Orforglipron: Does menopausal status really matter for weight loss?

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Menopause brings estrogen deficiency that can worsen obesity, raising a practical question for any weight-management therapy: does it work as well regardless of a woman's menopausal stage, or does its effect fade with the hormonal shift? A post-hoc analysis presented at the EASD Annual Meeting in Milan tests this directly for orforglipron, Eli Lilly's oral, small-molecule, non-peptide GLP-1 receptor agonist, using data from the ATTAIN-1 and ATTAIN-2 trials.

KEY TAKEAWAYS

- The Pivot: Orforglipron's weight-loss effect did not fade with menopausal transition, benefits were consistent whether women were pre-, peri- or post-menopausal.
- The Data: Body weight reductions ranged 8.9-14.4% with orforglipron across menopausal subgroups and both trials, against 0.3-2.9% with placebo, all statistically significant.
- The Action: Menopausal status should not factor into expectations of orforglipron's efficacy for weight management, based on this subgroup data.

The analysis included female participants with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) plus at least one obesity-related complication, drawn from ATTAIN-1 (participants without diabetes) and ATTAIN-2 (participants with type 2 diabetes). Women were grouped by menopausal status, pre-, peri- or post-menopause, and changes in body weight (BW), waist circumference (WC) and waist-to-height ratio (WHtR) at 72 weeks were compared between orforglipron 36mg and placebo within each subgroup.

Weight loss held up regardless of menopausal stage

Across both studies and all three menopausal subgroups, orforglipron produced significantly greater reductions in body weight, up to 13.5%, and waist circumference, up to 11cm, than placebo ($p<0.003$ throughout). Up to 83% of participants on orforglipron achieved at least a 5% body weight reduction, against roughly 30% on placebo. More orforglipron-treated participants also moved into a lower, healthier waist-to-height ratio category than those on placebo.

The numbers, study by study

In ATTAIN-1, at 72 weeks, orforglipron produced body weight reductions of 12.81% (pre-menopausal), 14.38% (peri-menopausal) and 14.07% (post-menopausal), against placebo reductions of 0.25%, 1.02% and 0.62% respectively ($p<0.001$ for all three). The proportion achieving at least 5% weight loss was 80.34%, 80.89% and 82.72% with orforglipron, against 19.51%, 25.46% and 22.94% with placebo.

In ATTAIN-2, which enrolled participants with type 2 diabetes, orforglipron produced body weight reductions of 11.30%

(pre-menopausal, p<0.05), 8.88% (peri-menopausal, p<0.001) and 13.62% (post-menopausal, p<0.001), against placebo reductions of 2.88%, 1.57% and 2.00%. At least 5% weight loss was achieved by 79.46%, 67.09% and 81.56% on orforglipron, against 30.04%, 20.13% and 26.98% on placebo.

These findings underscore the consistent efficacy of orforglipron across the menopausal spectrum, suggesting that hormonal fluctuations associated with menopause do not significantly impede its weight loss benefits. The magnitude of weight reduction observed in both ATTAIN-1 and ATTAIN-2, particularly the high proportion of participants achieving clinically meaningful weight loss (5%), highlights orforglipron's potential as a robust therapeutic option for women with obesity or overweight, irrespective of their menopausal status.

Beyond body weight, the consistent reductions in waist circumference and improvements in waist-to-height ratio are particularly relevant. Central adiposity, often measured by these metrics, is a strong predictor of cardiometabolic risk, including type 2 diabetes, cardiovascular disease, and certain cancers. The ability of orforglipron to favorably impact these parameters across all menopausal groups suggests a broader metabolic benefit that extends beyond simple weight loss, potentially contributing to improved long-term health outcomes for these patients.

Clinical Implications for Women's Health and Weight Management

The consistent efficacy of orforglipron across pre-, peri-, and post-menopausal women carries significant clinical implications for managing obesity and overweight, particularly given the unique challenges women face throughout their reproductive lifespan. Weight gain is a common concern during the menopausal transition, often attributed to hormonal shifts, changes in body composition, and lifestyle factors. This study provides compelling evidence that orforglipron offers a reliable and effective treatment option that is not attenuated by these physiological changes.

For pre-menopausal women, early intervention with effective weight management strategies can mitigate the long-term risks associated with obesity, including infertility, polycystic ovary syndrome (PCOS), and complications during pregnancy. The ATTAIN-1 data, showing substantial weight loss in this group, supports the use of orforglipron as a proactive measure. For peri-menopausal women, who often experience increased visceral fat accumulation and metabolic dysregulation, the observed benefits in both weight and waist circumference are particularly pertinent, offering a tool to counteract these adverse shifts. Finally, for post-menopausal women, who face heightened risks of cardiovascular disease, type 2 diabetes, and sarcopenia, the sustained weight loss and improvements in body composition provided by orforglipron could play a crucial role in reducing morbidity and improving quality of life. This consistency across groups simplifies treatment decisions for clinicians, as menopausal status does not appear to necessitate a differential approach to prescribing orforglipron for weight management.

However, it is important to acknowledge that while the study demonstrates consistent efficacy, it does not delve into potential differences in side effect profiles or patient adherence across menopausal groups. Future research could explore

whether specific menopausal stages are associated with variations in tolerability or treatment persistence, which could further refine clinical guidance. Additionally, the long-term impact of orforglipron on menopausal symptoms, bone density, or other hormone-related health outcomes was not a primary endpoint of these trials and warrants further investigation. While the ATTAIN studies provide robust short-to-medium term data, the sustained efficacy and safety beyond 72 weeks, particularly in diverse real-world populations, will be critical for fully understanding its role in chronic weight management.

Ultimately, these findings empower healthcare professionals to confidently consider orforglipron as a viable and effective treatment option for women with obesity or overweight, regardless of their menopausal status. The observed reductions in body weight and central adiposity offer a significant therapeutic advantage, providing a consistent pathway to improved metabolic health and reduced obesity-related complications across a woman's adult life. Clinicians should discuss these benefits with eligible patients, emphasizing the potential for substantial and sustained weight loss, alongside the importance of a comprehensive weight management plan that includes lifestyle modifications.

CLINICAL IMPLICATIONS

For clinicians managing obesity or overweight in women around the menopausal transition, this post-hoc analysis suggests menopausal stage is not a reason to expect a diminished response to orforglipron. The peri-menopausal ATTAIN-2 result (8.88% versus 1.57% for placebo) was the smallest of the six subgroup comparisons but was still highly significant and clinically meaningful.

As a post-hoc subgroup analysis rather than a pre-specified primary endpoint, this data is hypothesis-generating rather than definitive, subgroup sizes varied considerably (ATTAIN-2's pre-menopausal orforglipron arm had only 10 participants), and the trials were not powered to detect differences between menopausal subgroups. The consistency of direction and significance across both trials and all three subgroups is reassuring, but the smaller subgroups carry wider uncertainty than the headline numbers suggest.

Orforglipron is not yet approved; ATTAIN-1 and ATTAIN-2 are part of its ongoing phase 3 programme. This analysis does not address long-term durability beyond 72 weeks or outcomes after treatment discontinuation.

REFERENCES

1. Ciudin Mihai A, Tchang BG, Balmain AJ, Klise S, Mojdami D, Ye WW, Mi X, Hoffmann H. Menopausal stage and weight outcomes with orforglipron vs placebo: post-hoc subgroup analysis from ATTAIN-1 and ATTAIN-2. Presented at the European Association for the Study of Diabetes (EASD) Annual Meeting, Milan, Italy, 27 September-2 October 2026.

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