## Retatrutide — Basic Review Questions

1. What class of medication is retatrutide, and what is its regulatory status?

Answer: Retatrutide (also called LY3437943) is a first-in-class "triple agonist" — it activates three receptors at once: GLP-1, GIP, and glucagon. That makes it the next step beyond drugs like semaglutide (a single GLP-1 agonist) and tirzepatide (a dual GLP-1/GIP agonist). It is given as a once-weekly subcutaneous injection. Importantly, unlike semaglutide and liraglutide, it is not FDA-approved — it is investigational, with Phase 2 trials completed and Phase 3 (the TRIUMPH program) ongoing.

2. How does retatrutide work, and why doesn't the glucagon component raise blood sugar?

Answer: It activates three gut/metabolic hormone receptors, each adding something different. The GLP-1 receptor provides glucose-dependent insulin release, appetite suppression, and slowed stomach emptying (the foundation shared with semaglutide). The GIP receptor improves insulin sensitivity and how fat cells handle lipids. The glucagon receptor is the differentiating third axis: it increases energy expenditure (thermogenesis), drives the liver to burn fat, and promotes fat breakdown — effects the other drugs do not have. Glucagon would normally raise blood sugar, but the GLP-1 and GIP effects counterbalance that, so no net glucose increase or severe hypoglycemia was seen in trials.

3. How does retatrutide cause weight loss, and why is it more powerful than the dual agonists?

Answer: Through multiple mechanisms layered together. Like the GLP-1 drugs, it reduces appetite (via brain satiety centers) and slows stomach emptying. But the added glucagon axis also raises the body's resting energy expenditure (burning more calories) and increases fat breakdown — so it produces both reduced intake and increased energy use. This combination is why, in trials, it produced more weight loss than the GLP-1-only and GLP-1/GIP drugs.

4. What were the key Phase 2 trial findings?

Answer: The Phase 2 results were striking. In obesity, retatrutide produced about 24% body-weight loss at 48 weeks (with no plateau yet at the trial's end) — exceeding the published results of every currently approved agent. In type 2 diabetes, it lowered HbA1c by about 2.16%, with roughly a third of patients reaching normal (non-diabetic) glucose levels. Most dramatic was the liver: in people with fatty liver disease it reduced liver fat by about 86%, with most achieving normal liver fat — the largest such reduction reported for any drug. The key caveat is that all of this is Phase 2 data (under 400 patients, 48 weeks or less); Phase 3 results are not yet available.

5. How does retatrutide compare with semaglutide, tirzepatide, and CagriSema?

Answer: It represents the latest step in a clear progression of adding receptor targets. Semaglutide is a single (GLP-1) agonist giving roughly 15% weight loss; tirzepatide is a dual GLP-1/GIP agonist giving around 21%; CagriSema (amylin plus GLP-1) gives about 23%; and retatrutide, the triple GLP-1/GIP/glucagon agonist, reached about 24%

in Phase 2. The important insight is that each added receptor is not just “more of the same” — it adds a qualitatively new effect (GIP adds fat-cell and insulin benefits, glucagon adds fat-burning and thermogenesis), and retatrutide’s liver-fat effect in particular outstrips the others. However, the others have completed Phase 3 trials and are approved, while retatrutide is still investigational.

6. How is retatrutide dosed, and what are the main cautions?

Answer: Because the effects are powerful, dosing starts low (1 mg weekly, which is already meaningfully effective) and escalates slowly over months, with most patients finding their effective dose around 4–8 mg rather than the 12 mg maximum; a target of about 0.5–0.75 lb/week helps preserve muscle. Two monitoring points are distinctive: the glucagon axis causes a dose-dependent rise in heart rate (peaking around 24 weeks), so heart rate needs watching, and because the weight loss is so large, bone density should be tracked. Standard incretin-class precautions also apply (medullary thyroid cancer history, pancreatitis, pregnancy), and because it is investigational, approved agents should remain first-line for anything they can adequately treat.