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# Tirzepatide: Summary of the Emerging Data on the Novel GLP-1/GIP Dual Agonist

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## Introduction

The landscape for diabetes treatment is continuously evolving and the demand for medications that simultaneously manages multiple comorbidities, such as cardiovascular (CV) disease (CVD) and obesity, has become the mainstay in diabetes research. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-R) agonists (GLP-1RAs) have demonstrated additional benefits for patients with type 2 diabetes mellitus (T2DM), such as reducing body weight (BW), the risk of CV events, death in patients with established CVD, the risk of hospitalization for heart failure (HHF), and/or the risk of major adverse CV events (MACE) in patients with established CVD [1,2]. To meet this growing need for medications that may concurrently manage comorbid conditions associated with T2DM, new molecules are currently being developed and studied. One molecule, tirzepatide, a novel agent in the GLP-1R/glucose-dependent insulinotropic polypeptide (GIP) dual agonist class is currently under investigation by Eli Lilly and Company in subjects with T2DM, overweight or obese with weight-related co-morbidities, impaired liver function, and/or an increased CV risk.

### Mechanism of Action

Tirzepatide is a 39 amino acid peptide that has been modified to bind to both GIP and GLP-1Rs (GLP). Due to tirzepatide's dual mechanism, it activates GLP-1Rs, reducing food intake, increasing insulin secretion, decreasing glucagon secretion and delaying gastric emptying time with an added agonist activity on GIP receptors (GIPRs). Under normal conditions, the enteroendocrine K-cells secrete GIP with food intake to enhance glucose-dependent insulin secretion from the pancreas [3]. However, acute infusion studies have showed that in subjects with T2DM, insulinotropic effects of GIP are severely impaired either due to a decrease in GIP secretion or pancreatic beta-cell resistance to GIP. There is some evidence indicating that achieving adequate glycemic control can partially restore this decline in the insulinotropic effect, but no studies in humans have evaluated the effects of a treatment that targets and stimulates GIPRs alone. Therefore, the added mechanistic effect of the activation of GIPRs receptors, in addition to GLP-1Rs, may potentially help improve glycemic status. In addition to its role of an incretin hormone, GIPRs receptors are highly expressed in adipose tissues and, although not yet fully understood, studies in both rodents and humans have shown that GIP may play an important role in both lipolysis and lipogenesis in adipose tissue [4]. Furthermore, like GLP-1Rs, the stimulation of GIPRs in the brain also evinces a reduction in food intake [5].

### Clinical Studies

In pre-clinical and early phase clinical studies, tirzepatide demonstrated notable reductions in hemoglobin A1c (HbA1c) and (BW with improvements in markers of non-alcoholic steatohepatitis (NASH). In a 26-week, phase IIb study with tirzepatide, significant glucose control and weight loss was achieved with tirzepatide 10 mg and 15 mg compared to the active control, dulaglutide, in subjects with T2DM. In this study, eligible subjects with HbA1c levels of 7% to 10.5% being treated with metformin monotherapy were randomized to receive

either once weekly doses of tirzepatide 1 mg, 5 mg, 10 mg, or 15 mg, placebo, or dulaglutide 1.5 mg. At week 26, tirzepatide 15 mg and 20 mg significantly reduced mean HbA1c (-2.0% and -2.4%, respectively) compared to placebo (+0.1%) and dulaglutide (-1.1%), achieving its primary endpoint ($p < 0.005$). In addition, significant weight reduction was observed at week 26 in subjects that received tirzepatide 15 mg (-8.7 kg) and 20 mg (-11.3 kg) versus placebo (-0.4 kg) and dulaglutide (-2.7 kg) ($p < 0.05$). Gastrointestinal (GI) events such as nausea, diarrhea, and vomiting were the most commonly reported adverse events. These GI events were more prevalent and more commonly led to discontinuation in the tirzepatide 15 and 20 mg groups compared to dulaglutide and placebo. Hypoglycemic events defined as plasma glucose levels of ≤ 70 mg/dL were low and similar across all treatment groups with no incidence of severe hypoglycemia [5].

## Clinical Studies in Subjects with T2DM

The SURPASS program, which consists of more than six phase III clinical studies are being conducted for tirzepatide, in subjects with T2DM and are expected to conclude in 2021. Enrollment is complete for five of the SURPASS studies, SURPASS-1, SURPASS-2, SURPASS-3, SUPRPASS-4, and SURPASS-5. SURPASS-1 enrolled T2DM subjects whose blood glucose levels were not controlled with diet and exercise alone and is measuring a change from baseline in HbA1c to week 40 across four treatment arms (tirzepatide 5 mg, 10 mg, 15 mg, or placebo once weekly) [6]. The SURPASS-2 study enrolled T2DM subjects who were on a stable dose of metformin ≥ 1500 mg daily, and is comparing tirzepatide (5 mg, 10 mg, and 15 mg) to semaglutide once weekly, on the change in HbA1c from baseline to week 40 [7]. Both the SURPASS-1 and SURPASS-2 studies are expected to be completed by November 2020. The SURPASS-3 study randomized subjects with T2DM who were subjects on stable doses of metformin with or without an SGLT-2 inhibitor to one of the following four arms, tirzepatide 5 mg, 10 mg, or 15 mg once weekly or insulin degludec once daily. This study is examining the change in HBA1c from baseline to week 52 for tirzepatide doses 10 and 15 mg and is expected to be completed by January 2021 [8].

SURPASS-4 and SURPASS-5 studies have recently closed for enrollment. Where SURPASS-4 will be evaluating the safety and efficacy of tirzepatide 10 and 15 mg once weekly to insulin glargine once daily in subjects with T2DM and HbA1c levels between 7 to 10.5%. The SURPASS-5 study is further evaluating the efficacy and safety of tirzepatide in subjects with T2DM and whose blood glucose levels are inadequately controlled on insulin glargine with or without metformin with an HbA1c between 7% and 10.5%. In this study, the subjects have been randomized to either tirzepatide 5 mg, 10 mg, 15 mg, or placebo once weekly and will assess the primary outcome of change in HbA1c from baseline to week 40. This study is estimated to be completed by January 2021 [9].

The SURPASS-AP-COMBO study, currently open for enrollment, will be evaluating the mean change in HBA1c from baseline to week 40 and will include subjects with T2DM on metformin with or without a sulfonylurea. This study is planning to recruit a total of 956 subjects and these subjects will be randomized into one of following four arms, insulin glargine once daily, tirzepatide 5 mg, 10 mg or 15 mg once weekly [10]. The SURPASS-CVOT is expected to start enrollment in 2020 and plans to recruit approximately 12,500 subjects with T2DM subjects with established atherosclerotic cardiovascular disease and an HbA1c between 7.0% and 10.5%. This study will compare the efficacy of tirzepatide to dulaglutide once weekly on CV related death from CV causes, myocardial infarction, or stroke, over approximately five years [11].

## Clinical Studies in Overweight and Obese Subjects

Additional phase III studies evaluating tirzepatide in overweight or obese subjects with a body mass index (BMI) ≥ 30 kg/m$^2$ form the SURMOUNT program. SURMOUNT-1 is currently enrolling overweight or obese subjects who have weight-related co-morbidities such as hypertension, dyslipidemia, obstructive sleep apnea, and/or CVD without T2DM. These subjects will be randomized into four treatment arms (tirzepatide 5 mg, 10 mg, or 15 mg once weekly or placebo) with primary outcome measures of percent change from baseline in body weight and percentage of subjects who achieve ≥ 5% body weight reduction. This study will last 72 weeks and has planned for an extension phase for subjects with prediabetes and will continue for another two years [12].

### Clinical Studies in NASH Subjects

A phase II study, SYNERGY, is currently enrolling subjects to assess the effectiveness and safety of tirzepatide as a possible treatment option for NASH. In this double-blind study, approximately 196 subjects will be treated with either tirzepatide 5 mg, 10 mg, or 15 mg once weekly or placebo. These subjects must have a BMI between 27 and 50 kg/m2 with a histologic diagnosis of NASH with stage 2 or 3 fibrosis confirmed by a liver biopsy. Ultimately, the study will assess the percentage of subjects without NASH with no worsening of fibrosis on liver histology over the course of 52 weeks [13].

## Conclusion

The results of the completed phase II studies show promise for tirzepatide in subjects with T2DM for HbA1c reduction and body weight reduction. Furthermore, the results of the SURPASS, SURMOUNT, SURPASS-CVOT, and SYNERGY studies will demonstrate if there are additional opportunities to utilize tirzepatide to treat T2DM, overweight, obese, NASH, and/or patients at high risk for CVD.

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