Seltorexant, Adjunctive to Antidepressants, in Adults with Major Depressive Disorder with Insomnia Symptoms: Phase 3 Studies

Gahan Pandina,[1] Michael E. Thase,[2] Andrew D. Krystal,[3] Ewa Wajs,[4] Joseph M. Trombello,[1] Katherine Bevans,[5] Ryan Kelly,[1] Yun Zhang,[6] Haiyan Xu,[1] Sandra Ruschel,[7] Yanina Flossbach,[8] Sofie Mesens,[4] Lu Xia,[1] Thomas Laughren,[9] Wayne C. Drevets[6]

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GP, EW, JMT, KB, RK, YZ, HX, YF, SM, LX, WCD: Employees of Johnson & Johnson, and may hold company equity. **JMT** is also an unpaid volunteer Clinical Assistant Professor in the Department of Psychiatry at UT Southwestern Medical Center and owns equity in Merck. **MET:** Grant support from Acadia Pharmaceuticals Inc.; Alkermes; Axsome Therapeutics Inc.; Intra-cellular Therapies Inc.; Johnson & Johnson; Myriad; National Institute of Mental Health; Otsuka Pharmaceutical Company Ltd.; Patient-Centered Outcomes Research Institute (PCORI); Takeda Pharmaceutical Company Ltd. 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.; Takeda Pharmaceutical Company Ltd. Royalties from American Psychiatric Foundation; Guilford Publications; Herald House; Kluwer-Wolters; W.W. Norton & Company Inc. His spouse is employed by Peloton Advantage, which does business with most major pharmaceutical companies. **ADK:** Grant support from Johnson & Johnson; Axsome Therapeutics Inc; Neurocrine Biosciences; Reveal Biosensors; The Ray and Dagmar Dolby Family Fund; National Institutes of Health. Consultant to Adare; Axsome Therapeutics Inc.; Big Health; Eisai; Evecxia; Ferring Pharmaceuticals; Galderma; Harmony Biosciences; Idorsia; Johnson & Johnson; Jazz Pharmaceuticals; Millenium Pharmaceuticals; Merck & Company Inc; Neurocrine Biosciences; Neurawell; Pernix; Otsuka Pharmaceutical Company Ltd; Sage; Takeda Pharmaceutical Company Ltd; Angelini. **SR:** No conflicts of interest. **TL:** Director of Laughren Psychopharm Consulting LLC and in that capacity, he consults for Biohaven LLC and ANeurotech. Part time employee of the Massachusetts General Hospital Clinical Trials Network and Institute.

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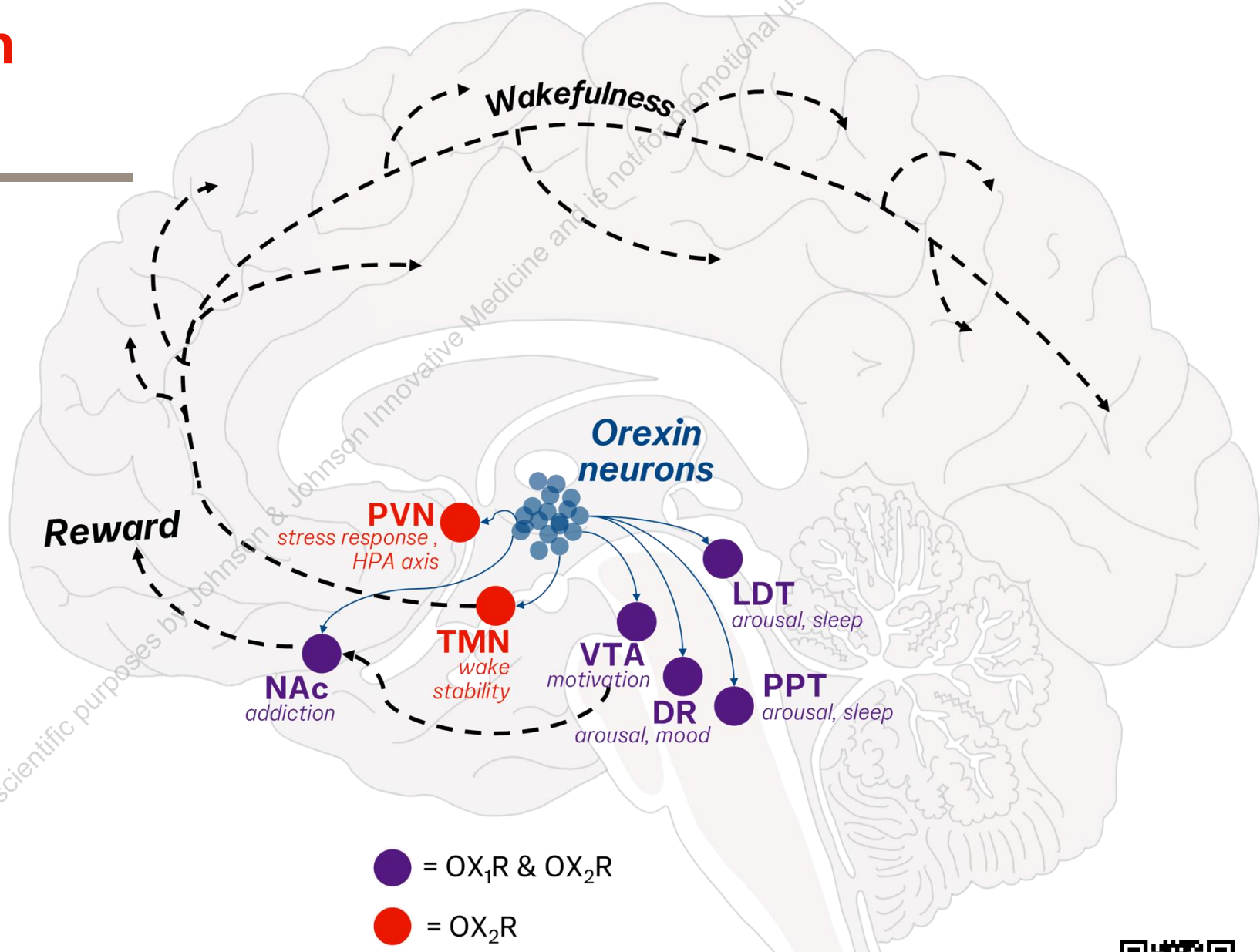
Orexin at the intersection of arousal and mood

Orexin circuits project broadly to brain regions implicated in the pathophysiology of mood disorders, interfacing directly with those governing wakefulness, stress response, reward, and emotional regulation.[1]

Why OX_2R selectivity for mood?

- Central to wake stability and stress-axis activation (TMN, PVN).
- Attenuates stress-driven HPA activation in preclinical models.
- Enables targeted modulation of hyperarousal without broad reward suppression.



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1. Han Y, et al. *Neurosci Bull*. 2020;36(4):432–448. DR, dorsal raphe; HPA, hypothalamic-pituitary-adrenal; LTD, laterodorsal tegmental nucleus; NAc, nucleus accumbens; OX_1R, orexin-1 receptor; OX_2R, orexin-2 receptor; PPT, pedunculopontine tegmental nucleus; PVN, paraventricular nucleus; TMN, tuberomammillary nucleus; VTA, ventral tegmental area.

Seltorexant is a first-in-class, selective, orexin-2 receptor antagonist

- Seltorexant is being developed as adjunctive treatment to standard antidepressant therapy for major depressive disorder (MDD) with insomnia symptoms (IS).
  - Seltorexant treats depression symptoms potentially by normalizing hyperarousal and promoting physiological sleep.
  - The antidepressant effects of seltorexant have been shown in Phase 1 and 2 clinical trials, with a safety and tolerability profile similar to that of placebo.[1-3]

- **Here, we report results from two international, Phase 3 studies.**
  - **NCT04533529 (Study 1): 6-week placebo-controlled double-blind (DB) phase, and 52-week open-label extension (OLE).**
  - **NCT04513912 (Study 2): 26-week DB phase with quetiapine extended release (XR) as an active comparator.**

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1. Recourt K, et al. *Transl Psychiatry*. 2019;9(1):216, 240. 2. Savitz A, et al. *Int J Neuropsychopharmacol*. 2021;24(12):965–976. 3. Mesens S, et al. *Mol Psychiatry*. 2025;30(6):2427–2435.

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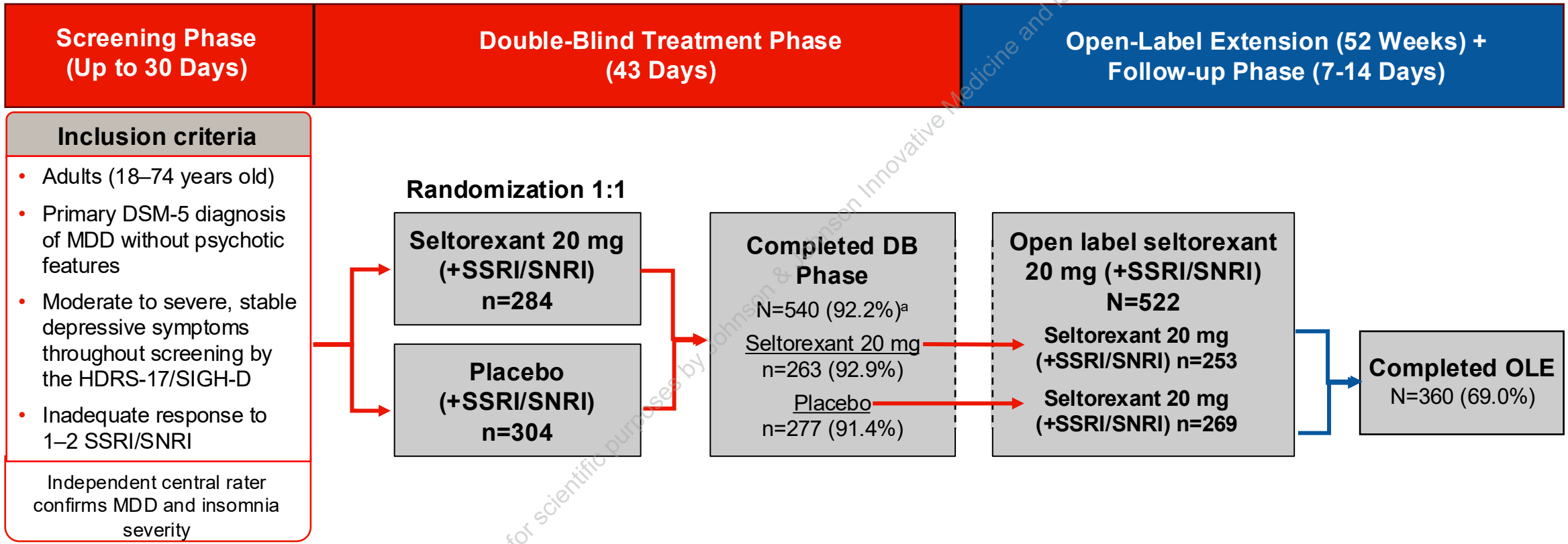
Study 1: DB phase (seltorexant vs placebo) and OLE in participants with MDD (with and without IS) on background therapy with SSRI/SNRI



High study completion rate with seltorexant treatment in the DB phase and OLE.

[a]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; SIGH-D, Structured Interview Guide for the Hamilton Depression Rating Scale; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor.

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Study 1: Demographics and baseline characteristics were similar between treatment arms

Demographics and baseline disease 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)
Clinician 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)

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

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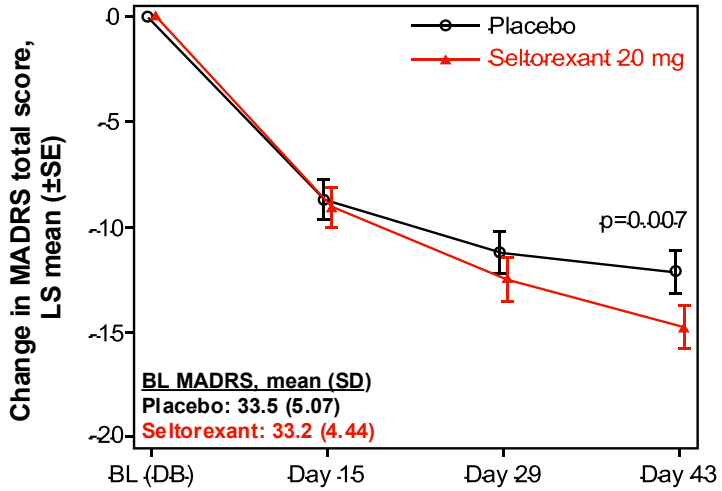
Study 1: The primary and key secondary efficacy endpoints significantly improved with seltorexant vs placebo at Day 43

Change from baseline over time[a] (DB phase; MDD with IS[b])

Primary outcome

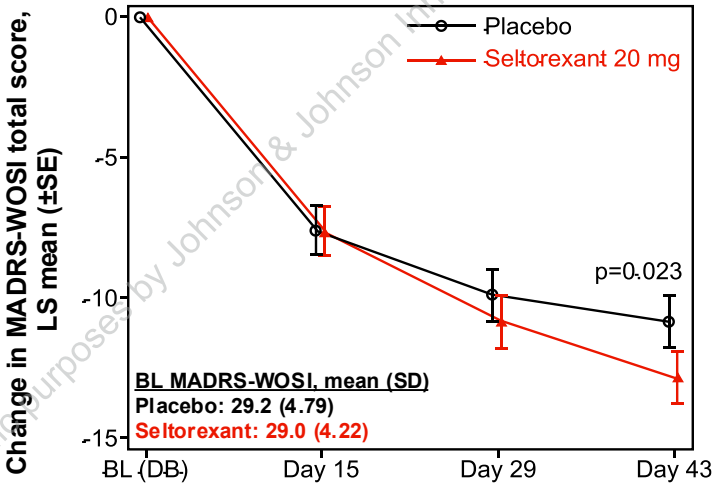
A. MADRS total score



Number of participants:				
Placebo	210	197	191	195
Seltorexant 20 mg	209	205	198	196

Key secondary outcome #1

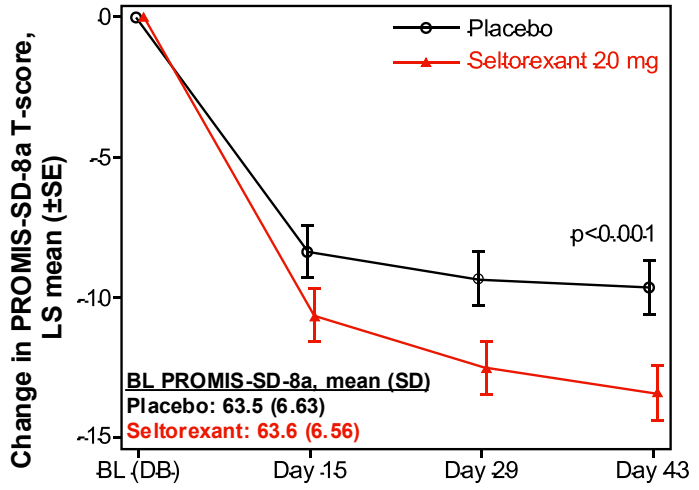
B. MADRS-WOSI total score



Number of participants:				
Placebo	210	197	191	195
Seltorexant 20 mg	209	205	198	196

Key secondary outcome #2

C. PROMIS-SD-8a T-score



Number of participants:				
Placebo	210	198	191	195
Seltorexant 20 mg	209	205	198	196

[a]Mixed effects model for repeated measures observed case. [b]Positive response for IS (item 4) on SCID-CT, and ISI total score (patient and clinician versions) ≥15 at second screening interview. BL, baseline; DB, double-blind; IS, insomnia symptoms; ISI, Insomnia Severity Index; LS, least squares; 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; SCID-CT, Structured Clinical Interview for The Diagnostic and Statistical Manual of Mental Illnesses, Fifth Edition, Axis I Disorders-Clinical Trials Version; SD, standard deviation; SE, standard error.

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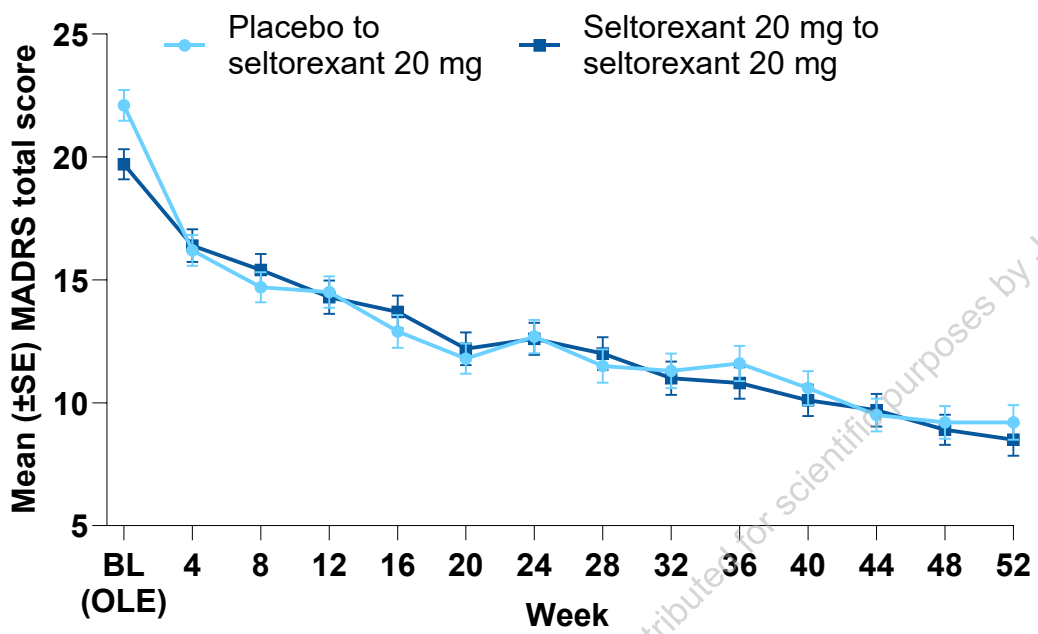
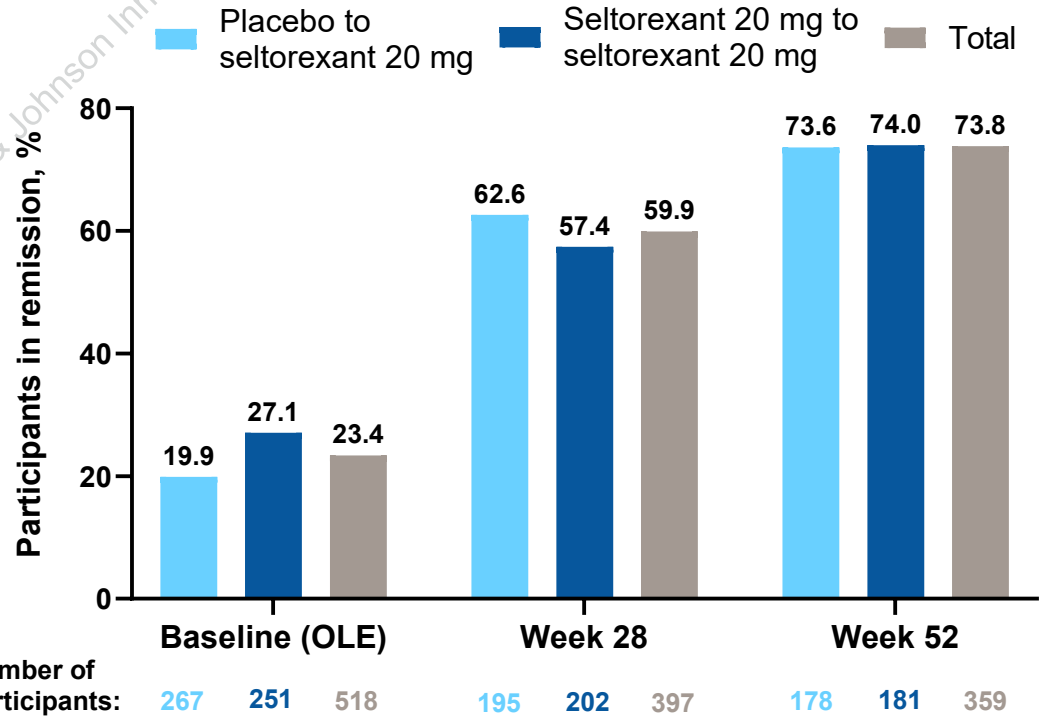
Study 1: Large proportion of participants who entered the OLE continued to show improvement in depression symptoms and achieved remission over 52 weeks

MADRS total score over time (OLE; MDD with and without IS)



Number of participants:	BL (OLE)	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo to seltorexant 20 mg	267	255	246	229	222	216	200	195	188	187	182	177	175	178
Seltorexant 20 mg to seltorexant 20 mg	251	248	238	226	223	217	208	202	199	198	185	184	184	181

Percentage of participants in remission[a] (OLE; MDD with and without IS)



Number of participants:	Baseline (OLE)			Week 28			Week 52		
Placebo to seltorexant 20 mg	267			195			178		
Seltorexant 20 mg to seltorexant 20 mg		251			202			181	
Total			518			397			359

[a]Remission (observed case) was defined as MADRS total score ≤12. BL, baseline; IS, insomnia symptoms; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OLE, open-label extension; SE, standard error.

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Study 1: Safety was comparable between the seltorexant and placebo groups in the DB phase, and no new safety concerns were identified in the OLE

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

DB phase	Placebo (n=303)	Seltorexant 20 mg (n=283)	OLE	Placebo to seltorexant 20 mg (n=269)	Seltorexant 20 mg to seltorexant 20 mg (n=253)
Any TEAEs, n (%)	124 (40.9)	104 (36.7)	Any TEAEs, n (%)	167 (62.1)	163 (64.4)
Related TEAEs[a]	52 (17.2)	34 (12.0)	Related TEAEs[a]	46 (17.1)	42 (16.6)
TEAEs leading to discontinuation of study drug, n (%)	7 (2.3)	6 (2.1)	TEAEs leading to discontinuation of study drug, n (%)	20 (7.4)	10 (4.0)
Related TEAEs leading to discontinuation of study drug[a]	5 (1.7)	3 (1.1)	Related TEAEs leading to discontinuation of study drug[a]	8 (3.0)	3 (1.2)
Serious TEAEs, n (%)	1 (0.3)	1 (0.4)	Serious TEAEs, n (%)	15 (5.6)	14 (5.5)
Related serious TEAEs[a]	0	0	Related serious TEAEs[a]	2 (0.7)	1 (0.4)
TEAEs leading to death,[b] n (%)	0	0	TEAEs leading to death,[b] n (%)	0	1 (0.4)

Incidence is based on the number of participants experiencing ≥1 TEAE, not the number of events. [a]TEAEs assessed by the investigator as related to study drug. [b]TEAEs 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.

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Study 1: Safety was comparable between the seltorexant and placebo groups in the DB phase, and no new safety concerns were identified in the OLE (cont'd)

DB phase

- The most common TEAE (≥5%) in either treatment group was headache (placebo: 8.9%; seltorexant: 8.8%).
  - All other TEAEs had an incidence of <5% and were comparable between the treatment groups.
- 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.

OLE

- The most common (≥5%) TEAEs were headache (11.9%), COVID-19 (8.8%), nasopharyngitis (8.4%), and weight increase (6.5%).
- The most common serious TEAEs were suicide attempts (n=7), depression (n=2), and suicidal ideation (n=2).
  - Of participants who reported suicide attempts: all had experienced significant, recent life stressors; 3 of 7 had previous suicide attempts; and 3 of 7 overdosed seltorexant (none required medical treatment).

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COVID-19; coronavirus disease 2019; DB, double-blind; OLE, open-label extension; TEAE, treatment-emergent adverse event.

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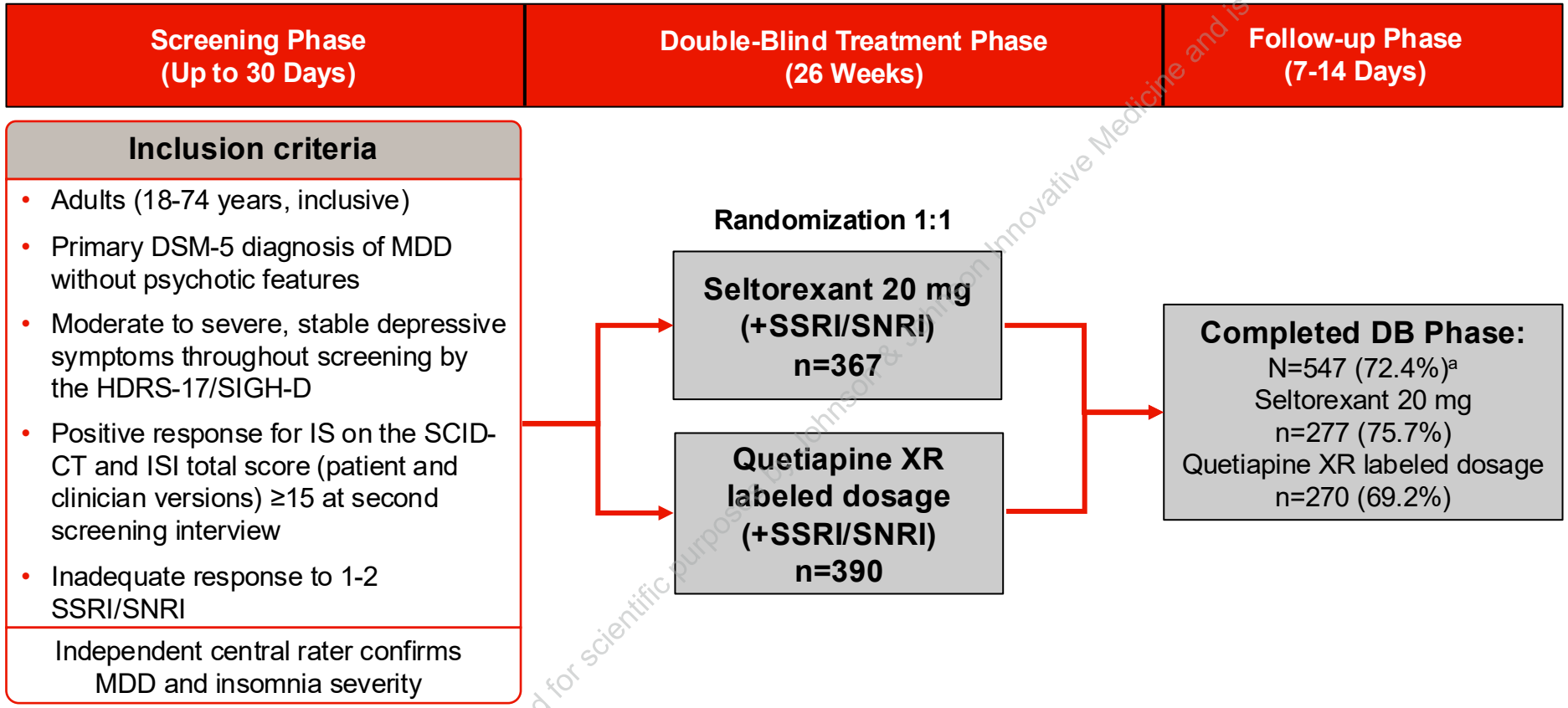
Study 2: DB phase (seltorexant vs quetiapine XR) in participants with MDD with IS on background therapy with SSRI/SNRI



Higher study completion rate with seltorexant treatment than with quetiapine XR.

[a]Denominator is 756 as 1 participant in the seltorexant group was randomized but not dosed. 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; XR, extended release.

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Study 2: Demographics and baseline characteristics were similar between treatment arms

Demographics and baseline disease 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)
Clinician ISI total score, 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)

Safety analysis set consists of all randomized participants who received ≥1 dose of study intervention. 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.

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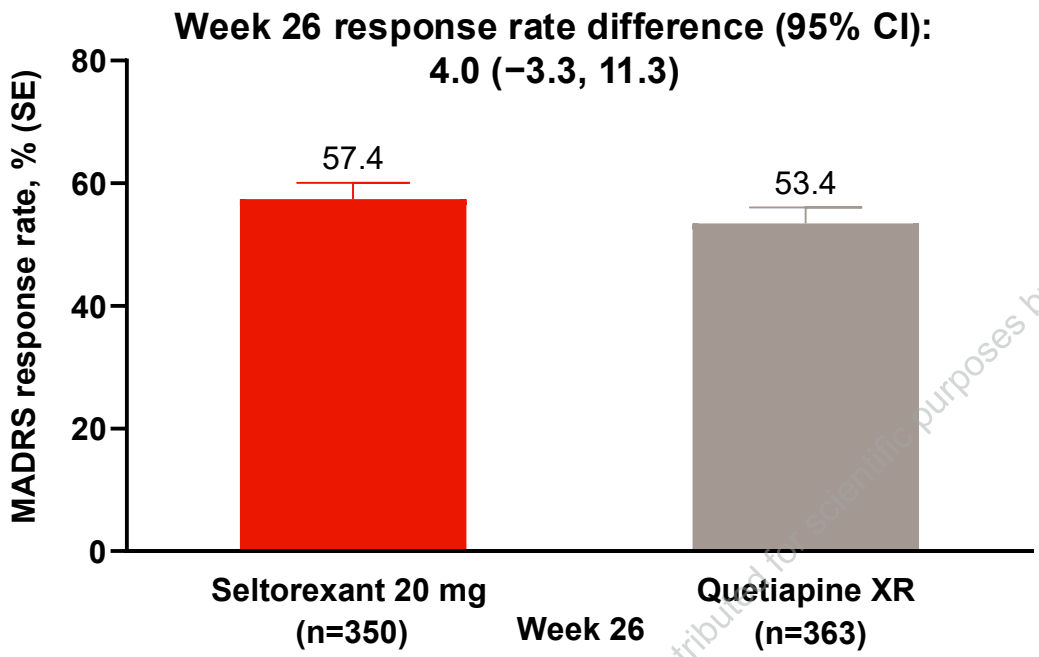
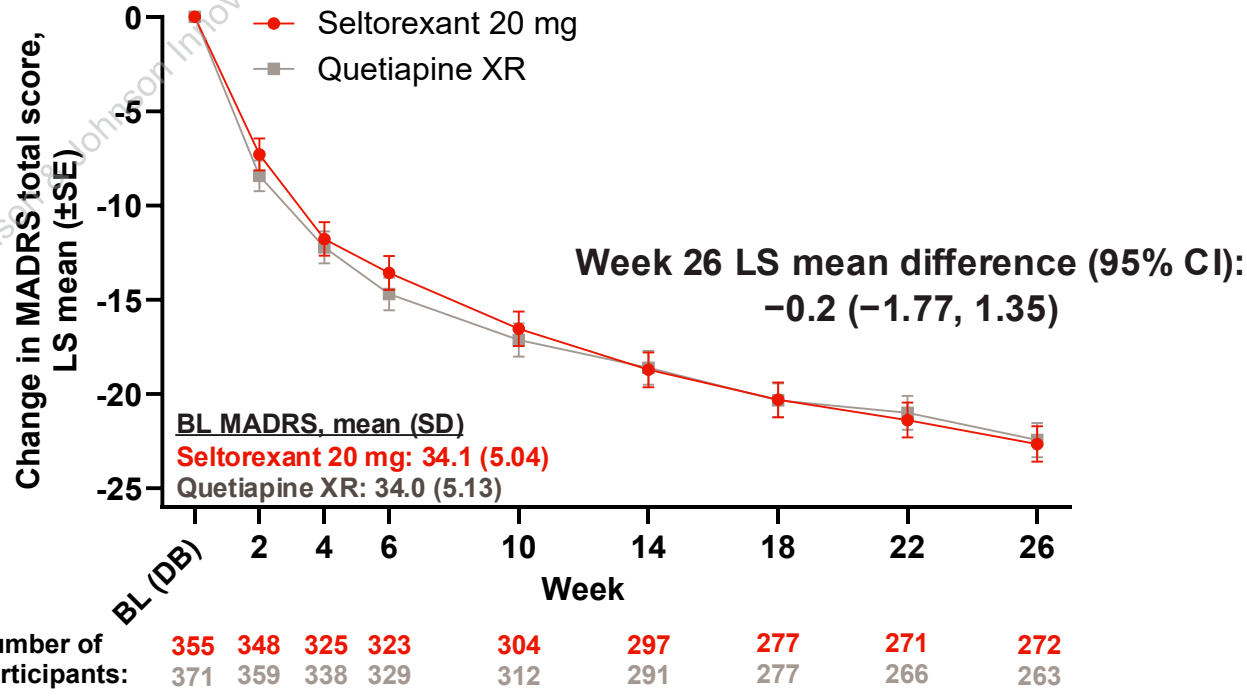
Study 2: Seltorexant treatment resulted in a similar robust MADRS response rate and improvement from baseline as quetiapine XR

MADRS response rate (primary analysis set)[a]



Change from baseline over time in MADRS total score (secondary analysis set)[b]



[a]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 Russian-Ukraine war in 2022. Participants with missing values at a given time point imputed as non-responders; comparison between treatment groups was based on stratified Cochran–Mantel–Haenszel test adjusted for region, age group, and baseline rumination level. [b]Secondary analysis set consists of all randomized participants who received ≥1 dose of study intervention and had baseline MADRS total score ≥24. 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.

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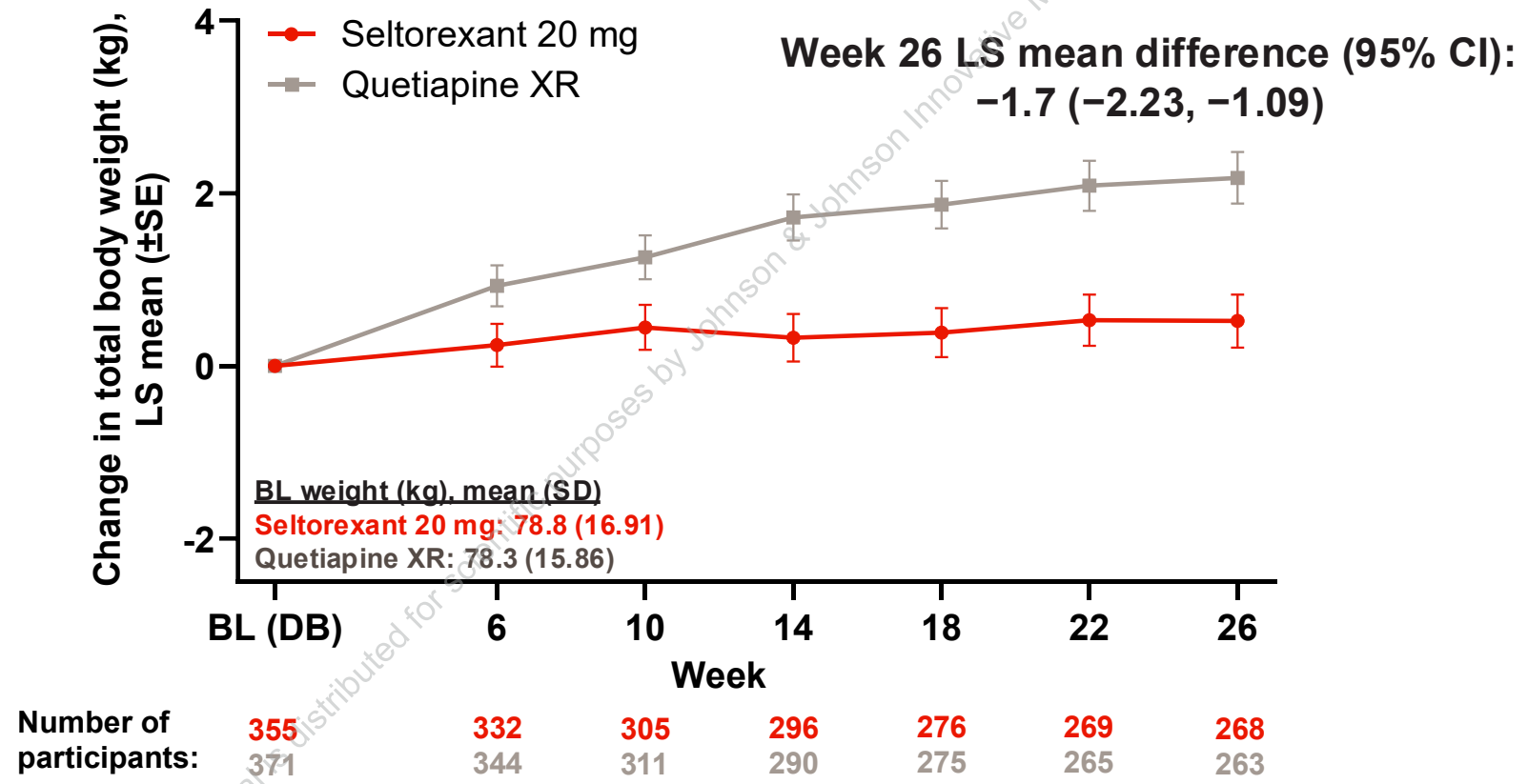
Study 2: Seltorexant was associated with less total body weight change compared with quetiapine XR

Change from baseline over time in total body weight (secondary analysis set)



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Secondary analysis set consists of all randomized participants who received ≥1 dose of study intervention and had baseline MADRS total score ≥24. 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.

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Study 2: Safety was generally favorable with seltorexant treatment compared with quetiapine XR

Overall summary of TEAEs (safety analysis set)

	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 drug discontinuation, n (%)	21 (5.7)	44 (11.3)
Related TEAEs leading to study drug 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)

Overall TEAE rates and TEAEs leading to discontinuation of study drug were lower for seltorexant vs quetiapine XR

>2× as common with quetiapine XR vs seltorexant

Safety analysis set consists of all randomized participants who received ≥1 dose of study intervention. Incidence is based on the number of participants experiencing ≥1 TEAE, not the number of events. [a]TEAEs assessed by the investigator as related to study drug. TEAE, treatment-emergent adverse event; XR, extended release.

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Conclusions

Study 1

- In the 6-week DB phase, adjunctive seltorexant demonstrated statistically and clinically significant improvement in depressive symptoms, beyond improvement of insomnia symptoms, in participants with MDD with IS experiencing an inadequate response to current antidepressant therapy.
  - The safety and tolerability profile of seltorexant in participants with MDD was similar to that of placebo, with a high study completion rate.
- In the 52-week OLE, adjunctive seltorexant was well tolerated in participants with MDD with a high study completion rate, and no new safety concerns were identified.
  - Large proportion of participants continued to show progressively accruing improvement.

Study 2

- Seltorexant and quetiapine XR demonstrated comparable, robust MADRS response at Week 26 with a numerically greater response rate observed with seltorexant.
  - Seltorexant showed a decrease in depression symptoms that was comparable to that of quetiapine XR.
- Seltorexant showed less total body weight change compared with quetiapine XR, along with fewer TEAEs, less somnolence, and more participants completing the 26-week period.

DB, double-blind; IS, insomnia symptoms; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OLE, open-label extension; TEAE, treatment-emergent adverse event; XR, extended release.

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