In Global Obesity Trial Daily Orforglipron GLP-1 Pill Achieves Over 11% Weight Loss

An international team of researchers evaluated the efficacy and safety of once-daily oral orforglipron versus placebo over 72 weeks in adults with obesity without diabetes mellitusv.

Study

This phase 3, multinational, randomized, double-blind, placebo-controlled ATTAIN-1 trial enrolled adults with obesity at 137 sites in nine countries.

Eligible participants had a body-mass index (BMI) ≥30, or BMI 27 to <30 with at least one complication (hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea). Key exclusions included diabetes mellitus and a weight change of more than 5 kg within 90 days.

Randomization (3:3:3:4) assigned orforglipron 6 mg, 12 mg, 36 mg, or placebo once daily, with dose escalation from 1 mg at baseline to the assigned dose (weeks 8, 12, and 20 milestones). All participants received individualized lifestyle counseling on maintaining a balanced diet and engaging in physical activity.

Stratification factors were country, sex, and prediabetes status (per American Diabetes Association (ADA) glycemic thresholds).

The primary endpoint was the percent change in body weight at week 72 using the prespecified treatment regimen estimand in the intention-to-treat population. The paper also reports an efficacy estimate that generally yields larger weight-loss estimates, underscoring the need for cautious cross-trial comparisons. Under this efficacy estimand, weight loss at week 72 was −7.8% (6 mg), −9.3% (12 mg), and −12.4% (36 mg), versus −0.9% with placebo.

Multiplicity-controlled key secondary endpoints included proportions achieving ≥5%, ≥10%, ≥15%, and for the 12 mg and 36 mg doses only, ≥20% weight loss; changes in waist circumference, systolic blood pressure, triglycerides, and non-high-density lipoprotein (HDL) cholesterol.

Additional measures included diastolic blood pressure, lipids (including low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL)), glycated hemoglobin (HbA1c), fasting glucose and insulin, high-sensitivity C-reactive protein (hs-CRP), and dual-energy x-ray absorptiometry (DXA) body composition in a subgroup.

Participants with prediabetes are continuing in an extension phase for up to two additional years; the current report covers 72 weeks for all patients. Analysis of covariance (ANCOVA) and logistic

regression were employed; missing data were imputed using the drop-out method. Safety analyses included all treated participants.

Findings

A total of 3127 participants were randomized (mean age, 45 years; 64.2% women; mean weight, 103.2 kg; mean BMI, 37.0). Baseline characteristics were balanced across groups, with 36.0% of participants having prediabetes.

Trial completion reached 85.1% overall, ranging from 80.9% (placebo) to 87.5% (orforglipron 36 mg). Treatment persistence through 72 weeks was higher with orforglipron than placebo.

At week 72, mean percent weight change (treatment-regimen estimand) was −7.5% (95% confidence interval (CI), −8.2 to −6.8) with 6 mg, −8.4% (95% CI, −9.1 to −7.7) with 12 mg, and −11.2% (95% CI, −12.0 to −10.4) with 36 mg, versus −2.1% (95% CI, −2.8 to −1.4) with placebo.

All orforglipron doses were superior (estimated treatment difference (ETD) vs placebo: −5.5, −6.3, and −9.1 percentage points, respectively; P<0.001).

Clinically relevant thresholds were met more often with orforglipron: ≥10% weight loss occurred in 33.3% (6 mg), 40.0% (12 mg), and 54.6% (36 mg), compared to 12.9% with placebo (P < 0.001).

In the 36-mg group, 37.3% achieved BMI <30 and 11.1% achieved BMI <25, compared with 15.7% and 0.9% with placebo.

Adjudicated major adverse cardiovascular events were uncommon across groups; three deaths occurred during the 72 weeks (two in orforglipron groups and one in placebo), without a pattern suggesting drug causality.

Weight loss at 72 weeks was similar to that observed at 36 weeks in an earlier phase 2 trial, suggesting a potential plateau effect over time.

Conclusion

Once-daily oral orforglipron produced statistically significant and clinically meaningful, dose-dependent weight loss over 72 weeks, with broad improvements in cardiometabolic risk factors, favorable body-composition changes, and a safety profile aligned with GLP-1 RAs.

Benefits extended to blood pressure, lipids (including non-HDL and LDL cholesterol), glycemia, and hs-CRP, with higher normoglycemia rates among those with prediabetes.

Gastrointestinal events were the most frequent adverse effects and were typically mild to moderate.

The magnitude of weight loss was lower than that typically reported with weekly injectable semaglutide or tirzepatide; yet, biomarker improvements were broadly similar, highlighting the clinical relevance of achieving at least a 10% weight reduction.

These findings support oral GLP-1 RA therapy as a practical option for adults with obesity who prefer pills or lack access to injections. Key limitations include the absence of an active comparator and BMI inclusion cutoffs that may not optimally reflect adiposity-related risk across all ancestries.

Further research is needed to confirm long-term outcomes and safety across diverse populations.

Source:

https://www.news-medical.net/news/20250918/Daily-orforglipron-GLP-1-pill-achieves-over-1125-weight-loss-in-global-obesity-trial.aspx