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Bumps and humps in the success of Tirzepatide as the first GLP1 and GIP receptor agonist

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ABSTRACT

Glucagon-like peptide 1 (GLP-1) receptor agonists have acquired importance in Type 2 diabetes (T2D) treatment due to their glycemic advantages, cardiorenal effects, and favorable body weight. Despite this, the continuous discovery of higher effectiveness treatments is critical to addressing ongoing difficulties in the accomplishment of metabolic targets in many T2D patients. Tirzepatide is a unimolecular dual GLP-1 and Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist that is being developed for the treatment of T2D. Tirzepatide was approved in May 13, 2022 by the United State Food and Drug Administration (USFDA) with the brand name Mounjaro as the first and the only GLP-1 and GIP receptor agonist to treat T2D. This review outlines essential features of tirzepatide including chemistry, synthesis, pharmacology and mechanism of action of tirzepatide as well as pharmacodynamics, pharmacokinetic and reported clinical trials.

1. Introduction

Type 2 diabetes (T2D) is a serious health issue that affects millions of individuals worldwide. It is a progressive and chronic disease in which the body fails to use or produce insulin properly, resulting in excessive blood glucose levels (sugar). Type 2 diabetes affects more than 30 million Americans. Despite the accessibility of several diabetic treatments, many patients fail to meet the required blood sugar targets. T2D pathogenesis is a complicated mechanism that is still being unraveled. Relative insulin insufficiency and an insulin resistance combination (during the initial stages of the illness) result in hyperglycemia. Chronic hyperglycemia induces glucose toxicity, which promotes pancreatic beta-cell failure and, in the late stages, exacerbates insulin insufficiency. As a result, a vicious cycle of hyperglycemia develops, leading to a deteriorating metabolic condition. T2D therapy thus comprises lifestyle modification and nutritional intervention to encourage weight loss, as well as pharmaceuticals to fight hyperglycemia and optimize metabolic parameters including lipids and blood pressure, and, in certain cases, metabolic surgery. The optimal glucose-lowering medicine is effective, does not cause weight gain (but does help in the decrease of body weight), has a minimal hypoglycemia risk, and has been shown to have cardiovascular benefits. In the last 15 years, new types of diabetic drugs have been available for the T2D treatment including glucagon-like peptide-1 receptor agonists (GLP-1 RA) (the first GLP-1 RA was exenatide, which is approved in 2005 by USFDA), DPP4 inhibitor (sitagliptin was the first DPP4i, which is approved in the year 2006) and SGLT2 inhibitors (dapagliflozin [EU] and canagliflozin [USA], which is approved in 2013 and 2012, respectively). These novel glucose-lowering medications are effective (Once-weekly semaglutide 1 mg reduces HbA1c by 1.5–1.8%) and help people lose weight (4.5–6.5 kg weight decrease with 1 mg semaglutide once a week). Despite these advancements in treatment, a large number of persons with T2D do not attain adequate glycemic control [1,2].

On May 13, 2022, USFDA approved tirzepatide injection with the brand name Mounjaro, a novel once-weekly GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist suggested as an addition to exercise and diet to enhance glycemic control in individuals with T2D [3] Tirzepatide is a 39-amino-acid synthetic peptide based on the natural GIP sequence that acts as a dual GLP-1/GIP receptor agonist [4]. Tirzepatide appears to have substantial glucose-lowering properties, with side effects equivalent to those of recognized GLP-1 receptor agonists, according to preclinical and clin-

Abbreviations: ADME, Adsorption, Distribution, Metabolism and Excretion; BMI, Body mass index; CIs, Confidence intervals; cAMP, Cyclic adenosine monophosphate; EPAC2, Exchange protein activated by cAMP2; (GEF)II, cAMP-guanine nucleotide exchange factor; GIP, Glucose-dependent insulinotropic polypeptide; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; HRs, Hazard ratios; MACE, Major adverse cardiovascular events; MTC, Medullary thyroid carcinoma; RCTs, Randomized Control Trials; T2D, Type 2 diabetes; USFDA, United State Food and Drug Administration; PKA, Protein kinase A; SC, subcutaneous; VDCC, Voltage-gated Ca2+ channels.

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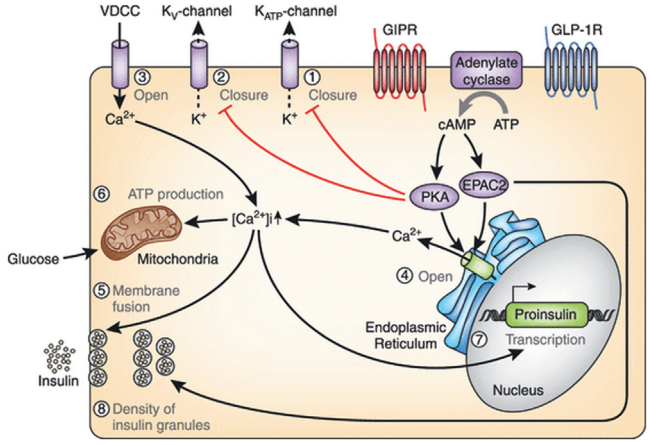


Fig. 1. Molecular mechanism of GLP-1 and GIP in T2D.

ical phase 1 and 2 studies. The phase 3 SURPASS clinical study program will look into tirzepatide's long-term safety, effectiveness, and cardiovascular outcomes. The approval of tirzepatide was based on the findings of the SURPASS study, which comprised injection insulin glargine, semaglutide 1 mg, and insulin degludec as active comparators. In late 2018, the phase 3 SURPASS worldwide clinical improvement strategy for tirzepatide commenced, including two regional studies in Japan and five global registration studies. The safety and effectiveness of tirzepatide 5, 10, and 15 mg alone and as an add-on to several standard-of-care drugs for T2D were investigated in these trials, which extended from 40 to 52 weeks. Tirzepatide is developed by Eli Lilly [1,5].

Tirzepatide's chemical formula is $C_{225}H_{348}N_{48}O_{68}$. It is conjugated to a 20C fatty diacid moiety that is attached to albumin, extending its half-life to five days and allowing for once-a-week administration. It has a molecular mass of 4810.52 Daltons. GIP and GLP-1 are hormones that regulate blood sugar levels [4,5] Tirzepatide is a first-in-class drug that improves blood sugar regulation by activating both the GIP and GLP-1 receptors. Tirzepatide is given as a weekly injection beneath the skin, with the dosage being changed as needed to reach blood sugar targets [3].

1.1. Involvement of GLP and GIP at molecular level in T2D

The molecular mechanisms of GLP-1 and GIP lie under insulinotropic actions. The adenylate cyclase activation and subsequent elevation of intracellular cyclic adenosine monophosphate (cAMP) levels occur when GLP-1 and GIP bind to their respective receptors. Protein kinase A (PKA) and exchange protein activated by cAMP2 (EPAC2)/cAMP-guanine nucleotide exchange factor (GEF)II are both activated by increased cAMP. PKA activation enhances KATP channel closure and enables membrane depolarization. The delayed rectifying K^+ (Kv) channel, a negative regulator of insulin production in pancreatic cells, is also inhibited by PKA, resulting in action potential lengthening. Depolarization activates the voltage-gated Ca^{2+} channels (VDCC), allowing for an rise in Ca^{2+} concentration in intracellular and the mobilization of Ca^{2+} from intracellular reserves via PKA and EPAC2-dependent processes. Improved concentrations of Ca^{2+} cause insulin-containing granules to fuse with the plasma membrane, resulting in insulin release from the cells. Improved levels of Ca^{2+} also increase the proinsulin gene transcription, resulting in a rise in the cell's insulin content. EPAC2 activation has been demonstrated to enhance the density of insulin-containing granules near the plasma membrane, allowing the cell to secrete more insulin (Fig. 1) [6].

1.2. Currently available GLP-1 receptor agonists

GLP-1 RAs prolong stomach emptying and improve satiety by increasing secretion of glucose-dependent insulin while reducing excessive glucagon secretion. Currently, seven GLP-1 RAs are approved (**Table 1**); lixisenatide once daily, exenatide twice daily, liraglutide once daily, semaglutide once weekly, oral semaglutide once daily, exenatide once weekly, and dulaglutide once weekly. Albiglutide (a once in a week GLP-1 RA) was withdrawn in 2017 due to a continuous fall in sales. Exception of oral semaglutide, all GLP-1 RA medications are given by SC injection. Although there are incidences of different adverse effects due to particular agents, the most prevalent adverse effects associated with the GLP-1 RA class are injection site responses and GI-related (vomiting, diarrhea and nausea) [7]. Lixisenatide and exenatide, two short-acting exendin-4 compounds, work by delaying stomach emptying and thereby lowering levels of postprandial glucose. The longer-acting GLP-1 RAs, on the other hand, have an effect on both fasting and postprandial glucose levels by inhibiting glucagon secretion and stimulating insulin release [8].

2. Chemistry of tirzepatide

2.1. Structure

Tirzepatide is a C20 fatty-diacid-added analogue of the human GIP hormone that is utilised to improve the compound's absorption and metabolism. Two (2-(2-aminoethoxy)ethoxy)acetic acid and a glutamic acid units bind the side chain of the lysine amino acid to the fatty-diacid component (eicosanedioic acid) (Fig. 2).This arrangement provides a significantly longer half life due to its high affinity for albumin, extending the period between dosages [9,10].

2.2. Synthesis

Eli Lilly and Company's patents were the first to reveal the synthesis of tirzepatide. At position 20 of the amino acids chain, lysine is protected by an allyloxycarbonyl protecting group, permitting a last sequence of chemical reactions in which the sidechain amine of that lysine is derivatized with the lipid-containing fragment. This chemical has been reported to be manufactured on a large scale [11].

3. Pharmacology of tirzepatide

Tirzepatide is a human hormone that increases insulin release from the pancreas and is an analogue of GIP. Tirzepatide is a 39-amino-acid linear polypeptide that has been modified in chemical manner with the help of lipidation to increase metabolic stability and absorption into cells. The drug is given as a subcutaneous injection once a week. In 2021, it completed phase III trials around the world.

4. Mechanism of action of tirzepatide

Tirzepatide binds to GIP more strongly than GLP-1, and this dual agonistic potential has been found to reduce hyperglycemia more effectively than a GLP-1 receptor agonist. This is because tirzepatide mimics the effects of endogenous GIP at the GIP receptor, according to signaling studies. Tirzepatide, on the other hand, has a preference for cAMP (a messenger involved in glycogen, sugar, and lipid metabolism control) synthesis over -arrestin recruitment at the GLP-1 receptor. This biassed agonism appears to promote insulin secretion due to its selectivity for the GIP receptor and unique signaling characteristics at GLP-1. Tirzepatide has also been demonstrated to enhance adiponectin level, an adipokine implicated in lipid and glucose metabolism regulation, after 26 weeks on the 10 mg dosage, the maximum increase from baseline was 26% [12,13].

5. Pharmacokinetics of tirzepatide

The tirzepatide's pharmacokinetics is comparable in healthy people and people with T2D. After four weeks of once-weekly treatment, steady-state plasma tirzepatide concentrations were attained.

Table 1
Comparison of currently available GLP-1 receptor agonists.

Drugs	Structural class	Dosage	Route of administration	Dosage instruction	Side effects
Exenatide; Brand name "Byetta" (Approved by FDA in 28 April 2005)	Exendin-4 derivative	For 1st month 5mcg twice daily, then 10mcg twice daily	SC	60 min. before meal	Vomiting, nausea, diarrhea, heartburn, dizziness, headache, sweating, weakness, difficulty swallowing or breathing, injection-site pain, blisters, swelling, nodules or itching, rapid heartbeat.
Liraglutide; Brand name "Victoza" (Approved by FDA in 25 January 2010)	Modified human GLP-1	For 1st week 0.6 mg once daily, then 1.2 mg (if needed 1.8 mg) once daily	SC	Any time	Heartburn, constipation, headache, sneezing, runny nose or cough, burning or pain or difficulty on urination, tiredness, redness or rash in injection site, vomiting, fainting or feeling dizzy, yellow skin or eyes.
Exenatide; Brand name "Bydureon " (Approved by FDA in 26 January 2012)	Exendin-4 derivative	2 mg once weekly	SC	Any time	Vomiting, nausea, diarrhea, fatigue, headache, decreased appetite, upset stomach, itchiness, redness in injection site, pancreatitis, kidney damage.
Dulaglutide; Brand name "Trulicity" (Approved by FDA in 18 September 2014	Modified human GLP-1	0.75–1.5 mg weekly once	SC	Any time	Heartburn, vomiting, feeling tired, itching, hives, fast heartbeat, swelling of tongue, lips, face, or throat, difficulty swallowing or breathing, vision changes.
Lixisenatide; Brand name "Adlyxin" (Approved by FDA in 27 July 2016	Exendin-4 derivative	For first two weeks 10mcg once daily, then 20mcg daily once	SC	60 min before meal	Vomiting, nausea, indigestion, headache, bloating, redness, itching, or pain at the site of injection, pounding heartbeat, decreased urination, very dry skin or mouth, difficulty breathing or swallowing.
Semaglutide; Brand name "Ozempic" (Approved by FDA in 5 December 2017	Modified human GLP-1	0.25–1 mg weekly once	SC	Any time	Recurrent fever, Belching, yellow skin or eyes, gaseous stomach pain, heartburn, indigestion, rapid heartbeat, vision changes, vomiting
Oral Semaglutide; Brand name "Rybelsus" (Approved by FDA in 20 September 2019)	Modified human GLP-1	3–14 mg daily once	By mouth	Any time	Abdominal pain, vomiting, nausea, diarrhea, loss of appetite, kidney problems, blurred vision, pancreatitis, trouble breathing.
Tirzepatide Brand name "Mounjaro" Approved by FDA in 13 May 2022	GIP and GLP-1 receptor agonist	2.5 mg once weekly	SC	Any time	Nausea, pancreatitis, vomiting, hypoglycemia, hypersensitivity, severe gastrointestinal disease, acute gallbladder disease, diabetic retinopathy.

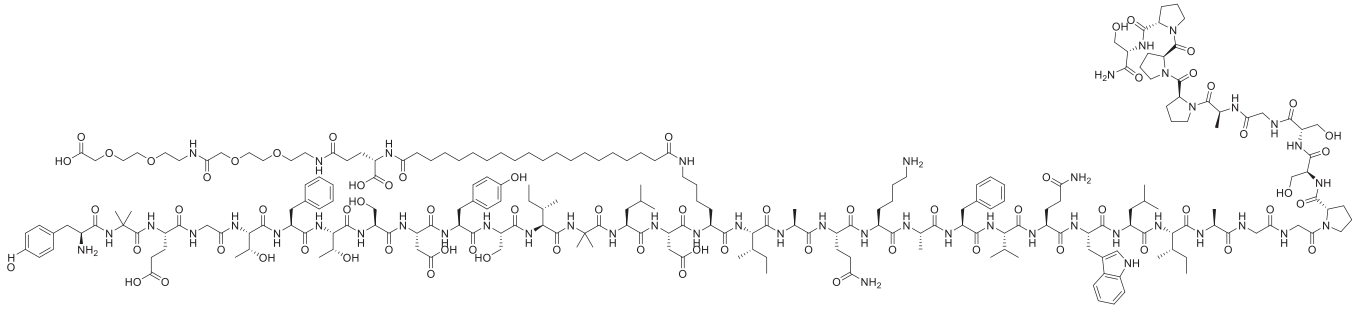


Fig. 2. Chemical structure of Tirzepatide.

Tirzepatide exposure rises in proportion to the dose [3,4]. The ADME properties are shown in the Table 2.

6. Pharmacodynamics of tirzepatide

Tirzepatide decreases fasting and postprandial glucose levels, declines body weight and food consumption in patients with T2D. In the first and second phases of Insulin Secretion, tirzepatide increases insulin secretion.

Sensitivity to Insulin after 28 weeks of treatment, tirzepatide improved insulin sensitivity in studies of hyperinsulinemic euglycemic clamp. Due to Glucagon Secretion, Tirzepatide lowers glucagon levels in the fasting and postprandial states. After 28 weeks of treatment, tirzepatide (at 15 mg dose) lowered fasting glucagon levels by 28% and after meal, glucagon AUC by 43%, compared to no differences in placebo. Emptying the stomach Tirzepatide slows the emptying of the stomach. The delay is most noticeable after the 1st dose and lessens over time. It reduces postprandial hyperglycemia by slowing post-meal glucose absorption [3,4].

7. Risks and related aspects

7.1. Thyroid C-Cell tumors

In a two years investigation at clinically relevant plasma exposures, tirzepatide induced a treatment-duration-dependent and a dose-dependent increase in the incidence of thyroid C-cell tumours (carcinomas and adenomas) in both sexes of rats. It's unknown whether tirzepatide causes thyroid C-cell cancers in people, particularly medullary thyroid carcinoma (MTC), because the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has yet to be established. Anyone with a family or personal history of MTC should avoid taking tirzepatide. Patients should be informed about the danger of MTC associated with the use of Tirzepatide, as well as the signs of thyroid cancer (e.g., dysphagia, a mass in the neck, persistent hoarseness, dyspnea). The usefulness of thyroid ultrasonography or routine serum calcitonin monitoring for early identification of MTC in tirzepatide patients is debatable. Due to the limited test specificity for serum calcitonin and

Table 2
ADME of tirzepatide.

Absorption	Tirzepatide takes 8 to 72 h to reach maximum plasma levels after subcutaneous injection. Tirzepatide has an 80 percent absolute bioavailability after subcutaneous (SC) injection. SC administration of tirzepatide in the thigh, upper arm or abdomen, resulted in similar exposure
Distribution	In patients with T2D, the mean apparent steady-state VD of tirzepatide after SC intake is approximately 10.3 L. Tirzepatide has a strong affinity for plasma albumin (99 percent).
Metabolism	Tirzepatide is broken down via β-oxidation of the C20 fatty di-acid motif, proteolytic cleavage of the peptide backbone, and amide hydrolysis.
Elimination/ Excretion	Tirzepatide metabolites are primarily excreted through urine and feces. In urine or feces, no intact tirzepatide is found. Tirzepatide has an apparent population mean clearance of 0.061 L/h and half-life of an elimination about five days, allowing for once in a week dosage.

the high background frequency of thyroid illness, such surveillance may raise the risk of needless treatments. MTC patients frequently have calcitonin values >50 ng/L and have significantly high serum calcitonin values. [3].

7.2. Pancreatitis

When patients were treated with GLP-1 receptor agonists that resulted acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. In clinical trials, adjudication confirmed 14 acute pancreatitis incidents in 13 Tirzepatide-treated patients (0.23 patients/100 years of exposure) compared to three events in three comparator-treated patients (0.11 patients/100 years of exposure). Tirzepatide were not investigated in individuals who have had pancreatitis in the past. It's unclear whether patients with a history of pancreatitis are more likely to develop pancreatitis when using Tirzepatide. After starting Tirzepatide, keep a close eye on patients for symptoms and signs of pancreatitis (such as persistent severe pain of abdomen). If pancreatitis is suspected, stop taking tirzepatide and seek medical attention.

7.3. Hypoglycemia associated with insulin or insulin secretagogues

Patients who use tirzepatide with insulin or an insulin secretagogue (such as a sulfonylurea) may experience an improved hypoglycaemia risk, such as severe hypoglycemia. A decrease in the dose of sulfonylurea or insulin may decrease the hypoglycaemia risk. Inform individuals who are taking these drugs together about the risk of hypoglycemia and the symptoms and sign of hypoglycaemia [3].

7.4. Acute kidney injury

Tirzepatide were linked to gastrointestinal side effects including nausea, vomiting, and diarrhea. These occurrences could produce dehydration, which could lead to acute renal damage if severe. Acute kidney damage and exacerbation of chronic renal failure have been reported in individuals treated with GLP-1 RA, necessitating hemodialysis in certain cases. Some of these side effects have been documented in people who don't have kidney disease. Patients who had vomiting, nausea, diarrhea, or dehydration accounted for the majority of the recorded occurrences. In individuals with renal impairment reporting severe gastrointestinal adverse events, monitor renal function when starting or increasing Tirzepatide dosages [3].

7.5. Hypersensitivity reactions

In clinical trials, Tirzepatide caused hypersensitivity reactions (e.g., eczema and urticaria), which were severe in sometimes. If hypersensitivity responses occur, stop taking tirzepatide immediately, treat as needed, and monitor until the symptoms and signs go away. Patients who have a severe hypersensitivity reaction to tirzepatide or any of the additives in tirzepatide should not take it. GLP-1 receptor agonists were linked to anaphylaxis and angioedema. Patients with a medical backgroud of anaphylaxis or angioedema in response to a GLP-1 RA should be treated with caution because it is uncertain if they will be prone to these responses with tirzepatide.

7.6. Severe gastrointestinal disease

Tirzepatide has been linked to gastrointestinal side effects, some of which have been severe. Tirzepatide were not tested in individuals with severe gastrointestinal disorders, such as severe gastroparesis, and is hence not indicated.

7.7. Acute gallbladder disease

In GLP-1 receptor agonist studies and postmarketing, acute gallbladder disease events including cholecystitis or cholelithiasis have been observed. Acute gallbladder disease (cholecystectomy, biliary colic, and cholelithiasis) has been reported by 0.6 percent of tirzepatide-treated patients and zero percent of patients treated with placebo in tirzepatide placebo-controlled clinical trials. Gallbladder diagnostic investigations and proper clinical follow-up are recommended if cholelithiasis is suspected [3].

8. Clinical trial information

Five clinical trials looked at three different doses of tirzepatide (5, 10, and 15 mg) as a stand-alone therapy or as a complement to other diabetes drugs. To see how effective Tirzepatide was compared to a GLP-1 RA (semaglutide), placebo, and two long-acting insulin analogues.

Individuals who received the highest indicated tirzepatide dose (15 mg) as a stand-alone medication had their hemoglobin A1c (a marker of blood sugar control) level reduced by 1.6 percent more than placebo, and 1.5 percent more than placebo when combined with a long-acting insulin. In studies comparing tirzepatide to other medications of diabetes, individuals who administered the highest prescribed tirzepatide dose saw their HbA1c drop by 0.9 percent more than insulin degludec, 0.5 percent more than semaglutide, and 1.0 percent more than insulin glargine.

Overweight was prevalent among those who took part in the study, with an average BMI of 32–34 kgs per square meter observed during recruiting. In patients randomly assigned to the maximum prescribed dose, Tirzepatide reduced weight 15 pounds more than placebo when neither was used with insulin and 23 pounds more than placebo when both were used with insulin. Tirzepatide resulted in an average weight loss of 29 pounds more than insulin degludec, 12 pounds more than semaglutide, and 27 pounds more than insulin glargine at the highest prescription dose. During the study, patients who were given insulin without Tirzepatide gained weight. The various reported clinical studies are shown in the Table 3 .

9. Meta-Analysis reports

In terms of glycemic control, the results of this meta-analysis of seven RCTs (6609 people) show that all three tirzepatide maintenance doses outperform placebo, basal insulin regimens and long-acting GLP-1 RA. All doses of tirzepatide surpassed all comparators in terms of loss of body weight. The tirazepatide treatment did not raise the risk of hypoglycemia, but it did raise the risk of gastrointestinal side effects, especially nausea. The 15 mg dose improved the likelihood of withdrawal

Table 3
Trials of tirzepatide.

Phase	Trial code	participants	Sponsor	Purpose of study	Completion date
Phase I	NCT04311424	6	Eli Lilly and Company	To see how much tirzepatide enters the bloodstream and how long it takes the body to eliminate it.	October 2, 2020
Phase I	NCT04004988	45	Eli Lilly and Company	To compare how much tirzepatide enters the bloodstream and how long it takes the body to eliminate it.	December 16, 2019
Phase I	NCT04050670	54	Eli Lilly and Company	To see how much tirzepatide enters into the blood circulation and how much it requires the body to eliminate it when injected under the skin of thigh and the upper arm vs the abdomen.	April 3, 2020
Phase I	NCT03940742	32	Eli Lilly and Company	To see how quickly tirzepatide enters the bloodstream and how long the body takes to get rid of it in individuals who have poor liver function versus healthy individuals.	September 22, 2020
Phase I	NCT04407234	36	Eli Lilly and Company	To understand more about how tirzepatide impacts stomach emptying in individuals with overweight.	January 7, 2021
Phase I	NCT03482024	45	Eli Lilly and Company	To see how quickly tirzepatide enters the bloodstream and how long does it take the body to get rid of it in people who have poor kidney function vs healthy people.	August 19, 2019
Phase I	NCT04235959	24	Eli Lilly and Company	To discover further about tirzepatide's side effects and safety in Chinese patients with T2D.	August 17, 2021
Phase III	NCT04657003	900	Eli Lilly and Company	To understand more about the impact of tirzepatide on body weight.	April 17, 2023
Phase III	NCT04660643	750	Eli Lilly and Company	To discover more about how tirzepatide helps individuals to maintain their loss of weight	May 17, 2023
Phase III	NCT04657016	800	Eli Lilly and Company	To discover more about how tirzepatide helps individuals maintain their weight or lose weight after undergoing a rigorous lifestyle change plan.	May 11, 2023
Phase III	NCT05024032	210	Eli Lilly and Company	To understand more about the effects of tirzepatide on body weight.	december 14, 2022
Phase I	NCT03375463	46	Eli Lilly and Company	Part A compares the formulation of medication tirzepatide solution to a powder formulation combined with water and administered subcutaneously; Part B assesses the tolerability and safety of the IV formulation of tirzepatide when injected into a vein; Part C evaluates tirzepatide's tolerability and safety after several subcutaneous weekly doses of a solution.	December 27, 2018
Phase III	NCT04844918	261	Eli Lilly and Company	To understand more about tirzepatide in obese individuals.	June 30, 2023
Phase III	NCT04255433	12,500	Eli Lilly and Company	To compare the safety and effectiveness of tirzepatide to dulaglutide in individuals with T2D with a high risk of cardiovascular disease.	October 17, 2024
Phase III	NCT04847557	700	Eli Lilly and Company	To determine the Tirzepatide'S safety and effectiveness in individuals with heart failure and obesity who have a maintained ejection fraction.	November 22, 2023
Phase I	NCT04081337	56	Eli Lilly and Company	To find out how tirzepatide impacts the number of calories burned and the amount of food consumed by individuals.	May 31, 2022
Phase I	NCT04050553	42	Eli Lilly and Company	To find out more about how tirzepatide impacts the body's reaction to hypoglycemia.	January 25,2022
Phase III	NCT03861039	443	Eli Lilly and Company	To see if the study drug tirzepatide, in conjunction with oral antihyperglycemic medicines, is safe in T2D patients over time.	February 16, 2021
Phase III	NCT05260021	90	Eli Lilly and Company	To discover more about tirzepatide's efficacy and safety in teens and children with T2D who are receiving basal insulin, metformin, or both.	December 31, 2027
Phase III	NCT04184622	2539	Eli Lilly and Company	To understand more about the impacts of tirzepatide on body weight.	May 24, 2024
Phase III	NCT03861052	636	Eli Lilly and Company	To investigate tirzepatide, is as safe and effective as dulaglutide in T2D patients in Japan.	March 31, 2021
Phase I	NCT04172987	40	Eli Lilly and Company	Tirzepatide's impact on how the body processes EE/NGM	February 9, 2021
Phase III	NCT03954834	478	Eli Lilly and Company	To compare the safety and effectiveness of tirzepatide with placebo in T2D individuals who are unable to control their condition with exercise and diet alone.	October 28, 2020
Phase II	NCT04166773	196	Eli Lilly and Company	To evaluate if tirzepatide, a once-weekly medication for nonalcoholic steatohepatitis, is effective and safe.	December 15, 2023
Phase III	NCT03987919	1879	Eli Lilly and Company	To examine the effects of tirzepatide vs semaglutide on blood sugar levels in T2D individuals.	February 15, 2021
Phase III	NCT04039503	475	Eli Lilly and Company	To evaluate the effectiveness and safety of tirzepatide vs placebo in T2D patients who are currently taking insulin glargine without or with metformin.	January 13, 2021
Phase III	NCT05412004	412	Eli Lilly and Company	To see how well tirzepatide works and how safe it is in individuals with overweight and obstructive sleep apnea who are both reluctant to utilize PAP therapy in GPI-1 and those who are on PAP therapy and plan to continue on it in GPI-2.	March 11, 2024
Phase III	NCT04093752	917	Eli Lilly and Company	To evaluate tirzepatide versus insulin glargine in T2D patients taking metformin without or with a sulfonylurea.	November 24, 2021

(*continued on next page*)

Table 3 (*continued*)

Phase	Trial code	participants	Sponsor	Purpose of study	Completion date
Phase I	NCT03322631	66	Eli Lilly and Company	To see if tirzepatide is safe and if there are any potential adverse effects.	November 28, 2018
Phase I	NCT04311411	111	Eli Lilly and Company	To see how tirzepatide impacts food consumption in overweight individuals.	October 4, 2022
Phase III	NCT04537923	1182	Eli Lilly and Company	To examine the effectiveness and safety of tirzepatide vs insulin lispro 3 times a day in T2D patients who are currently receiving insulin glargine without or with metformin.	November 18, 2022
Phase I	NCT03951753	85	Eli Lilly and Company	To find out how placebo and tirzepatide impact the capacity of body to adapt to blood sugar levels after a meal.	April 8, 2021
Phase III	NCT03730662	2002	Eli Lilly and Company	To compare the safety and effectiveness of tirzepatide given once a week versus insulin glargine given once daily in T2D individuals with a high risk of heart disease.	April 22, 2021
Phase II	NCT03311724	111	Eli Lilly and Company	To see how effective tirzepatide is in T2D individuals.	April 24, 2018
Phase III	NCT03882970	1444	Eli Lilly and Company	To see how tirzepatide compares to insulin degludec in terms of blood sugar levels T2D patients.	January 4, 2021
NA	NCT05078255	60	Filip Krag Knop	To see how effective GIP is in lowering blood sugar in people with T2D when combined with pharmacological GLP-1 receptor activation.	October 2023
Phase II	NCT03131687	318	Eli Lilly and Company	To see how effective tirzepatide is in T2DM individiuals.	August 1, 2018

due to unfavorable effects by at least thrice, regardless of comparison. More research is needed to evaluate if tirzepatide's good metabolic effects translate into long-term cardiovascular benefits. These findings are mostly applicable to those on metformin-based background medicine [14].

10. Role of tirzepatide in cardiovascular event risk assessment

This meta-analysis examined four-component major adverse cardiovascular events (MACE) such as myocardial infarction, cardiovascular death, stroke, and hospitalised unstable angina between control groups and pooled tirzepatide groups. To calculate hazard ratios (HRs) and confidence intervals (CIs) contrasting tirzepatide to control, a stratified Cox proportional hazards model with treatment as a fixed effect and trial-level cardiovascular risk as the stratification factor was utilised. A total of 4887 tirzepatide-treated and 2328 control patients were studied. At least one MACE event occurred in 142 participants, 109 from the high cardiovascular risk study and 33 from the six low cardiovascular risk trials. MACE had a risk ratio of 0.80, cardiovascular death had a risk ratio of 0.90, and all-cause death had a risk ratio of 0.80. There was no evidence of impact changes in any subgroups, albeit the evidence was stronger in individuals at high cardiovascular risk. When compared to controls, tirzepatide didn't rise the risk of MACE in patients with T2D [15].

11. Conclusion

Tirzepatide, a dual GLP-1/GIP receptor agonist, is a novel T2D incretin-based treatment. Tirzepatide act by promoting insulin secretion due to its selectivity for the GIP receptor and unique signaling characteristics at GLP-1 and also through enhancing adiponectin level. In this study, we underlying the all aspects of the tirzepatide including chemistry, synthesis, pharmacology and mechanism of action, pharmacodynamics, pharmacokinetic, reported clinical trials and meta-analysis. In Phase 1 investigations, tirzepatide was demonstrated to exhibit Pharmacokinetic parameters that were appropriate for once in a week dosage and dose-dependent impacts on body weight and glycemic management. The SURPASS (phase 3) clinical study will establish that tirzepatide has comparable safety, effectiveness, and cardiovascular results in the treatment of T2D diabetes. The SURPASS studies would also contribute to a better knowledge of incretin hormones, including GIP's role in energy metabolism.

Consent for publication

Not Applicable.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] T. Min, S.C. Bain, The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS clinical trials, Diabetes Therapy 12 (2021) 143–157, doi:10.1007/s13300-020-00981-0.
[2] V.R. Aroda, A. Ahmann, B. Cariou, F. Chow, M.J. Davies, E. Jódar, R. Mehta, V. Woo, I. Lingvay, Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1–7 trials, Diabetes Metab. J. 45 (2019) 409–418, doi:10.1016/j.diabet.2018.12.001.
[3] Eli Lilly and Company Investors News Release: FDA approves Lilly's Mounjaro™ (tirzepatide) injection, the first and only GIP and GLP-1 receptor agonist for the treatment of adults with type 2 diabetes. Available at: https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-mounjarotm-tirzepatide-injection-first-and, (Accessed June 8, 2022)
[4] T. Coskun, K.W. Sloop, C. Loghin, J. Alsina-Fernandez, S. Urva, K.B. Bokvist, X. Cui, D.A. Briere, O. Cabrera, W.C. Roell, U. Kuchibhotla, LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept, Mol. Metab. 18 (2018) 3–14, doi:10.1016/j.molmet.2018.09.009.
[5] J.P. Frías, Tirzepatide: a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) dual agonist in development for the treatment of type 2 diabetes, Expert. Rev. Endocrinol. Metab. 15 (2020) 379–394, doi:10.1080/17446651.2020.1830759.
[6] Y. Seino, M. Fukushima, D. Yabe, GIP and GLP-1, the two incretin hormones: similarities and differences, J. Diabetes Investig. 1 (2010) 8–23, doi:10.1111/j.2040-1124.2010.00022.x.
[7] J.M. Trujillo, W. Nuffer, B.A. Smith, GLP-1 receptor agonists: an updated review of head-to-head clinical studies, Ther. Adv. Endocrinol. Metab. 12 (2021) 2042, doi:10.1177/2042018821997320.

[8] M.A. Nauck, J.J. Meier, Management of endocrine disease: are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur. J. Endocrinol. (6) (2019) 211–234, doi:10.1530/EJE-19-0566.
[9] S. Østergaard, J.F. Paulsson, J. Kofoed, F. Zosel, J. Olsen, C.B. Jeppesen, J. Spetzler, L. Ynddal, L.G. Schleiss, B.O. Christoffersen, K. Raun, The effect of fatty diacid acylation of human PYY3-36 on Y2 receptor potency and half-life in minipigs, Sci. Rep. 11 (2021) 1–5, doi:10.1038/s41598-021-00654-3.
[10] M. Ahangarpour, I. Kavianinia, P.W. Harris, M.A. Brimble, Photo-induced radical thiol–ene chemistry: a versatile toolbox for peptide-based drug design, Chem. Soc. Rev. 50 (2021) 898–944, doi:10.1039/D0CS00354A.
[1] Inventors; Eli Lilly and Co, assignee, B.K. Bokvist, T. Coskun, R.C. Cummins, J. Alsina-Fernandez, GIP and GLP-1 co-agonist compounds. United States patent US 9,474,780. (2016).
[12] M.K. Thomas, A. Nikooienejad, R. Bray, X. Cui, J. Wilson, K. Duffin, Z. Milicevic, A. Haupt, D.A. Robins, Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes, J. Clin. Endocrinol. Metab. 106 (2021) 388–396, doi:10.2337/db19-980-P.
[13] Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program" (Press release). Eli Lilly and Company. 17 February 2021. (Accessed 10 June 2022).
[14] T. Karagiannis, I. Avgerinos, A. Liakos, S. Del Prato, D.R. Matthews, A. Tsapas, E. Bekiari, Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis, Diabetologia (2022) 1, doi:10.1007/s00125-022-05715-4.
[15] N. Sattar, D.K. McGuire, I. Pavo, G.J. Weerakkody, H. Nishiyama, R.J. Wiese, S. Zoungas, Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis, Nat. Med. 28 (2022) 591–598, doi:10.1038/s41591-022-01707-4.