

Double-Blind and Open-Label-Extension Results From a Phase-3 Trial of Adjunctive Seltorexant in Adults With Major Depressive Disorder With Insomnia Symptoms

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Background

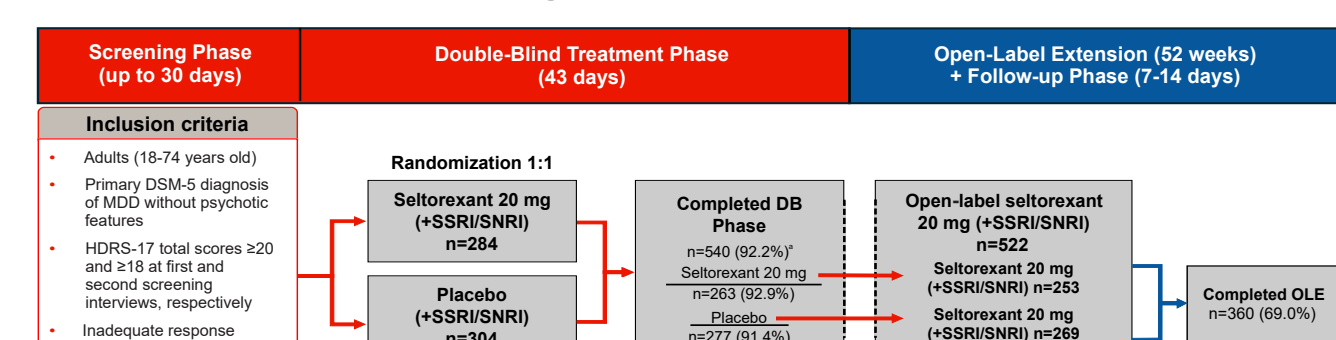
- Inadequate response to first-line therapies for major depressive disorder (MDD) is a critical treatment challenge.
 - Insomnia symptoms (IS) are prevalent among those with depression, affecting about two-thirds of patients, and may exacerbate the clinical presentation of MDD.¹
- Seltorexant is a first-in-class, selective, high-affinity, orexin-2 receptor antagonist, which normalizes hyperarousal and supports physiological sleep, that is being developed as an adjunctive treatment for MDD.
 - The antidepressant effects of adjunctive seltorexant versus placebo were shown in a phase 2 study, particularly in participants with MDD with IS.²
- Here we present the results of a phase 3, multicenter trial (NCT04533529) of seltorexant in participants with MDD on a background therapy with SSRI/SNRI, which consisted of two treatment phases: a double-blind (DB), 6-week, placebo-controlled phase and a 52-week, open-label extension (OLE).

Methods

- NCT04533529 included adults with a primary DSM-5 diagnosis of MDD without psychotic features and an inadequate response to 1-2 antidepressants administered at an adequate stable dose for ≥6 weeks but ≤24 months in the current episode (Figure 1).
 - 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.
- In the DB phase, eligible participants with MDD (with and without IS) were randomized 1:1 to receive seltorexant 20 mg or matching placebo for 6 weeks, while continuing their baseline SSRI/SNRI.
 - 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 in the DB phase and had a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥24.
 - The primary efficacy endpoint was change from baseline to Day 43 in MADRS total score.
 - Key secondary efficacy endpoints 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 the Patient Health Questionnaire-9 (PHQ-9) total score.

- Safety, including treatment-emergent adverse events (TEAEs), was assessed in participants with MDD (with and without IS) who received ≥1 dose of study drug in the DB phase.
- In the OLE, eligible participants from the DB phase received open-label 20 mg seltorexant for an additional 52 weeks while continuing their baseline SSRI/SNRI.
 - Change from OLE baseline over time in MADRS total score and remission, defined as MADRS total score ≤12, along with TEAEs were assessed in participants with MDD (with and without IS) who received ≥1 dose of study drug in the OLE.

FIGURE 1: Study design



*Denominator is 586 as 1 participant in each group was randomized but not dosed. DB, double-blind; DSM, Diagnostic and Statistical Manual of Mental Disorders; HDRS-17, Hamilton Depression Rating Scale-17; MDD, major depressive disorder; OLE, open-label extension; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor.

Results

Participants (MDD with and without IS)

- 588 participants with MDD were randomized in the DB phase (284 [216 with IS] in the seltorexant group and 304 [228 with IS] in the placebo group), of which 586 received ≥1 dose of study drug in the DB phase (Table 1).
- Of the 540 eligible participants from the DB phase, 522 (96.7%) received ≥1 dose of study drug in the OLE.
- There was a high study completion rate with seltorexant treatment in the DB phase (92.9% [263/283]) and in the OLE (69.0% [360/522]).

TABLE 1: Demographics and baseline characteristics (DB phase; MDD with and without IS)

	Placebo n=303	Seltorexant 20 mg n=283	Total N=586
Age, years, median (range)	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,* mean (SD)	20.1 (4.49)	20.0 (4.60)	20.0 (4.54)
Current antidepressant type, n (%)	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, weeks, mean (SD)	34.9 (20.74)	36.0 (22.53)	35.4 (21.61)

*Clinician-reported. DB, double-blind; HDRS-17, Hamilton Depression Rating Scale-17; ISI, insomnia symptoms; ISI, Insomnia Severity Index; MDD, major depressive disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

Efficacy

DB phase (MDD with IS)

- The primary and key secondary efficacy endpoints significantly improved with seltorexant versus placebo at Day 43 (Figure 2A–C).
 - 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.
 - LS mean difference (95% CI) in MADRS-WOSI total score change from baseline: -2.0 (-3.75, -0.28); 2-sided p=0.023.
 - 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.

- Self-reported depression symptoms also decreased with seltorexant versus placebo; LS mean difference (95% CI) in PHQ-9 total score change from baseline at Day 43: -2.1 (-3.30, -0.93).

OLE (MDD with and without IS)

- A large proportion of participants who entered the OLE continued to show improvement in depression symptoms (Figure 3) and achieved remission.
 - For the placebo to seltorexant group, the percentage of participants in remission (observed case) increased from 19.9% (53/267) at OLE baseline to 62.6% (122/195) at OLE Week 28 and 73.6% (131/178) by OLE Week 52.
 - For the seltorexant to seltorexant group, the percentage of participants in remission (observed case) increased from 27.1% (68/251) at OLE baseline to 57.4% (116/202) at OLE Week 28 and 74.0% (134/181) by OLE Week 52.
- Improvement in sleep disturbance also continued in the OLE.
 - For the placebo to seltorexant group, the mean (SD) change from OLE baseline to OLE Week 52 in PROMIS-SD-8a T-score was -10.8 (10.87; n=178).
 - For the seltorexant to seltorexant group, the mean (SD) change from OLE baseline to OLE Week 52 in PROMIS-SD-8a T-score was -7.4 (9.73; n=181).

Safety (MDD with and without IS)

- In the DB phase, the percentage of participants who experienced any TEAEs was comparable between the placebo and seltorexant groups, and in both the DB and OLE phases, few participants discontinued study drug due to TEAEs (Table 2).
- In the DB phase, 1 participant in each group experienced any serious TEAEs, all deemed unrelated to study drug (seltorexant: iron deficiency anemia; placebo: fall, lumbar spine compression fracture, spinal canal stenosis).
- In the OLE, the most common serious TEAEs were suicide attempts (n=7), depression (n=2), and suicidal ideation (n=2). All participants who reported suicide attempts had experienced significant, recent life stressors, 3 of 7 participants had previous suicide attempts, and 3 of 7 participants overdosed seltorexant (none required medical treatment).

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- Sunderajan P, et al. *CNS Spectrums*. 2010;15(6):394–406. 2. Savitz A, et al. *Int J Neuropsychopharmacol*. 2021;24(12):965–976.

FIGURE 2: LS mean (± SE) change from baseline over time* (DB phase; MDD with IS) in A. MADRS total score, B. MADRS-WOSI total score, and C. PROMIS-SD-8a T-score

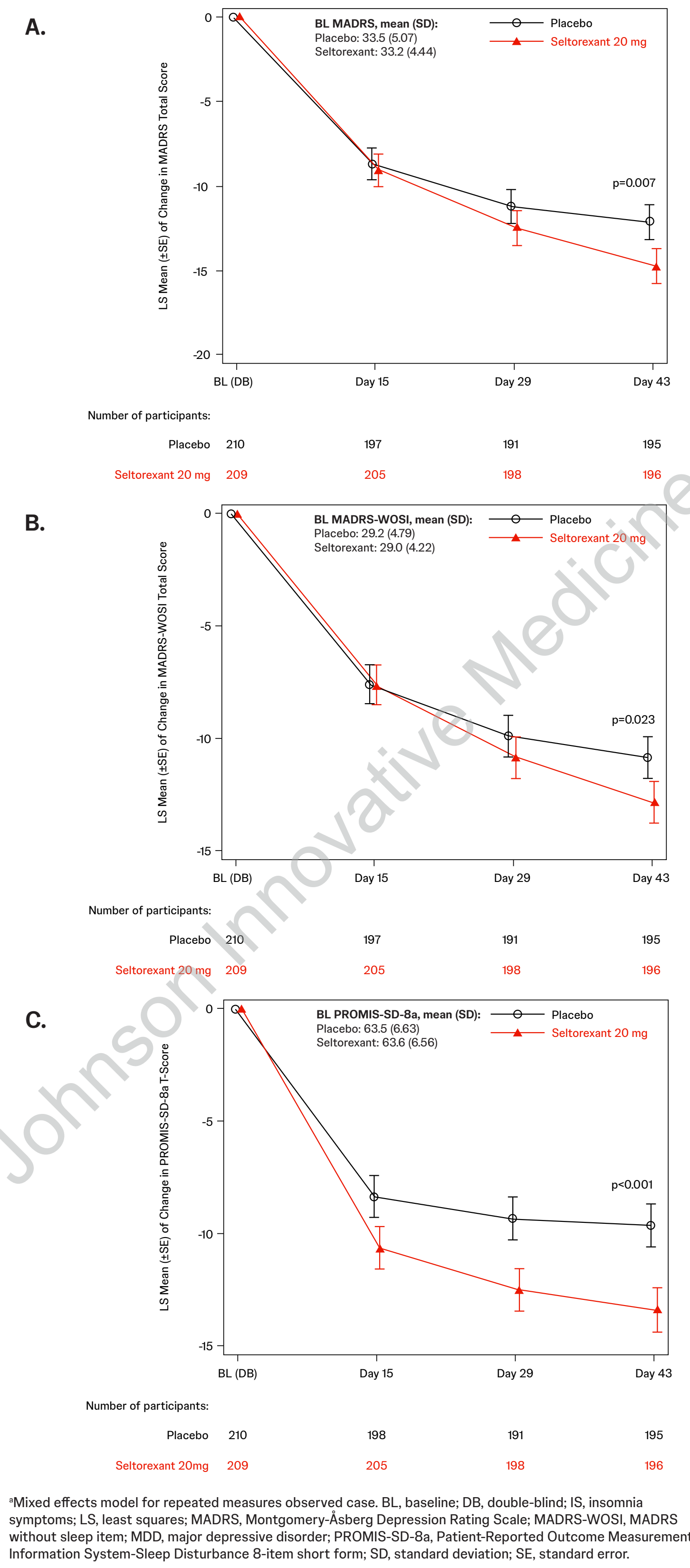


FIGURE 3: Mean (±SE) MADRS total score over time (OLE; MDD with and without IS)

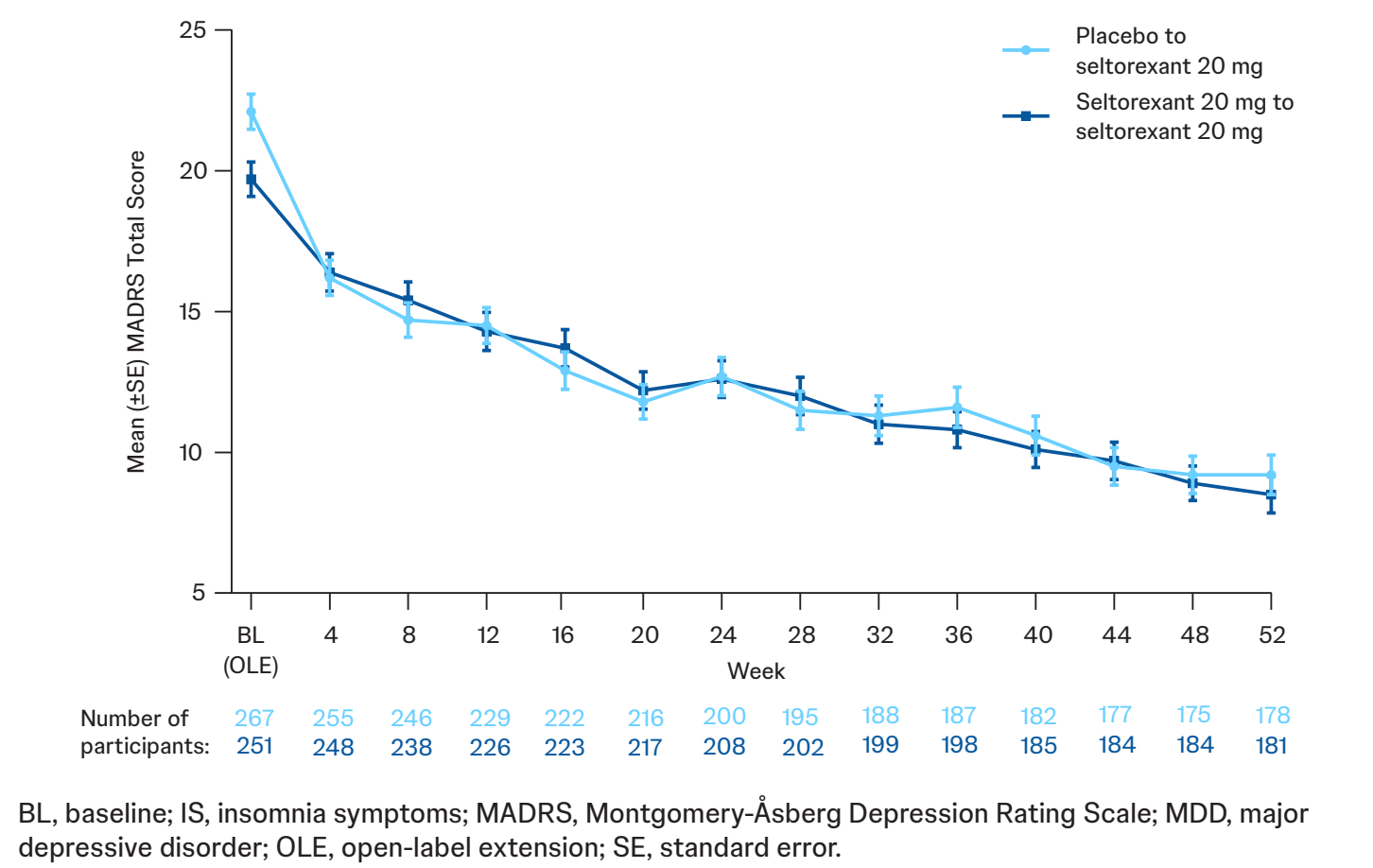


TABLE 2: Overall summary of TEAEs (DB phase and OLE; MDD with and without IS)

DB phase	Placebo (n=303)	Seltorexant 20 mg (n=283)
Any TEAEs, n (%)	124 (40.9)	104 (36.7)
Related TEAEs ^a	52 (17.1)	34 (12.0)
TEAEs leading to discontinuation of study drug, n (%)	7 (2.3)	6 (2.1)
Related TEAEs leading to discontinuation of study drug ^a	5 (1.7)	3 (1.1)
Serious TEAEs, n (%)	1 (0.3)	1 (0.4)
Related serious TEAEs ^a	0	0
TEAEs leading to death, ^b n (%)	0	0
OLE	Placebo to seltorexant 20 mg (n=269)	Seltorexant 20 mg to seltorexant 20 mg (n=253)
Any TEAEs, n (%)	167 (62.1)	163 (64.4)
Related TEAEs ^a	46 (17.1)	42 (16.6)
TEAEs leading to discontinuation of study drug, n (%)	20 (7.4)	10 (4.0)
Related TEAEs leading to discontinuation of study drug ^a	8 (3.0)	3 (1.2)
Serious TEAEs, n (%)	15 (5.6)	14 (5.5)
Related serious TEAEs ^a	2 (0.7)	1 (0.4)
TEAEs leading to death, ^b n (%)	0	1 (0.4)
Related TEAEs leading to death ^{a,b}	0	0

Incidence is based on the number of participants experiencing ≥1 TEAE, not the number of events. ^aTEAEs assessed by the investigator as related to study drug. ^bTEAEs leading to death based on fatal TEAE outcome. DB, double-blind; IS, insomnia symptoms; MDD, major depressive disorder; OLE, open-label extension; TEAE, treatment-emergent adverse event.

Key takeaway

- Results of this study support seltorexant as a safe and effective adjunctive antidepressant therapy to SSRI/SNRI in MDD with IS and highlight the long-term benefits of seltorexant treatment.

Conclusion

- In the 6-week DB phase, seltorexant demonstrated statistically and clinically significant improvement in depressive symptoms in participants with MDD with IS experiencing an inadequate response to current antidepressant therapy.

The safety and tolerability profile of seltorexant was similar to that of placebo, with a high study completion rate.

- In the 52-week OLE, seltorexant was well tolerated with a high study completion rate, and no new safety concerns were identified.

A significant proportion of participants continued to show progressively accruing improvement.

- Participants with sleep disturbance at baseline had significant improvement in sleep, which continued over the additional 52 weeks of OLE treatment.

Acknowledgements

This study was sponsored by Johnson & Johnson. Medical writing support was provided by Gabrielle Knafner, PhD, CMPP (System One) and graphic design support was provided by Samita Warang (SIRO Clinpharm Pvt Ltd); funded by Johnson & Johnson.

Disclosures

Gahan Pandina, Ewa Wajsz, Joseph M. Trombello, Ryan Kelly, Yun Zhang, Haiyan Xu, John Thippawong, Yanina Flossbach, Carla M. Canuso and Wayne C. Drevets are current/former employees of Johnson & Johnson and may hold stock/stock options in Johnson & Johnson. Dr. Trombello is also an unpaid volunteer Clinical Assistant Professor in the Department of Psychiatry at UT Southwestern Medical Center and owns equity in Merck. In the past 24 months, Michael E. Thase has received grant support from Acadia Inc.; Alkermes; Axsome Therapeutics Inc.; Intracellular, Inc.; Janssen Pharmaceuticals, Inc.; Myriad; National Institute of Mental Health; Otsuka Pharmaceutical Company, Ltd.; Patient-Centered Outcomes Research Institute (PCORI); and Takeda Pharmaceutical Company, Ltd. He is an advisor/consultant to Axsome Therapeutics, Inc.; Clexio Biosciences; GH Therapeutics; H. Lundbeck; A/S; Johnson & Johnson; Luye Pharma Group, Ltd.; Merck & Company, Inc.; Otsuka Pharmaceutical Company, Ltd.; Pfizer, Inc.; Sage Pharmaceuticals; Seelos Pharmaceuticals; Sunovion Pharmaceuticals, Inc.; and Takeda Pharmaceutical Company, Ltd. Dr. Thase receives royalties from American Psychiatric Foundation; Guilford Publications; Herald House; Kluwer-Wolters; and W.W. Norton & Company, Inc. His spouse is employed by Peloton Advantage, which does business with most major pharmaceutical companies. Andrew D. Krystal has received grant support from Janssen Pharmaceuticals; Axsome Pharmaceuticals; Neurocrine Biosciences; Reveal Biosensors; The Ray and Dagmar Dolby Family Fund; and the National Institutes of Health. He is a consultant to Axsome Therapeutics; Big Health; Eisai; Evecia; Ferring Pharmaceuticals; Galderma; Harmony Biosciences; Idorsia; Janssen Pharmaceuticals; Jazz Pharmaceuticals; Millenium Pharmaceuticals; Merck; Neurocrine Biosciences; Neurawell; Pernix; Otsuka Pharmaceuticals; Sage; Takeda; and Angelini. Sandra Ruschel was an investigator and enrolled patients into this study. 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. Previously presented at: Psych Congress; September 17–21, 2025; San Diego, CA, USA.

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