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

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Background

- Many individuals with major depressive disorder (MDD) experience inadequate response to standard therapies[1] and have residual symptoms, such as insomnia symptoms (IS) and/or deficits in cognitive function.[2]
- Further, sleep disturbance is associated with poor performance on cognitive tests for executive functioning,[3] and cognitive deficits may be an important contributor to short- and long-term functional outcome in MDD.[4]
- Seltorexant is a first-in-class, selective, high-affinity, orexin-2 receptor antagonist being developed for the treatment of MDD with IS (MDDIS).[5]
  - An exploratory phase 1b study in MDD found a greater improvement from baseline on the Symbol Sorting Test (SST), a measure of executive function, which is shown to be impaired in depression,[6] with seltorexant monotherapy compared with placebo.
- The 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 MDDIS who had shown an inadequate response to current standard antidepressants.[7]
  - 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 and Week 26 in participants with MDDIS treated with adjunctive seltorexant or adjunctive quetiapine XR from the NCT04513912 trial.

Methods

- NCT04513912 comprised participants aged 18-74 years with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, diagnosis of MDD without psychotic features, having moderate-to-severe IS and an inadequate response to 1-2 antidepressants at adequate dose and duration in the current depressive episode.
- Participants with cognitive impairment per investigator judgment or with neurodegenerative disorders were excluded, and participants ≥65 years required 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 comprises eight assessments based on classical neuropsychological tests spanning cognitive domains impacted in MDD[8]: SST, Digit Span Forward Test (DSFT), Digit Span Backward Test (DSBT), Word List Recall Test (WLRT), Visuospatial Block Recall Test (VBRT), Symbol Digit Matching Test (SDMaT), Trail Making Test Form B (TMT-B), and the Block Maze Test (BMT).
- Changes from baseline at Week 26 in the ReVeRe.D cognitive tests were explored as post hoc analyses in the safety analysis set, consisting of all randomized participants who received ≥1 dose of study intervention.
  - Least squares (LS) mean differences (95% confidence interval [CI]) between intervention groups were 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.
  - For each test, a Reliable Change Index (RCI) was derived to distinguish clinical change from measurement error and to determine the percentage of participants exhibiting a meaningful improvement (RCI z-value cut-off >1.96) or meaningful decline (RCI z-value cut-off <−1.96) at Week 26 by treatment group. Nominal p-values were generated post-hoc to assess statistical significance, uncontrolled for multiplicity. P-values were derived from a generalized Cochran-Mantel-Haenszel test for general association, adjusting for region, age group, and baseline rumination level.

Results

- Of 757 participants randomized, 756 (seltorexant, n=366; quetiapine XR, n=390) received ≥1 dose of study intervention and were included in the safety analysis set.
- Baseline 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.

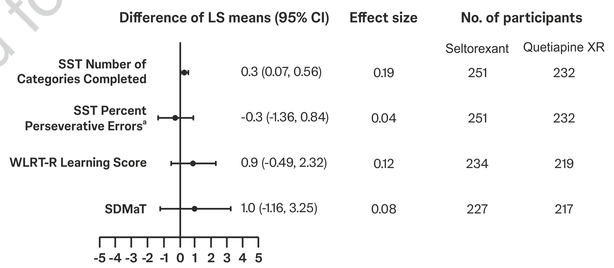
TABLE 1: Demographics and baseline characteristics

	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 learning score	22.01 (33.40), n=344	22.42 (33.79), n=370
WLRT 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, Word List Recall Test; XR, extended release

- Similar and generally small improvements from baseline were observed at Week 26 on the DSFT, DSBT, WLRT delayed recall trial score, VBRT, TMT-B, and BMT in the seltorexant and quetiapine XR groups.
- On the SST (executive function) number of categories completed and percent perseverative errors, the seltorexant group showed improvement from baseline at Week 26, whereas the quetiapine XR group exhibited minimal improvement.
  - LS mean difference between intervention groups at Week 26 was 0.3 (95% CI: 0.07, 0.56; effect size: 0.19) on the SST number of categories completed and −0.3 (95% CI: −1.36, 0.84; effect size: 0.04) on the SST percent perseverative errors (**Figure 1**).
  - On the SST number of categories completed, 12.4% of seltorexant participants showed meaningful improvement based on RCI >1.96 at Week 26 versus 6.5% for quetiapine XR (p=0.04), while meaningful decline (RCI <−1.96) occurred in 2.8% and 4.7% of participants (p=0.37), respectively (**Table 2**).
  - For SST percent perseverative errors, meaningful improvement based on RCI >1.96 at Week 26 was exhibited by 7.6% and 4.7% of participants in the seltorexant and quetiapine XR groups (p=0.18), respectively (**Table 2**).

FIGURE 1: Least-squares mean (95% CI) treatment difference of change in cognitive item scores from baseline to Week 26



Note: Positive values favor seltorexant and negative values favor quetiapine XR. [a]For SST percent perseverative errors, lower difference of LS means indicates fewer errors and better performance, therefore results actually favor seltorexant. CI, confidence interval; LS, least squares; SDMaT, Symbol Digit Matching Test; SST, Symbol Sorting Test; WLRT, Word List Recall Test; XR, extended release

- WLRT learning (verbal learning) scores improved from baseline at Week 26 in the seltorexant group but declined in the quetiapine XR group.
  - LS mean difference between intervention groups at Week 26 was 0.9 (95% CI: −0.49, 2.32; effect size: 0.12) (**Figure 1**).
  - 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 (p=0.76) (**Table 2**).
- On the SMDaT (processing speed), improvement from baseline at Week 26 was greater in the seltorexant group than the quetiapine XR group.
  - LS mean difference between intervention groups at Week 26 was 1.0 (95% CI: −1.16, 3.25; effect size: 0.08) (**Figure 1**).
  - Meaningful improvement based on RCI >1.96 was noted in 22.0% of seltorexant-treated versus 14.7% of quetiapine XR-treated participants (p=0.05) (**Table 2**).

TABLE 2: RCI outcomes at Week 26 by treatment group (meaningful improvement: RCI >1.96; meaningful decline: RCI <−1.96)

	Seltorexant 20 mg (n=366)	Quetiapine XR (n=390)
SST - Number of Categories Completed		
N	251	232
Change from baseline, mean (SD)	0.53 (1.586)	0.12 (1.701)
Participants with RCI >1.96, n (%)	31 (12.4)	15 (6.5)
% Difference (95% CI)[a]	5.9 (0.7, 11.0)	
2-sided p-value[b]	0.04	
Participants with RCI <−1.96, n (%)	7 (2.8)	11 (4.7)
% Difference (95% CI)[a]	−2.0 (−5.4, 1.5)	
2-sided p-value[b]	0.37	
SST - Percent Perseverative Errors		
N	251	232
Change from baseline, mean (SD)	-1.53 (7.542)	-0.50 (7.174)
Participants with RCI >1.96, n (%)	19 (7.6)	11 (4.7)
% Difference (95% CI)[a]	2.8 (−1.4, 7.1)	
2-sided p-value[b]	0.18	
Participants with RCI <−1.96, n (%)	10 (4.0)	10 (4.3)
% Difference (95% CI)[a]	−0.3 (−3.9, 3.2)	
2-sided p-value[b]	0.99	
WLRT - Learning Score		
N	234	219
Change from baseline, mean (SD)	0.84 (8.004)	-0.27 (7.443)
Participants with RCI >1.96, n (%)	4 (1.7)	3 (1.4)
% Difference (95% CI)[a]	0.3 (−1.9, 2.6)	
2-sided p-value[b]	0.76	
Participants with RCI <−1.96, n (%)	1 (0.4)	2 (0.9)
% Difference (95% CI)[a]	−0.5 (−2.0, 1.0)	
2-sided p-value[b]	0.54	
SDMaT - Total Correct Response		
N	227	217
Change from baseline, mean (SD)	3.22 (13.074)	1.87 (13.345)
Participants with RCI >1.96, n (%)	50 (22.0)	32 (14.7)
% Difference (95% CI)[a]	7.3 (0.1, 14.4)	
2-sided p-value[b]	0.05	
Participants with RCI <−1.96, n (%)	21 (9.3)	23 (10.6)
% Difference (95% CI)[a]	−1.3 (−6.9, 4.2)	
2-sided p-value[b]	0.66	

[a]The confidence intervals are based on Wald statistic. [b]The p-value is based on generalized Cochran-Mantel-Haenszel test for mean score difference between treatments adjusting for region, age group and baseline rumination level. CI, confidence interval; RCI, Reliable Change Index; SDMaT, Symbol Digit Matching Test; SST, Symbol Sorting Test; WLRT, Word List Recall Test; XR, extended release

- Limitations of these findings are that the entrance criteria were not designed to select participants with cognitive impairment, and these are post hoc exploratory analyses of variables 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 showed greater meaningful, long-term cognitive improvements on specific neurocognitive domains, including executive function and processing speed, in participants with MDDIS, as compared with quetiapine XR.

Conclusion

Seltorexant and quetiapine XR groups showed improvement on some cognitive tests at Week 26, which notably occurred alongside comparable improvements in depression severity in each group.

RCI analyses support that the larger numerical gains in executive function and processing speed observed at Week 26 with seltorexant compared with quetiapine XR were meaningful and statistically significant. Overall, meaningful decline was observed less frequently in each treatment group. In executive function, numeric differences in meaningful decline favored seltorexant compared to quetiapine XR.

The pattern of differences is 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 observed on other tests completed in the cognitive test battery suggest these trends toward improvement were not due to other nonspecific factors (i.e., practice effects).

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