Wegovy: Already Obsolete?

SCIENCE IN BRIEF

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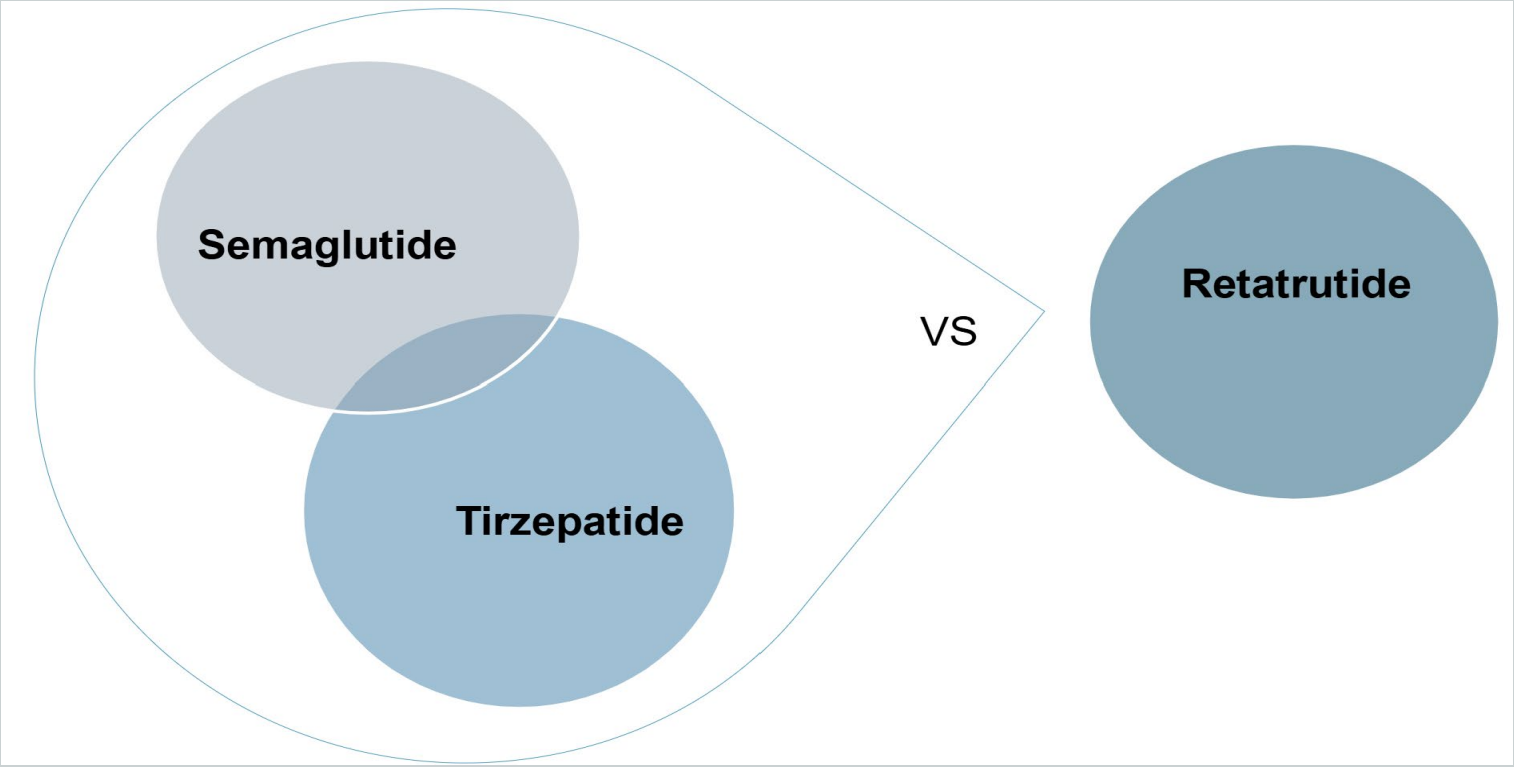


Retatrutide – Incredible Weight Loss

The novel incretin-based therapies Wegovy® (semaglutide) and Zepbound® (tirzepatide) have revolutionized weight management care. Semaglutide targets the glucagon-like-peptide-1 (GLP-1) receptor, while tirzepatide and VK2735 target GLP-1 and the glucose-dependent insulinotropic (GIP) receptor. These agents have shown weight loss benefits in large phase 2 and 3 trials. A new agent, retatrutide a GLP-1/GIP and glucagon (GCG) receptor agonist, has shown weight loss comparable to bariatric surgery. Policymakers, payors, healthcare providers, and patients are eager to know the results of the phase 3 trials of retatrutide.

KEY MESSAGES

- Semaglutide has shown an average weight loss of 14.9% of bodyweight at 52-weeks
- Tirzepatide has shown an average weight loss of 18.5% of bodyweight at 72-weeks
- VK2735 showed an average weight loss of 14.7% of bodyweight at 13-weeks
- Retatrutide recently showed an average weight loss of 24.2% of bodyweight at 48-weeks
- Retatrutide weight loss had not plateaued at the end of the trial period
- Retatrutide's results were comparable to that of bariatric surgery
- The future of incretin-based therapies looks incredibly compelling

ABOUT THE BRIEF

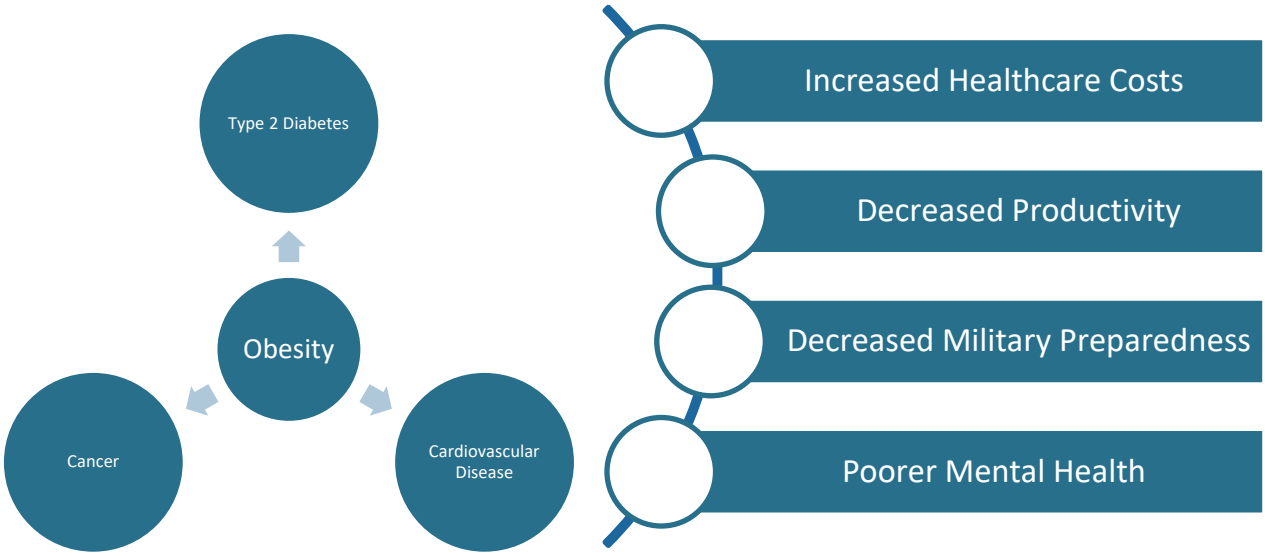
This science brief reviews the reviews the work by Jastreboff AM, Kaplan LM, Frías JP-Triple-Hormone Receptor Agonist Retatrutide for Obesity – A Phase 2 Trial, August 2023. This brief is. The review appraises findings from their research on the weight loss benefits of retatrutide and its potential superiority over comparable agents. This brief describes some of the conclusions and implications for practice.

BACKGROUND

The obesity epidemic in America has been rapidly expanding. The prevalence of obesity has increased from 30.5% in 2000 to 41.9% in 2017.[1] Obesity can lead to other diseases, such as type 2 diabetes, cardiovascular disease, and some cancers, which are among the leading causes of premature death in the United States.[2] Also, obesity is estimated to cost nearly $180 billion in 2020, and the medical costs for patients with obesity were nearly $1,900 more than for patients with a healthy weight.

Novel medications have been developed to try to aid patients in weight loss. Wegovy® (semaglutide)[3], Zepbound (tirzepatide)[4], and VK2735[5] have shown weight loss of ~15-18% of body weight in phase 2 and 3 clinical trials. Thus, pharmacological treatment of obesity is now a reality. Retatrutide is a novel weight loss medication targeting three receptors instead of one or two. The phase 2 trial results of retuatrutide were compelling, with an average weight loss of 24.2% of body weight at 48 weeks, and the weight loss had yet to plateau. These results appear as efficacious as bariatric surgery.

UNDERSTANDING THE COSTS AND CONSEQUENCES OF OBESITY



CURRENT STATE: GLP-1 AND GLP-1/GIP AGONISTS

Wegovy® (semaglutide) has revolutionized weight management care for patients. Wegovy is a glucagon-like-peptide-1 (GLP-1) receptor agonist that helps lower blood glucose levels via stimulation of insulin production and secretion from pancreatic beta-cells and reducing glucagon production from pancreatic alpha-cells. It also slows the emptying of the stomach. In phase 3, double-blind, placebo-controlled, STEP-1 trial, adult patients with a body-mass index (BMI) of 30 or greater who did not have diabetes, the mean change in body weight from baseline to week 68 was -14.9% with semaglutide compared to -2.4% with placebo with approximately 86.5% of patients having a 5% weight reduction or more.[5] These incredible results have moved the utilization of GLP-1 receptor agonists into weight management clinics across the globe. However, newer technologies are already being developed that may make the single mechanism GLP-1 receptor agonists obsolete.

Zepbound® (tirzepatide) is a dual agonist at both the glucose-dependent insulinotropic (GIP) receptor as well as GLP-1. The addition of GIP to GLP-1 receptor agonism is thought to act synergistically to enhance appetite suppression, energy intake, and metabolic function. In phase 3, randomized, placebo-controlled, multinational, SURMOUNT-3 trial consisting of adult patients with a BMI of 30 or greater who did not have diabetes, the mean change in body weight from baseline to week 72 was -18.4% compared to -2.5% with placebo.[7] Approximately 87.5% of patients had a 5% or greater weight reduction. Thus, tirzepatide showed enhanced weight loss compared to semaglutide, though cross-trial comparisons are difficult to quantify.

The technological advancement of targeting GLP-1 and alternative receptors is advancing rapidly. A competitor to tirzepatide, VK2735, which is being studied as a subcutaneous injection as well as an oral pill, recently had phase 2 clinical data presented, showing a 14.7% reduction in body weight at 13 weeks. However, the trial has not yet been published. The effects suggested at the press briefing are comparable to those seen with semaglutide and tirzapetide. An oral agent could also be appealing to patients unable to or afraid of sticking themselves with needles as well, which is currently not an option for obese patients.

RETATRUTIDE

Retatrutide is a triple agonist of GLP-1, GIP, and glucagon (GCG) receptor. The prevailing theory is that multi-receptor agonism will lead to synergistic effects to better control appetite, energy intake, utilization, and metabolic function. The results of a recently published phase 2, double-blind, randomized, placebo-controlled study of retatrutide at various doses in patients with a BMI of 27 to >30 or >= 30 with at least one weight-related condition. All 338 patients were randomized to various doses of retatrutide with a minimum dose of 1 mg weekly to a maximum of 12 mg weekly or placebo.[8]

At 24 weeks the 1-mg group showed a mean percentage change in weight of -7.2% while the 12-mg group showed -17.5%, and placebo produced a mean percentage change in weight of -1.6%. At 48 weeks, the 1-mg group had a mean percentage change in weight of -8.7%; the 12-mg group had a mean percentage change of -24.2% and the placebo had a mean percentage weight change of -2.1%. One of the most important factors when examining this study's results is that these weight decreases have yet to plateau – i.e., patients are still expected to lose weight while maintaining on treatment. The lack of a weight loss plateauing effect has not been seen with the current GLP-1 and GLP-1/GIP receptor agonists. Along with substantial weight loss, improvements in cardiometabolic measures were also seen. There were clinically significant waist circumference reductions, systolic and diastolic blood pressures, A1c reductions, fasting blood glucose

reductions, and lipid levels. In addition to these clinically significant cardiometabolic measurements, 72% of participants who had prediabetes reverted to normoglycemia with retatrutide treatment.

Side effects were generally reported as mild to moderate in severity, with the most common adverse events in the retatrutide group being gastrointestinal. The most common gastrointestinal adverse events were nausea, decreased appetite, diarrhea, vomiting, and constipation. The rates and severities were comparable to those seen with semaglutide and tirzepatide. Of note, the gastrointestinal side effects were higher in the higher dose groups and higher among patients who started with a higher initial dose than those who were titrated more slowly. This information will aid in refining the dose-escalation scheme for the phase 3 trial and improve the side-effect profile of retatrutide.

The strengths of this trial include that the study met predefined power, it had an extended duration of 48 weeks, the proportion of men to women was equal as previous trials of GLP-1 receptor agonists have shown that women may have a better response to therapy and that the trial population was ~35% Hispanic or Latino. Limitations include that the trial was only conducted in the United States, and only 4% of patients had a BMI of <30 with an obesity-related condition, so the results may not represent populations with lower BMI.

CONCLUSION

This phase 2 study will better inform the proper dosing and study design of the phase 3 trial of retatrutide. While only a phase 2 trial, the results are awe-inspiring and comparable to bariatric surgery- some patients hadn't even experienced a weight-loss plateau. The phase 3 trial should be multinational, leading to increased generalizability. However, the future of retatrutide looks bright.

One of the potential pitfalls of utilizing GLP-1 receptor agonists and GIP/GLP-1 receptor agonists is rebound weight gain once patients come off the medications. The SURMOUNT-4 trial was a phase 3 randomized withdrawal trial of tirzepatide. Patients received 36 weeks of tirzepatide and were subsequently randomized to continuation of tirzepatide or placebo.[9] At 88 weeks (the 36-week run-in period plus an additional 52 weeks of tirzepatide vs. placebo) the mean weight percentage change was -5.5% with tirzepatide vs. 14% with placebo. Thus, withdrawing tirzepatide led to a substantial regain of the lost weight, whereas continued maintenance treatment augmented initial weight reduction. This leads many to speculate that patients will be required to be on maintenance therapy their entire lifetime unless habits are changed and lifestyle modifications lead to the maintenance of weight targets. It remains to be seen if the "weight-rebound" effect will be similar to that of retatrutide, though the phase 3 trial should investigate this.

While semaglutide has been instrumental in weight management and potentially curtailing the current obesity epidemic, the novel, multi-receptor agent retatrutide appears to increase weight loss in patients compared to semaglutide. The comparative costs of these agents will most certainly need to be assessed. The fact that patients gain weight back once stopping semaglutide and tirzepatide, may require patients to be on maintenance dosing for the entirety of their life. It is still too early to see if retatrutide has a "weight-rebound."

Future areas of study should investigate if extending the interval between injections or if a lower dose during the maintenance phase can be utilized, leading to cost savings. Along with this, the concept of PEGylating these polypeptides may be investigated. PEGylating should increase the half-lives of the agents and thus increase the interval between injections from weekly to every other week or even greater.

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