Metabolic Profiles of Participants With Major Depressive Disorder with Insomnia Symptoms in a Phase 3 Trial of Seltorexant Versus Quetiapine Extended Release as Adjunctive Therapy

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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 prevalent among approximately two-thirds of those with depression and may exacerbate the clinical presentation of MDD.[1,2]
- Use of quetiapine extended release (XR) or other atypical antipsychotics as adjunctive therapy is common not only in cases of inadequate improvement in depressive symptoms but also in the presence of clinically relevant IS in MDD patients.
  - However, this class of atypical antipsychotics has tolerability issues associated with metabolic changes or weight change that may lead to non-adherence.
- Seltorexant is a first-in-class, selective, high-affinity, orexin-2 receptor antagonist being developed for the treatment of MDD with IS.
- A global, 26-week, double-blind, phase 3, randomized controlled trial (NCT04513912) of seltorexant with quetiapine XR as a comparator, both adjunctive to standard antidepressants, in participants with MDD with IS who had responded inadequately to antidepressant therapy found:
  - Seltorexant resulted in similar Montgomery-Åsberg Depression Rating Scale response rates (primary endpoint) as quetiapine XR.
  - Seltorexant resulted in fewer treatment-emergent adverse events and a higher completion rate than quetiapine XR.
- Here we present the metabolic profiles of participants with MDD with IS who received adjunctive seltorexant vs adjunctive quetiapine XR treatment from the NCT04513912 trial.

Methods

- NCT04513912 included participants aged 18–74 years with a Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnosis of MDD without psychotic features, with IS, and an inadequate response to 1–2 antidepressants at adequate dose and duration in the current depressive episode.
- Participants with Type 1 or 2 controlled diabetes mellitus at screening (hemoglobin A1C [HbA1C] ≤8.5% and glucose ≤150 mg/dL) were eligible if otherwise medically stable, and if on a stable regimen of glucose-lowering medications for ≥2 months prior to screening.
- Participants were randomized 1:1 to receive oral seltorexant 20 mg or quetiapine XR (flexible, labeled dosage) for 26 weeks while continuing their background SSRI/SNRI.
- Total body weight (key secondary endpoint), fasting insulin, fasting glucose, and HbA1C values were measured, along with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score, calculated as fasting insulin x fasting glucose / 22.5 (where fasting glucose >3.5 mmol/L).
  - Low (<1.9) and high (≥2.9) HOMA-IR values imply insulin sensitivity and significant insulin resistance, respectively.
- Subgroup analyses of change from baseline at Week 26 in HOMA-IR and fasting insulin in participants with diabetes (HbA1C ≥6.5%, or fasting glucose >7 mmol/L, or non-fasting glucose ≥11.1 mmol/L, or there is a reported medical history of diabetes), obesity (body mass index [BMI] ≥30 kg/m^2), or HOMA-IR ≥2.9 at baseline were explored.

Results

- Of 757 participants randomized, 756 received ≥1 dose of study intervention (**Table 1**).
- BMI categories and other baseline metabolic characteristics were well balanced across treatment groups.
- ~70% of participants had at least one of the following baseline characteristics: a. diabetes, b. overweight/obese, or c. HOMA-IR ≥2.9.

TABLE 1: 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)
HbA1C, %, mean (SD)	5.5 (0.6)	5.4 (0.5)[a]	5.5 (0.5)
HOMA-IR ≥2.9, n (%)	104 (28.4)	107 (27.4)	211 (27.9)
Diabetes,[b] n (%)	39 (10.7)	27 (6.9)	66 (8.7)
Metabolic and lipid-management pharmacotherapies, n (%)	29 (7.9)	16 (4.1)	45 (6.0)
BMI (kg/m^2) category, n (%)			
Underweight/ normal, <18.5–<25	125 (34.2)	132 (33.8)	257 (34.0)
Overweight, 25–<30	110 (30.1)	129 (33.1)	239 (31.6)
Obese, ≥30	131 (35.8)	129 (33.1)	260 (34.4)

Safety analysis set includes all randomized participants who received ≥1 dose of study intervention. [a]n=389. [b]HbA1C ≥6.5%, or fasting glucose >7 mmol/L, or non-fasting glucose ≥11.1 mmol/L, or there is a reported medical history of diabetes. BMI, body mass index; HbA1C, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; SD, standard deviation; XR, extended release.

Weight

- Less total body weight change occurred with seltorexant vs quetiapine XR treatment (**Figure 1**; nominal 2-sided p<0.001).
  - Weight change with seltorexant treatment was comparable to that observed in long-term studies of SSRIs.[3,4]
- Weight change at Week 26 was generally observed in all BMI subgroups (**Figure 2**).
  - However, mean increases in total body weight were numerically lower for seltorexant than for quetiapine XR (**Figure 2**).

Metabolic profile

- In participants with diabetes, obesity, or HOMA-IR ≥2.9 at baseline, HOMA-IR (**Figure 3** and **Table 2**) and fasting insulin levels (**Figure 4**) displayed a trend towards improvement from baseline after seltorexant treatment, while a trend towards worsening was observed with quetiapine XR treatment.

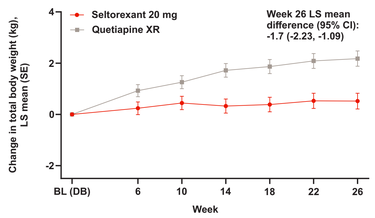
Metabolic profile (cont'd)

- Over 26 weeks, both the seltorexant and quetiapine XR groups showed shifts in HOMA-IR.
  - Among participants with baseline HOMA-IR <1.9, 11.9% (n=14) in the seltorexant group and 14.7% (n=17) in the quetiapine XR group progressed to HOMA-IR ≥2.9.
  - Conversely, among those with baseline HOMA-IR ≥2.9, 32.9% (n=23) in the seltorexant group and 17.2% (n=11) in the quetiapine XR group improved to HOMA-IR <1.9.
- No clinically relevant differences in mean glucose or HbA1C levels at Week 26 were observed between treatment groups, which may be attributed to the fact that most participants had baseline HbA1C values within the target range set by the study entrance criteria, and glycemic control was already optimized in those with diabetes.

Limitations

- Although fasting was required for insulin and glucose measurements, we could not confirm that all participants indeed fasted before blood was collected for analysis.

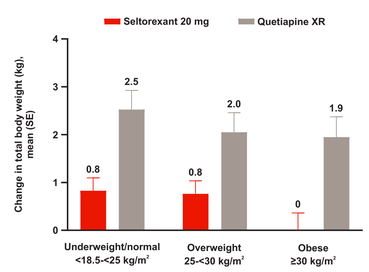
FIGURE 1: Change from baseline over time in total body weight (kg) (secondary analysis set)



No. of participants:	355	332	305	296	276	269	268
	371	344	311	290	275	265	263

Secondary analysis set consists of all randomized participants who received ≥1 dose of study intervention and had baseline Montgomery-Åsberg Depression Rating Scale total score ≥24. Based on mixed model for repeated measures observed case. BL, baseline; CI, confidence interval; DB, double-blind; LS, least squares; SE, standard error; XR, extended release.

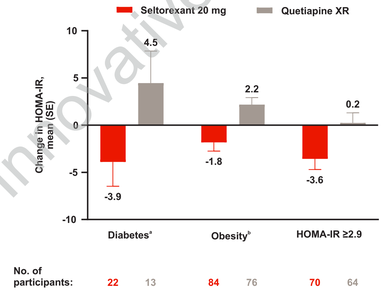
FIGURE 2: Change from baseline at Week 26 in total body weight (kg) by baseline body mass index category (safety analysis set)



No. of participants:	103	90	79	91	97	93

Safety analysis set includes all randomized participants who received ≥1 dose of study intervention. Based on mixed model for repeated measures observed case. SE, standard error; XR, extended release.

FIGURE 3: Change from baseline at Week 26 in HOMA-IR in participants with diabetes, obesity, or HOMA-IR ≥2.9 at baseline (safety analysis set)



No. of participants:	22	13	84	76	70	64

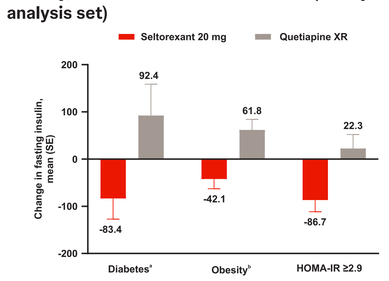
Safety analysis set includes all randomized participants who received ≥1 dose of study intervention. [a]HbA1C ≥6.5%, or fasting glucose >7 mmol/L, or non-fasting glucose ≥11.1 mmol/L, or there is a reported medical history of diabetes. [b]≥30 kg/m^2. HbA1c, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; SE, standard error; XR, extended release.

TABLE 2: HOMA-IR geometric means at baseline and Week 26 in participants with diabetes, obesity, or HOMA-IR ≥2.9 at baseline (safety analysis set)

HOMA-IR[a]	Seltorexant 20 mg n=366	Quetiapine XR n=390
Diabetes[b]		
Baseline	4.48 (1.92, 10.46); n=39	5.59 (2.23, 13.99); n=26
Week 26	3.53 (1.64, 7.62); n=22	8.40 (2.99, 23.63); n=14
Obesity[c]		
Baseline	3.25 (1.38, 7.66); n=127	2.85 (1.36, 6.01); n=123
Week 26	2.84 (1.41, 5.72); n=85	3.82 (1.56, 9.35); n=78
HOMA-IR ≥2.9		
Baseline	5.56 (2.92, 10.58); n=104	5.17 (2.87, 9.32); n=107
Week 26	3.02 (1.39, 6.56); n=70	4.03 (1.67, 9.72); n=64

Safety analysis set includes all randomized participants who received ≥1 dose of study intervention. [a]Expressed as: geometric mean (exp(mean(logs) - 1*SD(logs)), exp(mean(logs) + 1*SD(logs))). [b]HbA1C ≥6.5%, or fasting glucose >7 mmol/L, or non-fasting glucose ≥11.1 mmol/L, or there is a reported medical history of diabetes. [c]≥30 kg/m^2. HbA1c, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; SD, standard deviation; XR, extended release.

FIGURE 4: Change from baseline at Week 26 in fasting insulin in participants with diabetes, obesity, or HOMA-IR ≥2.9 at baseline (safety analysis set)



No. of participants:	22	13	86	77	71	65

Safety analysis set includes all randomized participants who received ≥1 dose of study intervention. [a]HbA1C ≥6.5%, or fasting glucose >7 mmol/L, or non-fasting glucose ≥11.1 mmol/L, or there is a reported medical history of diabetes. [b]≥30 kg/m^2. HbA1c, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; SE, standard error; XR, extended release.

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Key takeaway

Seltorexant showed overall less total body weight change and more favorable trends in insulin resistance in participants with metabolic risk. Therefore, this might be an attractive long-term adjunctive treatment compared with antipsychotics in patients with underlying risk factors.

Conclusion

- Change in body weight was more limited after 26 weeks of treatment with seltorexant as compared with quetiapine XR.
- In participants who had either diabetes, or were obese, or had HOMA-IR ≥2.9 at baseline, HOMA-IR and insulin levels displayed a trend towards improvement from baseline after seltorexant treatment, while a trend towards worsening was observed with quetiapine XR treatment.
- Shifts in HOMA-IR and fasting insulin levels in the absence of significant changes in fasting glucose or HbA1C levels suggest seltorexant may be associated with a lower risk of worsening and a higher likelihood of improving insulin sensitivity, warranting further investigation.
- Many participants in this trial had either diabetes, or were overweight/obese, or showed significant insulin resistance at baseline, highlighting an unmet need for adjunctive treatment options that are better tolerated, and less likely to contribute to weight gain or insulin resistance in MDD.

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Disclosures

Gahan Pandina, Sofie Mesens, Lu Xia, Ewa Wajs, Joseph M. Trombello, Ryan Kelly, Yun Zhang, Haiyan Xu, 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. **Previously presented at:** 64th Annual Meeting of the American College of Neuropsychopharmacology (ACNP); Nassau, Bahamas; January 12–15, 2026.

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