

Survodutide: Is 9.8% weight loss enough for its GI cost?

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Weight loss on incretin drugs is smaller in people with type 2 diabetes than in people without it, and survodutide is no exception. The full SYNCHRONIZE-2 results, published in the New England Journal of Medicine and presented at EASD 2026, show a mean loss of 9.8% at the higher dose over 76 weeks, with a clear gastrointestinal cost.¹

KEY TAKEAWAYS

- **The Pivot:** The glucagon and GLP-1 dual agonist survodutide produced significant weight loss in adults with obesity and type 2 diabetes over 76 weeks, but less than the 13.0% seen in people without diabetes.
- **The Data:** In 752 adults, mean weight change was -8.2% (3.6 mg), -9.8% (6.0 mg) and -3.9% (placebo), with HbA1c down 0.9, 0.8 and 0.2 points, and 26.4% and 25.9% on survodutide stopping because of adverse events versus 8.8%.
- **The Action:** Read the weight loss as comparable to semaglutide in indirect comparison, and note the gastrointestinal burden, the exclusion of insulin users and the pending cardiovascular outcomes trial before expecting a role in practice.

Survodutide is an investigational once-weekly dual agonist of the glucagon receptor and the GLP-1 receptor. The rationale is that GLP-1 agonism lowers energy intake and glucose, while glucagon receptor agonism also reduces intake and has lipolytic effects in the liver. The drug is about 8 times more potent at the GLP-1 receptor than at the glucagon receptor, which the authors say offsets any hyperglycaemic effect of glucagon. In the SYNCHRONIZE-1 trial in people without diabetes, the mean loss was 13.0%. See also our earlier coverage of survodutide in obesity and liver disease.¹

SYNCHRONIZE-2 was a 76-week, double-blind, placebo-controlled phase 3 trial at 133 sites in 19 countries, run from November 2023 to March 2026 and funded by Boehringer Ingelheim. It randomised 755 adults with type 2 diabetes and a BMI of 27 or more 1:1:1 to survodutide 3.6 mg, 6.0 mg or placebo, and 752 received at least 1 dose. Mean age was 55.7 years, mean BMI 36.5, mean HbA1c 7.4% and mean weight 104.1 kg, and 49.3% were men. All participants received dietitian counselling and a target calorie deficit of about 500 kcal a day.¹

The Numbers

The primary analysis used the treatment-regimen estimand, which counts everyone regardless of whether they stopped treatment or took other obesity drugs. Mean weight change at week 76 was -8.2% with 3.6 mg, -9.8% with 6.0 mg and -3.9% with placebo, so the differences from placebo were -4.3 and -5.9 percentage points (P1

The larger thresholds show how far the drug separates from placebo. A reduction of at least 10% occurred in 36.4%, 45.8% and 11.2%, at least 15% in 20.8%, 25.5% and 4.0%, and at least 20% in 10.4%, 11.2% and 1.6%. Under the efficacy estimand, which models full adherence and excludes prohibited medication, the mean losses were -10.4%, -13.1% and -3.1%, for differences of -7.4 and -10.0 percentage points. Confidence intervals for the efficacy estimand were not adjusted for multiplicity.¹

Glycaemic control improved modestly, which reflects a low starting point. HbA1c fell by 0.9 points with 3.6 mg, 0.8 with 6.0 mg and 0.2 with placebo from a baseline of 7.4%, differences of 0.7 and 0.6 points (P1

The authors place the result against semaglutide and tirzepatide trials in type 2 diabetes, while warning that trial designs differ. The 6.0 mg placebo-adjusted loss under the treatment-regimen estimand, 5.9 points, was similar to semaglutide's 6.2. Under the efficacy estimand, 10.0 points was numerically above semaglutide at 7.6, almost identical to tirzepatide 10 mg at 10.1 and below tirzepatide 15 mg at 12.4. No head-to-head trial exists, so these are context, not rankings.¹

Tolerability and the Limits of the Trial

Gastrointestinal events were the main cost. They occurred in 72.8% with 3.6 mg and 77.7% with 6.0 mg, against 38.6% with placebo. Nausea affected 47.6% and 57.4% versus 11.2%, and vomiting 34.4% and 39.0% versus 5.6%. These events were mostly mild to moderate and clustered during dose escalation, but 26.4% and 25.9% of survodutide patients stopped the trial drug because of an adverse event, compared with 8.8% on placebo. Serious adverse events were similar across groups at 9.2%, 8.4% and 10.8%.¹

The authors say the rates appear higher than with other GLP-1-based drugs and attribute part of the difference to a strict dose-escalation scheme. Flexibility was widened only in a protocol amendment, by which time most participants had no more than 3 months left on treatment. They suggest slower, more flexible escalation might reduce side effects and improve adherence, but that is a hypothesis this trial did not test. By week 76, 66.2% were still on their assigned treatment.¹

Other findings were reassuring but limited. There were no deaths during treatment, no adjudicated pancreatic or thyroid cancers, and 1 case of acute pancreatitis, in the placebo group. Two adjudicated major cardiovascular events occurred, both on 3.6 mg. Heart rate rose by 2.7 to 2.9 beats per minute, hypoglycaemia occurred in 8.0% and 9.2% versus 4.0% (one level 3 event, in a patient taking a sulfonylurea), and cholelithiasis in 0.4% and 1.6% versus none. Dizziness was more common at the higher dose, at 12.4% versus 3.2%.¹

The trial excluded people taking insulin and enrolled participants with fairly good control at baseline, so the results do not cover patients with more advanced diabetes. Black participants made up about 5% of each group. It was not designed to assess long-term cancer risk, and cardiovascular outcomes are being examined in the separate SYNCHRONIZE-CVOT trial. Medical writing support came from an agency, and Boehringer Ingelheim funded the study. Analogous trials of mazdutide and retatrutide in type 2 diabetes are also under way.¹

CLINICAL IMPLICATIONS

For clinicians, survodutide looks like another effective option for obesity in type 2 diabetes, not a leap beyond tirzepatide. A placebo-adjusted loss of 5.9 points under the primary estimand sits close to semaglutide in the authors' own comparison, and the drug is not approved. The case for it will depend on whether the glucagon component adds benefits beyond weight, particularly for liver disease, which affects about a third of people with type 2 diabetes and which earlier phase 3 data suggest it improves.

Tolerability is the practical sticking point. Around 3 in 4 patients had a gastrointestinal event and roughly 1 in 4 stopped treatment, 3 times the placebo rate. If slower titration closes that gap, as the authors suggest, the drug's profile would look different, but that needs testing. Patients on sulfonylureas should have doses reviewed, as the single severe hypoglycaemia event occurred in one.

The evidence still has holes. There are no insulin-treated patients, no cardiovascular outcome data yet, and the trial population had relatively well-controlled diabetes at baseline. The SYNCHRONIZE-CVOT results and the trials of other glucagon-based drugs will do more to settle where survodutide fits than this single study can.

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REFERENCES

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2. Presented at: European Association for the Study of Diabetes (EASD) Annual Meeting; September 28-October 2, 2026; Milan, Italy (session in Dublin Hall, October 1, 2026).

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