RESEARCH SUMMARY

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Jastreboff AM et al. DOI: 10.1056/NEJMoa2301972

CLINICAL PROBLEM

Obesity is projected to affect nearly one quarter of the world population by 2035. Retatrutide, a single peptide with agonism toward three receptors — the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors — showed promise for weight reduction in an early trial involving patients with type 2 diabetes, but its effects in patients without diabetes are unknown.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of retatrutide in adults without diabetes but with obesity or overweight plus ≥1 weight-related condition.

Intervention: 338 adults 18 to 75 years of age with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 to 50 or a BMI of 27 to <30 plus ≥1 weight-related condition were assigned to receive subcutaneous retatrutide with the dose adjusted to reach one of four maintenance doses or placebo once weekly for 48 weeks. All participants also took part in a lifestyle intervention. The primary end point was the percentage change in weight from baseline to 24 weeks.

RESULTS

Efficacy: The percentage change in weight at 24 weeks at all doses of retatrutide was greater than that with placebo. Weight loss with retatrutide was dose-dependent, with weight decreasing further by week 48.

Safety: Gastrointestinal adverse events occurred substantially more often with retatrutide than with placebo; these events were usually mild to moderate in severity and were more common at higher doses of retatrutide.

LIMITATIONS AND REMAINING QUESTIONS

- Participants were all from the United States, and 88% were White.
- Because only 4% of the participants had overweight (BMI, 27 to <30) plus an obesity-related condition, the results may not be generalizable to this population.

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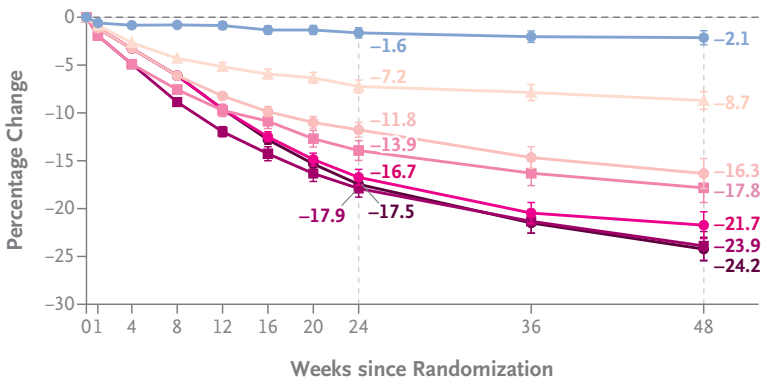
Changes in Body Weight



Adverse Events

Events	Assigned Maintenance						
	Placebo (N=70)	1 mg (N=69)	4 mg ID, 2 mg (N=33)	4 mg ID, 4 mg (N=33)	8 mg ID, 2 mg (N=35)	8 mg ID, 4 mg (N=35)	12 mg ID, 2 mg) (N=62)
Nausea	8 (11)	10 (14)	6 (18)	12 (36)	6 (17)	21 (60)	28 (45)
Diarrhea	8 (11)	6 (9)	4 (12)	4 (12)	7 (20)	7 (20)	9 (15)
Vomiting	1 (1)	2 (3)	4 (12)	4 (12)	2 (6)	9 (26)	12 (19)
Constipation	2 (3)	5(7)	5 (15)	2 (6)	4 (11)	4 (11)	10 (16)
Antidrug antibodies during treatment	1(1)	3(4)	4 (12)	5 (16)	5 (16)	2 (6)	11 (18)

Data are number of participants (percent). Data on antidrug antibodies were missing for 10 patients.

CONCLUSIONS

In adults with obesity without diabetes, once-weekly treatment with subcutaneous retatrutide led to substantial, dose-dependent reductions in weight at 24 and 48 weeks.