

Weekly Journal Scan

Is tirzepatide in the surpass lane over GLP-1 receptor agonists for the treatment of diabetes?

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The results of Efficacy and Safety of a Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide in Patients with type 2 Diabetes (SURPASS-1): A Double-Blind, Randomised, Phase 3 Trial have been published in *Lancet*. doi:10.1016/S0140-6736(21)01324-6.

Key Points

- SURPASS-1¹ is an industry-funded, double-blind, randomized, placebo-controlled, phase 3 trial of the dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, tirzepatide, in people with type 2 diabetes (T2DM) inadequately controlled by diet and exercise alone, naive to injectable diabetes therapy.
- After a 3-week screening or lead-in period, 478 participants (mean baseline glycated haemoglobin [HbA_{1c}] 7.9%, age 54 years, 48% women, diabetes duration 4.7 years, and body mass index 32 kg/m²) were randomly assigned (1:1:1) to once-a-week tirzepatide (5, 10, or 15 mg) as monotherapy, or placebo in a single-dose pen. Participants given tirzepatide followed a slow dose escalation regimen fixed at 2.5-mg dose increments of tirzepatide every 4 weeks until the maintenance dose was reached.
- The primary endpoint was the mean change in HbA_{1c} from baseline to 40 weeks. The study had at least 90% power to establish superiority for a tirzepatide dose compared with placebo at a two-sided significance level of 0.0167. The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.
- At 40 weeks, HbA_{1c} significantly decreased from baseline by a least squares mean (LSM) of −1.9% with tirzepatide 5 mg, −1.9% with 10 mg, and −2.1% with 15 mg, vs. +0.04% with placebo. An HbA_{1c} concentration of <7.0% was reached in 87–92% of participants with tirzepatide vs. 19% with placebo; an HbA_{1c} concentration of 6.5% or less was reached in 81–86% of participants with tirzepatide vs. 10% with placebo; and an HbA_{1c} concentration of <5.7% was reached in 31–50% of participants with tirzepatide vs. 1% with placebo. At 40 weeks, bodyweight significantly decreased from baseline by an LSM of −7.0 kg with tirzepatide 5 mg, −7.8 kg with 10 mg, and −9.5 kg with 15 mg, vs. −0.7 kg with placebo. The effect of tirzepatide on bodyweight was progressive and dose dependent.
- The most frequent adverse events with tirzepatide vs. placebo were mild-to-moderate gastrointestinal events, including nausea (12–18% vs. 6%), diarrhoea (12–14% vs. 8%), and vomiting (2–6% vs. 2%), a safety profile consistent with GLP-1 receptor agonists. Clinically significant or severe hypoglycaemia was not reported with tirzepatide. Sixty six (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. A greater number of study drug discontinuations were observed with tirzepatide 15 mg, and most discontinuations in the 15-mg group were for reasons other than adverse events.

Comment

Over the last few years, advances in peptide engineering have enabled the design of single agents possessing activity at more than one molecular target. Many of these were designed to activate G-protein-coupled receptors (GPCRs) that control glucose homeostasis and energy balance in the setting of obesity and T2DM. The most advanced

of these agents is the dual GIP receptor (GIPR) and GLP-1 receptor (GLP-1R) agonist, tirzepatide (LY3298176).² Combined activation of both receptors may act synergistically, thus providing additive effects on glycaemic control and body weight in comparison to GLP-1 analogues. Preclinical studies have confirmed that GIPR–GLP-1R co-agonists improve several hallmarks of the metabolic syndrome, such as obesity, hyperglycaemia, and dyslipidaemia.³ The incremental beneficial

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effects of this dual therapy can be explained by three main factors: (i) dual actions on pancreatic β cells to enhance insulin secretion, (ii) GIP-driven improvements in white adipose tissue function, and (iii) strong anorexigenic effect from integrating the activation signals of both receptor pathways in the brain.²

Clinical data from the SURPASS global clinical development program have shown consistent and statistically significant HbA_{1c} and body weight reductions vs. several comparators, including placebo (SURPASS-1),¹ the GLP-1R agonist semaglutide (SURPASS-2),⁴ and insulin degludec (SURPASS-3).⁵ In SURPASS-2,⁴ tirzepatide (5, 10, and 15 mg) was found noninferior and superior to semaglutide with respect to the mean change in the HbA_{1c} level from baseline to 40 weeks. Up to 92% of participants on tirzepatide achieved an HbA_{1c} of <7% and up to 51% achieved an HbA_{1c} <5.7%. In SURPASS-3,⁵ tirzepatide (at all doses) was superior to titrated insulin degludec, with greater reductions in HbA_{1c} and bodyweight at Week 52 and a lower risk of hypoglycaemia. Of note, tirzepatide showed a similar safety profile to that of GLP-1R agonists.

The SURPASS-1 trial is the first to show a highly favourable glucometabolic profile and suggests potential effects of tirzepatide in reducing cardiometabolic risk.¹ Although the study findings are overall robust, the study has some limitations including its short duration (i.e. participants who received the 15-mg dose were only exposed to this dose for 20 weeks, given the slow dose escalation schedule) and the fact that the gastrointestinal adverse events were self-reported. Taken together, data from SURPASS-1, -2, and -3 trials indicate that a therapeutic regimen based on dual GIP and GLP-1 receptor agonism might be superior to other glucose-lowering drugs (e.g. semaglutide) and confer more effective cardiovascular protection. Indeed—as compared to GLP-1R-based approaches—tirzepatide was more effective in lowering HbA_{1c}, fasting triglycerides, and blood pressure while improving insulin sensitivity (independent of bodyweight). Moreover, tirzepatide dose-dependently decreased levels of apoC-III and apoB and the number of large triglyceride-rich lipoprotein and LDL particle subfractions, suggesting an improvement in the atherogenic lipoprotein profile.⁶

These data provided the rationale for the design of the SURPASS-CVOT trial (NCT04255433, expected completion in 2024), which is

investigating the efficacy and safety of tirzepatide compared to the GLP-1R agonist dulaglutide in preventing major cardiovascular events in 12,500 participants with T2DM over a follow-up of 6 years. Should SURPASS-CVOT demonstrate that superiority of tirzepatide on pharmacodynamic endpoints translates into superiority on clinical endpoints; this finding may trigger a new wave of mechanistic opportunities for the management of cardiovascular risk in T2DM.

Conflict of interest: F.P. is the recipient of a H.H. Sheikh Khalifa bin Hamad Al Thani Foundation Assistant Professorship at the Faculty of Medicine, University of Zürich. C.P. received consultant and speaker fees from Acticor Biotech, Amgen, Bayer, Eli Lilly, GlaxoSmithKline, Tremereau, and Zambon and grant support (to the institution) for investigator-initiated research from AIFA (Italian Drug Agency), Bayer, Cancer Research UK, and European Commission; he chairs the Scientific Advisory Board of the International Aspirin Foundation.

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