetiapine XR; least squares (LS) mean difference (95% CI): −1.7 (−2.23, −1.09) (**Figure 3**).
  - In accordance with the predefined testing sequence, weight change was not formally evaluated due to the non-significant result for the primary endpoint.
- Mean (SD) change from baseline to Week 26 in MADRS total score was −23.0 (10.12) for seltorexant and −22.7 (9.54) for quetiapine XR; LS mean difference (95% CI): −0.2 (−1.77, 1.35) (**Figure 4**).
- Mean (SD) change from baseline to Week 26 in PHQ-9 was −12.1 (6.36) for seltorexant and −12.5 (5.95) for quetiapine XR; LS mean difference (95% CI): 0.2 (−0.70, 1.19) (**Figure 5**).
- Mean (SD) change from baseline to Week 26 in PROMIS-SD T-score was −20.18 (11.70) for seltorexant and −21.07 (11.27) for quetiapine XR; LS mean difference (95% CI): 0.9 (−0.75, 2.49) (**Figure 6**).

Safety

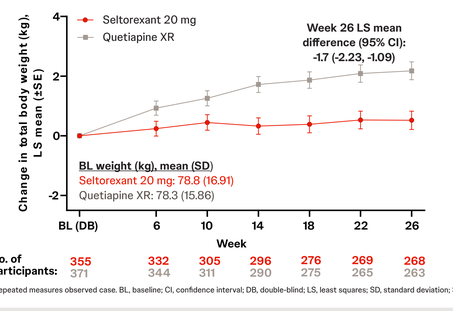
- Overall TEAE rates and TEAEs leading to study intervention discontinuation were lower for seltorexant vs quetiapine XR (**Table 2**).
  - TEAEs (≥5% of participants) >2x as common with quetiapine XR vs seltorexant were somnolence, increased weight, and dry mouth.
- No deaths occurred in the DB phase.

FIGURE 2: MADRS response rate at Week 26 (primary analysis set)



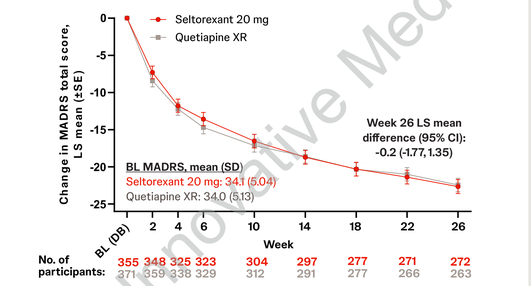
Participants with missing values at a given time point are imputed as non-responders. CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error; XR, extended release.

FIGURE 3: Change from baseline over time in total body weight (kg) (secondary analysis set)



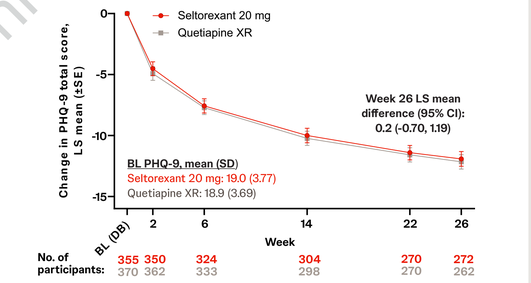
Based on mixed model for repeated measures observed case. BL, baseline; CI, confidence interval; DB, double-blind; LS, least squares; SD, standard deviation; SE, standard error; XR, extended release.

FIGURE 4: Change from baseline over time in MADRS total score (secondary analysis set)



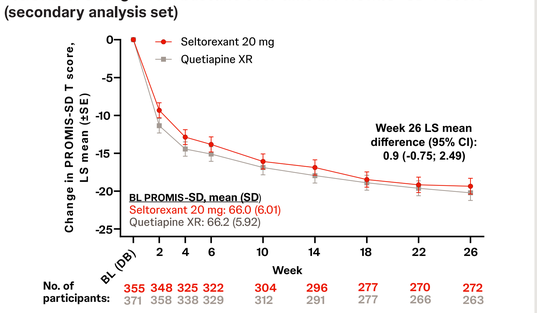
Based on mixed model for repeated measures observed case. BL, baseline; CI, confidence interval; DB, double-blind; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SE, standard error; XR, extended release.

FIGURE 5: Change from baseline over time in PHQ-9 total score (secondary analysis set)



Based on mixed model for repeated measures observed case. BL, baseline; CI, confidence interval; DB, double-blind; LS, least squares; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation; SE, standard error; XR, extended release.

FIGURE 6: Change from baseline over time in PROMIS–SD T-score (secondary analysis set)



Based on mixed model for repeated measures observed case. BL, baseline; CI, confidence interval; DB, double-blind; LS, least squares; PROMIS-SD, Patient-Reported Outcome Measurement Information System-Sleep Disturbance; SD, standard deviation; SE, standard error; XR, extended release.

TABLE 2: Overall summary of TEAEs (safety analysis set)

Participants with 1 or more:	Seltorexant 20 mg n=366	Quetiapine XR n=390
TEAEs, n (%)	198 (54.1)	264 (67.7)
Related TEAEs[a]	106 (29.0)	202 (51.8)
Serious TEAEs, n (%)	5 (1.4)	6 (1.5)
Related serious TEAEs[a]	0	0
TEAEs leading to study intervention discontinuation, n (%)	21 (5.7)	44 (11.3)
Related TEAEs leading to study intervention discontinuation[a]	15 (4.1)	42 (10.8)
TEAEs in ≥5% of participants, n (%)		
Headache	42 (11.5)	43 (11.0)
Somnolence	23 (6.3)	94 (24.1)
Nausea	11 (3.0)	20 (5.1)
Dry mouth	10 (2.7)	38 (9.7)
Weight increase	20 (5.5)	54 (13.8)
Fatigue	13 (3.6)	23 (5.9)

[a]Assessed by the investigator as related to study intervention. TEAE, treatment-emergent adverse event; XR, extended release.

Key takeaway

While the primary endpoint was not met, adjunctive seltorexant showed similar efficacy and enhanced safety and tolerability compared with adjunctive quetiapine XR. Seltorexant's favorable benefit-risk profile may provide a potential adjunctive treatment option for patients with MDD with IS.

Conclusion

Adjunctive seltorexant treatment resulted in similar response rates with less weight gain compared with adjunctive quetiapine XR treatment.

Fewer TEAEs and higher completion rates were observed in participants receiving adjunctive seltorexant versus adjunctive quetiapine XR.

These and prior findings, along with the novel targeted mechanism of action, suggest that seltorexant may effectively address an important unmet medical need in MDD with IS.

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Disclosures

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REFERENCE:

1. Savitz A, et al. *Int J Neuropsychopharmacol.* 2021;24(12):965–976.

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