Impact of Seltorexant on Cognitive Performance of Adults with Major Depressive Disorder with Insomnia Symptoms

AUTHORS: Amy Wegener[1,2], Ryan Kelly[1], Yun Zhang[3], Randall L. Morrison[1], Yanina Flossbach[4], Sofie Mesens[5], Wayne C. Drevets[3], Gahan Pandina[1]

AFFILIATIONS: [1]Johnson & Johnson, Titusville, NJ, USA; [2]Drexel University College of Medicine, Philadelphia, PA, USA; [3]Johnson & Johnson, San Diego, CA, USA; [4]Johnson & Johnson, Allschwil, Switzerland; [5]Johnson & Johnson, Beerse, Belgium

Background

- Many individuals with major depressive disorder (MDD) experience inadequate response to standard therapies and have residual symptoms, such as insomnia symptoms (IS), and/or subsequent deficits in cognitive function.
- Further, sleep disturbance is associated with poor performance on cognitive tests for executive functioning,[1] and cognitive deficits may be an important contributor to short- and long-term functional outcome in MDD.[2]
- Seltorexant is a first-in-class, selective, high-affinity, orexin-2 receptor antagonist being developed for the treatment of MDD with IS.
  - An exploratory phase 1b study in MDD found a numerically greater improvement from baseline on the Symbol Sorting Test (SST), a measure of executive function, which is shown to be impaired in depression,[3] with seltorexant monotherapy compared with placebo.
- A global, 26-week, double-blind, phase 3, randomized controlled trial (NCT04513912) evaluated the efficacy and safety of seltorexant with quetiapine extended release (XR) as a comparator, both adjunctive to antidepressant therapy, in participants with MDD with IS who had shown an inadequate response to current standard antidepressants.
  - Results indicated that adjunctive seltorexant showed similar improvements in depressive symptoms to adjunctive quetiapine XR, with ≥50% improvement from baseline in Montgomery-Åsberg Depression Rating Scale total score at Week 26 of 57.4% for seltorexant and 53.4% for quetiapine XR.
  - In addition, fewer treatment-emergent adverse events and higher completion rates were observed in participants receiving adjunctive seltorexant versus adjunctive quetiapine XR.
- Here we present cognitive performance at baseline, Week 10, and Week 26 in participants with MDD with IS treated with adjunctive seltorexant or adjunctive quetiapine XR from the NCT04513912 trial.

Methods

- NCT04513912 included participants aged 18-74 years with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, diagnosis of MDD without psychotic features, with moderate-to-severe insomnia symptoms, and an inadequate response to 1-2 antidepressants at adequate dose and duration in the current depressive episode.
- Participants with cognitive impairment per investigator judgement or with neurodegenerative disorders were excluded, and participants ≥65 years must have had a Mini Mental State Examination ≥25 (or ≥23 for those with less than high school equivalent education).
- Participants were randomized 1:1 to receive oral seltorexant 20 mg or quetiapine XR (flexible, labeled dosage) for 26 weeks while continuing their background selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors.
- Cognition was evaluated as part of the safety objectives using the novel iPad-administered ReVeRe.D cognitive test battery.
  - ReVeRe.D consists of eight assessments based on classical neuropsychological tests spanning cognitive domains impacted in MDD[4]: SST, Digit Span Forward Test (DSFT), Digit Span Backward Test (DSBT), Word List Recall Test (WLRT-R), Visuospatial Block Recall Test (VBRT), Symbol Digit Matching Test (SDMaT), Trail Making Test (TMT-B), and the Block Maze Test (BMT).
- Changes from baseline at Weeks 10 and 26 on the ReVeRe.D cognitive tests were explored in the safety analysis set, consisting of all randomized participants who received ≥1 dose of study intervention.
  - Least square (LS) mean differences (95% confidence interval [CI]) between intervention groups was based on a mixed-effect model for repeated measures with treatment, country, age group, baseline rumination level, time, and time-by-intervention interaction as factors, and baseline cognitive item score as a covariate. 95% CIs were not adjusted for multiplicity.
  - The number of participants with a meaningful improvement at Week 26 was evaluated based on the reliable change index (RCI) z-value cut-off >1.96. RCI distinguishes clinical change from measurement errors.

Results

- Of 757 participants randomized, 756 received ≥1 dose of study intervention and were included in the safety analysis set.
- Baseline disease and cognitive characteristics were well balanced across treatment groups (**Table 1**).
- Test compliance for participants who completed the study ranged from 70% to 86% across the various evaluations.

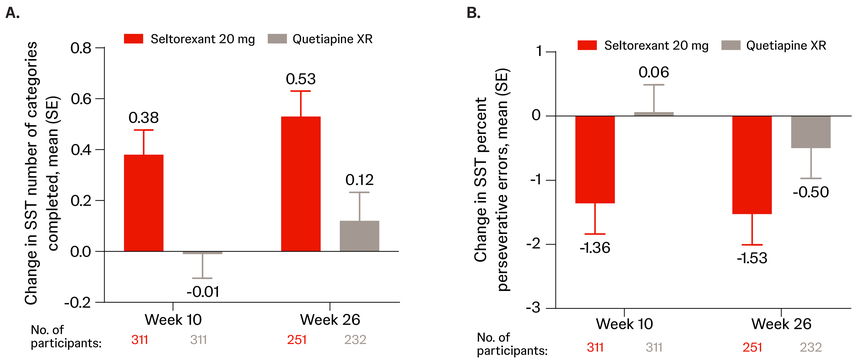
TABLE 1: Demographics and baseline characteristics

	Seltorexant 20 mg n=366	Quetiapine XR n=390
Age, years, median (range)	49.0 (19, 74)	49.0 (18, 72)
Female, n (%)	281 (76.8)	277 (71.0)
Male, n (%)	85 (23.2)	113 (29.0)
MADRS total score, mean (SD)	33.7 (5.45)	33.3 (5.78)
Clinician-rated ISI total score, mean (SD)	23.0 (3.03)	22.9 (2.89)
ReVeRe.D cognitive assessments, mean (SD)		
SST number of categories completed	4.55 (1.90), n=358	4.76 (1.82), n=378
SST percent perseverative errors	13.90 (7.79), n=358	13.11 (7.45), n=378
DSFT	6.30 (1.64), n=358	6.33 (1.60), n=378
DSBT	5.40 (2.06), n=358	5.47 (1.93), n=378
WLRT-R learning score	22.01 (33.40), n=344	22.42 (33.79), n=370
WLRT-R delayed recall trial score	11.00 (3.74), n=344	10.99 (3.66), n=365
VBRT	7.15 (2.67), n=349	7.24 (2.49), n=372
SDMaT	31.89 (17.34), n=335	32.72 (15.62), n=367
TMT-B	85.58 (53.27), n=342	80.58 (51.72), n=367
BMT	26.30 (8.60), n=345	26.07 (8.29), n=370

ReVeRe.D statistics and n values are from participants who completed the baseline assessments. BMT, Block Maze Test; DSBT, Digit Span Backward Test; DSFT, Digit Span Forward Test; ISI, Insomnia Severity Index; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SDMaT, Symbol Digit Matching Test; SST, Symbol Sorting Test; TMT-B, Trail Making Test; VBRT, Visuospatial Block Recall Test; WLRT-R, Word List Recall Test; XR, extended release.

- On the SST (executive function) number of categories completed and percent perseverance errors, the seltorexant group improved by Week 10, which was maintained through Week 26, whereas the quetiapine XR group exhibited minimal improvement (**Figure 1**).
  - LS mean difference between intervention groups at Week 26 was 0.3 (95% CI 0.07, 0.56) on the SST number of categories completed and -0.3 (95% CI -1.45, 0.80) on the SST percent perseverative errors.
  - Number of participants with a meaningful improvement at Week 26 based on RCI >1.96 was 31 (12.4%) for seltorexant and 15 (6.5%) for quetiapine XR on the SST number of categories completed, and 19 (7.6%) for seltorexant and 11 (4.7%) for quetiapine XR on the SST percent perseverative errors.

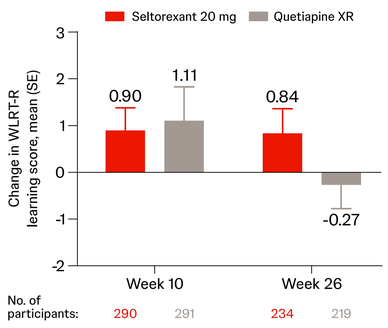
FIGURE 1: Change from baseline at Weeks 10 and 26 in SST A) number of categories completed and B) percent perseverative errors



SE, standard error; SST, Symbol Sorting Test; XR, extended release.

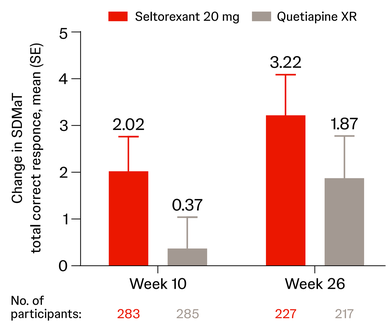
- At Week 10, WLRT-R learning scores (verbal learning) improved from baseline in the seltorexant and quetiapine XR groups. This performance improvement continued through Week 26 for seltorexant; however, the quetiapine XR group declined by Week 26 (**Figure 2**).
  - LS mean difference between intervention groups at Week 26 was 0.9 (95% CI -0.49, 2.32).
  - Number of participants with a meaningful improvement at Week 26 based on RCI >1.96 was 4 (1.7%) for seltorexant and 3 (1.4%) for quetiapine XR.
- On the SDMaT (processing speed), the seltorexant group improved by Week 10. At Week 26, improvement remained higher for seltorexant compared with quetiapine XR (**Figure 3**).
  - LS mean difference between intervention groups at Week 26 was 1.0 (95% CI -1.16, 3.25).
  - Number of participants with a meaningful improvement at Week 26 based on RCI >1.96 was 50 (21.1%) for seltorexant and 32 (14.5%) for quetiapine XR.

FIGURE 2: Change from baseline at Weeks 10 and 26 in WLRT-R learning score



SE, standard error; WLRT-R, Word List Recall Test; XR, extended release.

FIGURE 3: Change from baseline at Weeks 10 and 26 in SDMaT



SDMaT, Symbol Digit Matching Test; SE, standard error; XR, extended release.

- Similar and generally small improvements from baseline were observed on the DSFT, DSBT, VBRT, TMT-B, and BMT in the seltorexant and quetiapine XR groups.
- Limitations of these findings are that the entrance criteria were not designed to select participants with cognitive impairment, and cognitive assessments were included as a safety endpoint in the phase 3 trial.
  - The study was not designed for formal statistical comparisons of cognition between treatment groups.

Key takeaway

Seltorexant had greater long-term cognitive improvements on specific neurocognitive domains, including executive function, verbal learning, and processing speed, as compared with quetiapine XR.

Conclusion

No decline in cognitive functioning was observed with seltorexant treatment, and both the seltorexant and quetiapine XR groups showed improvement on some cognitive tests at Weeks 10 and 26, with the greatest improvements noted at Week 26, which notably occurred alongside comparable improvements in depression severity in each group.

Significant differences in executive function favoring seltorexant were observed, which corresponded to meaningful improvements relative to quetiapine XR. Modest effects on verbal learning and processing speed trended toward favoring seltorexant. The pattern of differences was directly relevant to functional impairment observed in MDD. These differences were particularly compelling since the entrance criteria were not designed to select participants with cognitive impairment. The minimal effects on other tests suggest these trends toward improvement were not due to other nonspecific factors (i.e., practice effects).

These findings can inform the design of future studies and analyses aimed at evaluating how treatment interventions influence cognitive performance in individuals with MDD with IS.

Acknowledgements

This study was sponsored by Johnson & Johnson. Medical writing support was provided by Gabrielle Knafler, PhD, CMPP (System One), and graphic design support was provided by Sandeep Chavan (SIRO Medical Writing Pvt. Ltd.), funded by Johnson & Johnson.

Disclosures

A. Wegener is a research fellow at Johnson & Johnson. All other authors are current/former Johnson & Johnson employees and may hold stock/stock options in Johnson & Johnson.

Presented at: 22nd Annual Scientific Meeting of The International Society for CNS Clinical Trials and Methodology (ISCTM); Washington, DC; February 18-20, 2026

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