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REVIEW ARTICLE

THE IMPACT OF TIRZEPATIDE ON BODY MASS IN THE CLINICAL TRIALS SURMOUNT AND SURPASS

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Introduction: Obesity and type 2 diabetes mellitus (T2DM) represent significant public health challenges globally, necessitating the development of effective therapeutic interventions. Tirzepatide (TZP), a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist has emerged as a promising treatment modality for these conditions. The aim of this review is to provide an in-depth analysis of data from clinical trials conducted within the SURPASS and SURMOUNT programs, aiming to evaluate TZP's efficacy and safety in the management of obesity.

Methods: A literature review was conducted focusing on the full accessibility of sources. Databases such as PubMed, IEEE Xplore, ScienceDirect, and Google Scholar were searched. Searches were performed using keywords such as: "tirzepatide", "tirzepatide and obesity", "GIP and GLP-1 receptor agonists", "tirzepatide and SURPASS", "tirzepatide and SURMOUNT".

Results: The comprehensive trials reveal evidence supporting benefits in weight reduction among patients with T2DM. Furthermore, the favorable safety profile observed in these trials enhances TZP's appeal as a therapeutic option for individuals with obesity and T2DM.

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Discussion and conclusion: In conclusion, TZP emerges as a promising therapeutic agent with the potential to revolutionize the management of obesity and T2DM, offering comprehensive benefits beyond glycemic control and weight reduction. Despite these promising results, further research is warranted to elucidate TZP's impact on weight in populations with obesity without diabetes, as well as its long-term safety and economic implications. Such investigations will be crucial in forming personalized treatment strategies and optimizing the clinical utility of TZP in diverse patient populations.

Keywords: Tirzepatide, obesity, SURMOUNT, SURPASS

INTRODUCTION

Obesity is a complex, chronic disease characterized by the abnormal and excessive accumulation of body fat, which adversely affects the health of individuals. The diagnosis of obesity is based on the body mass index (BMI) [23]. According to the World Health Organization (WHO) criteria, overweight in adults is defined as a BMI equal to or greater than 25, while obesity is defined as a BMI equal to or greater than 30 [27]. For children, definitions of overweight and obesity are developed based on percentile charts, taking into account age.

The prevalence of obesity has steadily increased globally over time. According to WHO data from 2022, 890 million people worldwide suffer from obesity, while the number of overweight people globally is approximately 2.5 billion. Compared to 1990, the percentage of overweight adults worldwide increased from 23% to 43% after 32 years, while the number of obese adults doubled from 1990 to 2022. In the case of children aged 5 to 19 years, the percentage of obese individuals increased from 8% in 1990 to 20% in 2022. It is worth noting that obesity affects women more frequently in all age groups [27].

Increasing body weight leads to a range of health consequences. Obesity may contribute to the development of diabetes and heart disease, and is associated with an increased risk of malignant tumors [15]. A meta-analysis encompassing 1483 studies showed that children born to overweight or obese mothers have an increased risk of developing nervous system dysfunction. According to the Organization for Economic Co-operation and Development (OECD), overweight and obese individuals have a life expectancy that is, on average, about four years shorter than those who maintain a healthy body weight [28]. Being overweight or obese increases the risk of death by 22%-91%, which poses a significantly greater threat than previously thought. Estimates suggest that one in six deaths in the USA is linked to overweight or obesity [8].

According to the World Obesity Atlas 2023, published by the World Obesity Federation, it is predicted that by 2035, the global cost of treating overweight and obesity will amount to $4.32 trillion annually if preventive measures and treatment do not improve. This amount represents nearly 3% of the global gross domestic product, which is comparable to the impact of the COVID-19 pandemic in 2020. The same forecasts suggest that most of the world's population (51%, or over 4 billion people) will be affected by overweight or obesity by 2035 if current trends persist. One in four individuals (almost 2 billion) will suffer from obesity. Moreover, childhood obesity may more than double by 2035 compared to the level in 2020. It is projected that obesity rates among boys will double, reaching 208 million (a 100% increase), and among girls, they will more than double to 175 million (a 125% increase). Additionally, the pace of obesity growth among children will be faster than among adults [6].

The American Association of Clinical Endocrinologists and the American College of Endocrinology identify three main therapeutic strategies for obesity: diet, pharmacotherapy, and surgery. The fundamental method of treating obesity is lifestyle modification, including dietary control, increased physical activity, and counseling. Typically, this leads to a weight loss of 5% to 10%. Non-pharmacological treatments such as diet, increased physical activity, and lifestyle changes should be applied to all patients. In case of ineffective lifestyle changes, pharmacotherapy is recommended. Currently, the Food and Drug Administration (FDA) has approved several medications for obesity treatment. Short-term options include drugs, such as phentermine, while long-term options include: orlistat, phentermine-topiramate, bupropion-naltrexone, liraglutide (3.0 mg), and semaglutide (2.4 mg). The ultimate and most effective method of treatment is metabolic and bariatric surgery. The recommendations provide a concise algorithm for the management of obesity,

taking into account BMI and coexisting diseases [29]. For individuals with a BMI above 27 kg/m^2 who have complications and comorbidities associated with obesity, such as hypertension, carbohydrate or lipid metabolism disorders, coronary artery disease, and obstructive sleep apnea, pharmacological treatment should be considered. Additionally, treatment should also be considered for individuals with a BMI above 30 kg/m^2, regardless of accompanying diseases.

The final step in the treatment of obesity is bariatric surgery. There are minor discrepancies in the indications for surgical treatment of obesity, depending on the guidelines. Recommendations from the American College of Cardiology (ACC), American Heart Association (AHA), The Obesity Society (TOS), American Association of Clinical Endocrinologists (AACE), and American College of Endocrinology (ACE) suggest considering bariatric procedures for patients with a body mass index (BMI) of at least 40 kg/m^2 or BMI of at least 35 kg/m^2 with obesity-related complications. Additionally, according to the AACE/ACE guidelines from 2019, patients with a BMI of at least 30 kg/m^2 with type 2 diabetes and who have not responded to behavioral and pharmacological treatments should be considered for surgery [29]. The latest guidelines from 2022 formulated by the American Society for Metabolic and Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders recommended considering bariatric procedures for a broader group of patients, including those with a BMI equal to or greater than 30 kg/m^2 who have not achieved weight loss [7].

According to the guidelines, there is no upper age limit for metabolic and bariatric surgery; however, older patients must receive particularly careful medical care. Frailty, rather than age alone, is independently associated with a higher rate of postoperative complications [7]. Polish recommendations in this area suggest performing surgeries on patients aged 18 to 65 years. The safe upper age limit for patients undergoing bariatric surgery is considered to be 65 years. However, it should be noted that surgical treatment may be considered in older individuals if the patient's overall condition is good, and the benefits outweigh the risks [2]. It should be noted that bariatric surgeries are also performed in patients under 18 years of age. Patients meeting strictly defined criteria outlined in the Polish recommendations for bariatric and metabolic surgery may be included in the surgery treatment [2].

In recent years, several therapeutic methods have been developed aiming to treat obesity, including pharmacological approaches. One potentially revolutionary drug in this field is tirzepatide (TZP). It is a substance that acts as a dual agonist of GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. Currently, numerous studies are being conducted to further understand the efficacy and safety of this drug. As a result, TZP may obtain new therapeutic indications, which could be significant for individuals suffering from obesity.

The aim of this study is to compare the results of the SURMOUNT and SURPASS clinical trials in terms of the safety and impact on weight loss in patients who received TZP. This analysis aims to investigate potential differences in the safety profile and efficacy of this drug in different research conditions, which may contribute to a better understanding of its potential benefits and limitations in the context of obesity therapy.

METHODS

The literature review was conducted without any time, language, or study type restrictions, focusing on all available sources. We utilized databases such as PubMed, IEEE Xplore, ScienceDirect, and Google Scholar. Keywords used in the search included: "tirzepatide," "tirzepatide and obesity," "dual GIP and GLP-1 receptor agonists," "tirzepatide and SURPASS," "tirzepatide and SURMOUNT." Inclusion criteria comprised studies addressing at least one of the following topics: TZP, obesity, SURMOUNT, SURPASS, dual GIP and GLP-1 receptor agonists. Exclusion criteria included non-peer-reviewed articles, duplicates, and articles unrelated to the topic. In total, 1135 results were identified and subjected to further evaluation. The selection process proceeded in several stages:

1. Initial Selection – Removal of duplicates and review of titles and abstracts for compliance with inclusion criteria.
2. Full-Text Assessment – Detailed analysis of the content of articles qualified after the initial selection to confirm their compliance with inclusion criteria.
3. Final Selection – Selection of the most valuable publications based on their methodological quality, significance of results, and relevance to the review's objective.

After applying all exclusion criteria, 25 publications about the impact of TZP on weight reduction, its mechanisms of action, as well as potential side effects and therapy safety were ultimately

chosen for analysis. The selected articles encompassed a wide range of studies, including clinical trials, meta-analyses, and systematic reviews.

Mechanism of action of the drug

TZP acts as an agonist of the GIP and GLP-1 receptors, which are abundantly present in various cells, including pancreatic α and β cells, intestines, kidneys, brain, heart, and adipocytes. GLP-1 and GIP receptor analogs exhibit actions that increase glucose-dependent insulin secretion, thereby preventing postprandial hyperglycemia. Additionally, they inhibit glucagon secretion and reduce appetite by suppressing the hunger center, increasing feelings of fullness, which leads to weight loss [10]. The action of incretin drugs is dependent on glucose concentration – they do not affect the body when glucose levels are too low. Therefore, their use does not carry the risk of hypoglycemia. By prolonging the absorption time of nutrients in the intestine, TZP reduces the rise in insulin release, which beneficially affects blood pressure and lowers LDL (low-density lipoprotein) and triglyceride levels. Additionally, it inhibits the formation of atherosclerosis, although it does not reverse existing atherosclerosis [20,21].

History of the drug

The drug TZP was developed by the company Eli Lilly and Company (USA). On May 11, 2016, phase 1 studies and the main objective of the study was to determine the safety profile of TZP, and identify potential adverse effects associated with it, evaluating TZP pharmacokinetics, including the amount of substance entering the bloodstream as well as the time required for its elimination from the body. The impact of TZP on blood glucose levels and its potential hypoglycemic effects was also evaluated [16]. A year later, in 2017, phase 2 studies began involving 318 participants. The main goal was to investigate the efficacy and safety of TZP in participants with T2DM [11]. In 2019, Eli Lilly and Company (NYSE: LLY) published the results of several studies aiming to understand the role of TZP in lowering glycated hemoglobin levels and body weight in people with TZP [33]. The following year, the results of the phase 3 SURPASS 1-5 studies were published. Based on these results, in May 2022, the FDA approved TZP under the brand name Mounjaro as an adjunct to diet and physical activity to improve the control of TZP in adults [25]. In the same year, the FDA granted TZP (Mounjaro) a Fast Track designation for the treatment of adults with obesity or overweight accompanied by obesity-related conditions. SURMOUNT-1 and SURMOUNT-2 studies began, which were completed in 2023. Additionally, in July 2023, the results of the SURMOUNT-3 and SURMOUNT-4 studies were announced. In November 2023, the FDA approved TZP under the trade name Zepbound for the chronic treatment of obesity in adults with BMI ≥30 kg/m2 or in some patients with overweight (BMI ≥27 kg/m2) with at least one obesity-related condition (such as hypertension, dyslipidemia, TZP, obstructive sleep apnea, or cardiovascular diseases) for use in combination with a reduced-calorie diet and increased physical activity. The approval of Zepbound was based on the results of the phase 3 SURMOUNT-1 (adults with obesity or overweight without TZP) and SURMOUNT-2 (adults with obesity or overweight with TZP) studies, both of which demonstrated statistically significant weight loss compared to individuals receiving placebo after 72 weeks of treatment [9]. The European Medicines Agency (EMA), like the FDA, expanded the indications for the use of the drug in the same therapeutic area in November [24].

To the best of our knowledge, there is currently a lack of real-world evidence regarding the assessment of the effectiveness and safety of TZP in patients with BMI ≥30 or other disease state factors, as the drug was relatively recently approved by the FDA and EMA in November 2023.

SURMOUNT PROGRAM

The SURMOUNT program is a comprehensive research initiative comprising a series of clinical trials evaluating the efficacy and safety of TZP in the treatment of overweight and obesity. A comprehensive examination of TZP's potential therapeutic benefits in terms of weight reduction, improvement in quality of life, and overall health status could mark a breakthrough in the treatment of individuals struggling with overweight or obesity. Moreover, researchers have undertaken an analysis of TZP's potential impact on reducing the risk of cardiovascular diseases and enhancing physical fitness in individuals with obesity. The SURMOUNT clinical trials are phase 3 studies, multicenter, randomized, double-blind, placebo-controlled (SURMOUNT-1-4), or with a control group comprising patients treated with semaglutide (SURMOUNT 5).

The inclusion criteria were consistent across SURMOUNT-1, 3, 4, and 5 studies, necessitating a BMI ≥30 or a BMI ≥27 if accompanied by conditions such as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Additionally, patients were required to have a history

of at least one unsuccessful dietary effort to lose weight and be 18 years or older. Slightly different criteria were applied in SURMOUNT-2, where the inclusion criteria included a BMI of ≥27 kg/m^2 and TZP with HbA1c ≥7% to ≤10% at screening, on stable therapy for the last 3 months prior to screening. Additionally, the requirement of a history of at least one unsuccessful dietary effort to lose weight and being 18 years or older was also mentioned earlier. In all trials, outcome measures included percent change from baseline in body weight and the percentage of participants achieving ≥5% body weight reduction from baseline. Detailed information about the methodology of these studies is provided in Table 1.

Abbreviations: TZP - tirzepatide, PBO - placebo, BW - body weight, HbA1c - Hemoglobin A1c, T2DM - Type 2 Diabetes Mellitus, SC- subcutaneously

The SURMOUNT program comprises five clinical studies:

1. SURMOUNT-1 and SURMOUNT-2: Both studies focus on evaluating the efficacy and safety of specified doses of TZP. SURMOUNT-1 and did not include patients with diabetes. Several indications are suggesting that individuals with diabetes may exhibit a limited response to weight loss, prompting the design of SURMOUNT-2, which includes patients with T2DM [14].
2. SURMOUNT-3 and SURMOUNT-4: These studies investigate the efficacy and safety of TZP at maximum tolerated doses [1].
3. SURMOUNT-5: Its aim is to assess the efficacy and safety of TZP compared to semaglutide in adults with overweight or obesity who also have other health issues related to their weight but do not have TZP. This study is currently ongoing, with an estimated completion date of November 6, 2024 [32].

The studies were conducted in accordance with the recommendations for Good Clinical Practice and the principles of the Helsinki Declaration. Prior to the commencement of the study, each participating institution obtained approval from an independent ethics committee or institutional review board. All participants provided written consent to participate in the study, thereby confirming their awareness and voluntary participation [1,14,20,32,34].

At baseline, the parameters collected included demographic and clinical data: gender, age, BMI, fasting body weight, waist circumference, blood pressure, comorbidities, concomitant medications, and metabolic parameters, including fasting glucose levels, HbA1c, and fasting lipid levels. The primary efficacy endpoints of the therapy were the percentage change in body weight and the proportion of participants achieving a 5% decrease in body weight.

Tab. 1. Study populations, methodology, and endpoints SURMOUNT clinical trials.

Trial	SURMOUNT-1 [18]	SURMOUNT-2 [14]	SURMOUNT-3 [34]	SURMOUNT-4 [1]	SURMOUNT-5 [32]
Identifier	NCT04184622	NCT04657003	NCT04657016	NCT04660643	NCT05822830
Aim of the study	Evaluation of the efficacy and safety of TZP in obese or overweight adults who did not have diabetes.	Evaluation of the efficacy and safety of TZP, for weight management in obese adults with T2DM	Evaluation of the efficacy and safety of TZP in obese or overweight adults (but not suffering from diabetes) who successfully lost ≥5% of baseline weight during a 12-week lead-in period that provided intensive lifestyle intervention	Evaluation of the efficacy and safety of TZP in obese or overweight adults (but not suffering from diabetes) with diet and physical activity	Evaluation of the efficacy and safety of TZP compared with semaglutide in obese or overweight adults with weight--related comorbidities without T2DM
Inclusion criteria	BMI ≥30 kg/m^2, or ≥27 kg/m^2 and previous diagnosis with at least one of the following comorbidities* and history of at least 1 unsuccessful dietary effort to lose BW and 18 years and older	BMI of ≥27 kg/m^2 and T2DM with HbA1c ≥7% to ≤10% at screening, on stable therapy for the last 3 months prior to screening, and history of at least 1 self-reported unsuccessful dietary effort to lose BW and 18 years and older	BMI ≥30 kg/m2 or ≥27 kg/m2 and previously diagnosed with at least 1 of the following comorbidities*: and history of at least 1 unsuccessful dietary effort to lose BW and 18 Years and older	BMI ≥30 kg/m^2, or ≥27 kg/m^2 and previous diagnosis with at least one of the following comorbidities*: and history of at least 1 unsuccessful dietary effort to lose BW and 18 years and older	BMI ≥30 kg/m^2, or ≥27 kg/m^2 and previous diagnosis with at least one of the following comorbidities*: and history of at least 1 unsuccessful dietary effort to lose BW and 18 years and older
Randomized	YES	YES	YES	YES	YES
Double-Blind	YES	YES	YES	YES	NO
Placebo	YES	YES	YES	YES	NO
Intervention/treatment	Receive once-weekly, SC TZP (5 mg, 10 mg or 15 mg) or PBO in the ratio of 1:1:1:1	Receive once-weekly, SC TZP (10 mg and 15 mg) or PBO in the ratio of 1:1:1	Receive once-weekly, SC Receive once-weekly, TZP (10 mg or 15 mg) or PBO in the ratio of 1:1	Receive once-weekly, SC maximum tolerated dose TZP (10 mg or 15 mg) or PBO in the ratio of 1:1	Receive once-weekly, SC TZP 15 mg or semaglutide 2,4 mg
Treatment duration	72 weeks	72 weeks	72 weeks	88 weeks	74 weeks

* hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

Tab. 2. Baseline characteristics of patients included in SURMOUNT 1-4 clinical trials.

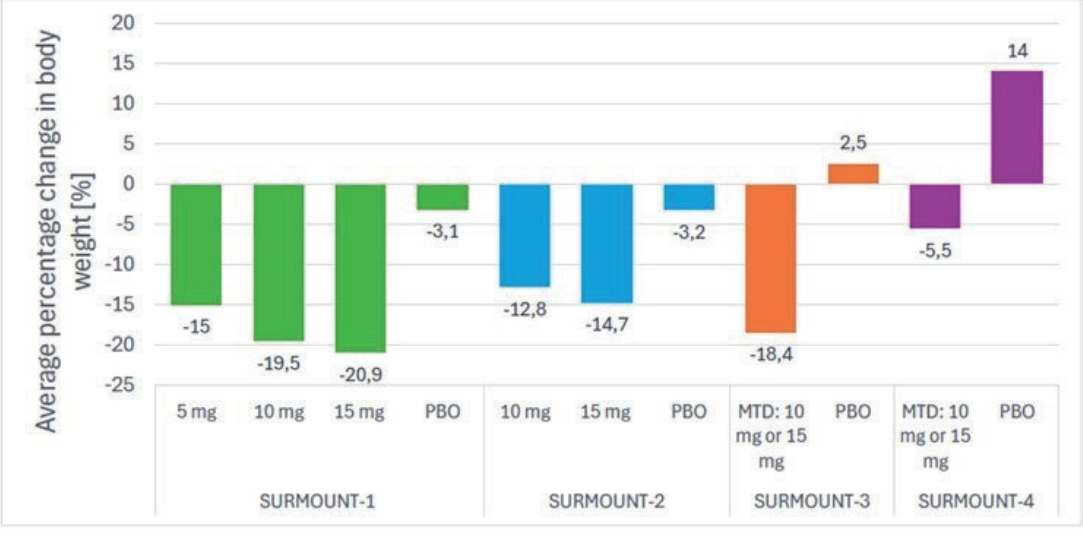
Trial	SURMOUNT-1 [18]	SURMOUNT-2 [14]	SURMOUNT-3 [34]	SURMOUNT-4 [1]
Identifier	NCT04184622	NCT04657003	NCT04657016	NCT04660643
Total (n)	2539	938	806	783
Female, n(%)	1714 (67.5)	476 (50.7)	534 (66.3)	546 (69.7)
Male, n(%)	825 (32.5)	462 (49.3)	272 (33.7)	237 (30.3)
Age (years), mean ± SD	44.9 ±12.5	54.2 ±10.6	44.9 ± 12.5	47.6 ±12.9
Weight, (kg), mean ± SD	104.8 ± 22.1	100.7 ± 21.1	109.7 ± 24.2	107.0 ± 22.5
BMI (kg/m2), mean ± SD	38.0 ± 6.8	36.1 ± 6.6	38.9 ±7.1	38.3 ± 6.6
waist circumference (cm), mean ± SD	114.1 ± 15.2	115.0 ± 14.4	116.2 ± 16.2	115.1 ± 14.6
Systolic blood pressure (mmHg), mean ± SD	123.3 ± 12.7	130.5 ± 12.1	125.6 ± 13.3	126.1 ±13.0
Diastolic blood pressure (mmHg), mean ± SD	79.5 ± 8.2	79.8 ± 8.4	81.3 ± 8.8	80.9 ± 8.3
HbA1c, mean ± SD	5.6 ± 0.4	8.0 ± 0.9	5.5 ± 0.4	5.5 ± 0.4
eGFR (obliczenia CKD-EPI, ml/min/1,73m2), mean ± SD	98.1 ± 18.0	95.2 ± 18.2	100.1 ± 16.8	97.6 ± 17.5

Abbreviations: SD- standard deviation, BMI- body mass index, HbA1c- glycated hemoglobin, eGFR- estimated glomerular filtration rate, CKD-EPI- Chronic Kidney Disease Epidemiology Collaboration

A total of 5766 participants were enrolled across the five studies. Data from Table 5 depict the baseline clinical characteristics of each study group. The mean age of participants ranged from 44.9 to 54.4 years, with a mean BMI ranging from 36.1 to 38.9. Women constituted the majority of the participants, ranging from 50.7% to 69.7% of the total population depending on the study. Table 2 illustrates the individual clinical characteristics of the participants at the initiation of the studies.

In the SURMOUNT-1 study, after 72 weeks of treatment, the mean percentage change in body weight was -15.0% (95% confidence interval [CI]: -15.9 to -14.2) among participants receiving weekly doses of TZP at 5 mg, -19.5% (95% CI, -20.4 to -18.5) at doses of 10 mg, and -20.9% (95% CI, -21.8 to -19.9) at doses of 15 mg. In the placebo group, a weight reduction of -3.1% (95% CI, -4.3 to -1.9) was observed. These differences were statistically significant (P<0.001 in all comparisons with placebo) [18]. In SURMOUNT-2, after 72 weeks of TZP treatment at doses of 10 mg and 15 mg, the estimated mean changes in body weight were -12.8% and -14.7%, respectively, compared to -3.2% in the placebo group. The differences compared to placebo were -9.6 percentage points (95% CI -11.1 to -8.1) for TZP 10 mg and -11.6 percentage points (95% CI -13.0 to -10.1) for TZP 15 mg (all P<0.0001) [14]. In the SURMOUNT-3 study, from randomization to week 72, TZP use resulted in a weight reduction of 18.4% compared to placebo, which led to a weight gain of 2.5%. The difference between treatment

Fig. 1. Mean percentage change in body weight in SURMOUNT 1-4 studies.



Abbreviations: PBO- placebo, MTD- maximum tolerated dose

Tab. 3. Study populations, methodology and endpoints SURPASS clinical trials.

Trial/ Identifier	Country/ countries treatment	Aim of the study	Inclusion criteria (combined)	Randomized, Double-blind, Placebo	Intervention/treatment	Primary Outcome Measures-Change from baseline in HbA1c	Secondary Outcome Measures-Change in body weight
SURPASS-1 [31] NCT03954834	India, Japan, Mexico, USA	Comparison of the efficacy and safety of TZP to PBO in participants with T2DM not under control with diet and exercise alone.	BMI ≥23 kg/m^2, T2DM, HbA1c ≥7.0% and ≤9.5%, naïve to diabetes injectable therapies, have not used any OAMs*, stable weight**, ≥ 18 years	YES, YES, YES	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or PBO in ratio a 1:1:1:1 for 40 weeks	YES	YES
SURPASS-2 [12] NCT03987919	8 countires	Comparison of the effect of the TZP to semaglutide on blood sugar levels in participants with T2DM	BMI ≥25 kg/m^2, T2DM, HbA1c ≥7.0% and ≤10.5%, stable treatment with unchanged dose of Met >1500 mg/day*, stable weight** ≥ 18 years	YES, NO, NO	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or 1 mg Semaglutide in ratio a 1:1:1:1 for 40 weeks	YES	YES
SURPASS-3 [22] NCT03882970	13 countries	Comparison of the effect of the TZP to insulin degludec on blood sugar levels in participants with T2DM	BMI ≥25 kg/m^2, T2DM, HbA1c ≥7.0% and ≤10.5%, stable treatment with unchanged dose of Met or Met + an SGLT-2 inhibitor*, stable weight**, ≥ 18 years	YES, NO, NO	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or Insulin Degludec in ratio a 1:1:1:1 for 52 weeks	YES	YES
SURPASS-4 [5] NCT03730662	14 countries	Comparison of the efficacy and safety of the TZP taken once a week to insulin glargine taken once daily in participants with T2DM and increased CVR	BMI ≥25 kg/m^2, T2DM, HbA1c ≥7.0% and ≤10.5%, stable treatment with an unchanged dose of at least 1 and no more than 3 types of OAMs (Met, SGLT-2 inhibitors, sulfonylureas)*, increased risk for CVR, stable weight**, ≥ 18 years	YES, NO, NO	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or Insulin Glargine in ratio a 1:1:1:3 for 52 weeks	YES	YES
SURPASS-5 [4] NCT04039503	8 countries	Comparison of the efficacy the safety of the TZP to placebo in participants with T2DM that are already on insulin glargine, ± Met	BMI ≥23 kg/m^2, T2DM, HbA1c ≥7.0% and ≤10.5%, have been treated with insulin glargine once daily ± Met*, stable weight**, ≥ 18 years	YES, YES, YES	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or placebo in a ratio of 1:1:1:1 for 40 weeks	YES	YES
SURPASS-6 [30] NCT04537923	15 countries	Comparison of the safety and efficacy of the study drug TZP to insulin lispro (U100) in participants with T2DM who are already on insulin glargine (U100) ± Met	BMI ≥23 kg/m^2 and ≤45 kg/m^2 at screening, T2DM, HbA1c ≥7.5% and ≤11%, have been treated with basal insulin or met ≥1500 mg/day sulfonylureas or DDP-4, stable weight**, ≥ 18 years	YES, NO, NO	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or prandial thrice-daily insulin lispro in ratio 1:1:1:3 for 52 weeks	YES	YES
SURPASS-J mono [17] NCT03861052	Japan	The reason for this study is to see if the study drug TZP is effective and safe compared to dulaglutide in participants with T2DM in Japan.	BMI ≥23 kg/m^2, T2DM, HbA1c ≥6,5% or ≥7% and ≤10.0%***, stable weight**, ≥ 18 years	YES, YES, NO	once-weekly, SC TZP (5 mg, 10 mg or 15 mg) or dulaglutide 0,75 mg in a ratio of 1:1:1:1	YES	YES
SURPASS-J combo [19] NCT03861039	Japan	Determine the long-term safety of the drug TZP in combination with oral antihyperglycemic medications in participants with T2DM.	BMI ≥23 kg/m^2, T2DM, HbA1c ≥7.0 and ≤11.0 %, have taken OAMs for at least 3 months before screening, stable weight**, ≥ 20 years	YES, NO, NO	once-weekly, SC TZP (5 mg, 10 mg or 15 mg) in a ratio of 1:1:1 for 52 weeks	YES	YES
SURPASS-AP combo [13] NCT04093752	China, South Korea, Australia and India	Comparison of the study drug TZP and insulin glargine in participants with T2DM on Met ± sulfonylurea.	BMI ≥23 kg/m^2, T2DM, HbA1c ≥7.5 and ≤11.0%, treated with stable Met ± sulfonylurea, insulin-naive, stable weight**, ≥ 18 years	YES, NO, NO	once-weekly SC TZP (5 mg, 10 mg or 15 mg) or insulin glargine in a ratio of 1:1:1:1 for 52 weeks	YES	YES
SURPASS-CVOT [26] NCT04255433	30 countries	Assess the efficacy and safety of TZP to dulaglutide in participants with T2DM and increased CVR	BMI ≥25 kg/m^2, T2DM, HbA1c ≥7.0% and ≤10.5%, have confirmed atherosclerotic cardiovascular disease, ≥ 40 years	YES, YES, NO	once-weekly SC TZP 15 mg or dulaglutide 1.5 mg in a ratio of 1:1, Treatment duration is event-driven	no data	no data

Abbreviations: PBO- placebo, TZP – tirzepatide, T2DM- type-2 diabetes mellitus, OAMs- oral antihyperglycemic medications, Met- metformina, SGLT-2-Sodium-glucose co-transporter-2, DDP-4 dipeptidyl peptidase 4 inhibitors, BMI- body mass index, SC- subcutaneously, CVR- cardiovascular risk.

* for at least 3 months before screening, ** (± 5%) for at least 3 months before screening, *** for participants who are OAMs-naïve at screening, ≥7.0% to ≤10.0% at both screening and baseline, for participants who have been taking OAM monotherapy at screening, ≥6.5% to ≤9.0% at screening, and ≥7.0% to ≤10.0% at baseline, ****Treated with stable metformin with or without sulfonylurea (metformin ≥1000 milligrams/day; sulfonylurea should be at least half the maximum dose) for at least 2 months

Tab. 4. Baseline characteristics of patients included in SURPASS clinical trials.

Trial, Identifier	Number of participants (n)	Female, n (%)	Male, n (%)	Age (years), mean ± SD	Weight, (kg), mean ± SD	BMI (kg/m2), mean ± SD	Systolic blood pressure (mmHg), mean ± SD	Diastolic blood pressurei (mmHg), mean ± SD	HbA1c, mean ± SD	eGFR (CKD-EPI, ml/min/1,73m2), mean ± SD
SURPASS-1 [31] NCT03954834	478	231 (48.3)	247 (51.7)	54.1±11.9	85.9±19.8	31.9±6.6	127.6±14.1	79.4±8.8	7.94±0.87	94.1±19.7
SURPASS-2 [12] NCT03987919	1879	997 (53.0)	882 (47.0)	56.6±10.4	93.7±21.9	34.2±6.9	130.6±13.8	79.2±9.0	8.28±1.03	96.0±17.1
SURPASS-3 [22] NCT03882970	1437	635 (44.2)	802 (55.8)	57.4±10.0	94.3±20.1	33.5±6.1	131.5±13.3	79.2±8.9	8.17±0.91	94.1±17.0
SURPASS-4 [5] NCT03730662	1995	749 (37.4)	1246 (62.6)	63.6±8.6	90.3±18.7	32.6±5.5	134.4±15.4	78.4±9.4	8.52±0.88	81.3±21.1
SURPASS-5 [4] NCT04039503	475	211 (44.4)	264 (55.6)	60.6±9.9	95.2±21.6	33.4±6.1	137.9±15.7	80.7±10.8	8.31±0.85	85.5±17.8
SURPASS-6 [30] NCT04537923	1428	824 (57.7)	604 (42.3)	58.8±9.75	90.7±18.5*	33.3±5.4*	No data	No data	8.8±0.99**	89.3±19.6*
SURPASS-J mono [17] NCT03861052	636	155 (24.37)	481 (75.63)	56.6±10.3	78.2±14.5	28.1±4.4	130.8±14.4	82.8±9.9	8.18±0.87	79 (71-86)**
SURPASS-J combo [19] NCT03861039	443	107 (24.2)	336 (75.8)	57.0±10.8	77.5±16.1	27.9±4.8	129.9±13.8	79.8±10.2	8.56±1.09	80 (72.86)**
SURPASS-AP combo [13] NCT04093752	907	400 (44.1)	507 (55.9)	54.1(11.4)	76.6(14.5)	27.9(4.0)	128.94(13.86)	82.76(9.32)	8.71(0.96)	895***

*only for patients treated with TZP, ** median (interquartile range), *** number of patients with ≥60 eGFR

Abbreviations: SD- standard deviation, BMI- body mass index, HbA1c- glycated haemoglobin, eGFR- estimated glomerular filtration rate, CKD-EPI- Chronic Kidney Disease Epidemiology Collaboration

and placebo was -20.8 percentage points, which was statistically significant (P < 0.001) (95% CI -23.2%, -18.5%; P < 0.001) [34]. In the SURMOUNT-4 study, the mean change in weight from week 36 to week 88 was -5.5% for TZP and 14.0% for placebo. The difference between TZP and placebo was -19.4% and was statistically significant (P < 0.001) (95% CI, -21.2% to -17.7%; P < 0.001) [1]. A summary and comparison of the study endpoints' results are depicted in Figure 1.

SURPASS PROGRAM

The clinical research program SURPASS was designed to assess the efficacy and safety of TZP as a therapy improving glycemic control in individuals with TZP. Phase III clinical trials of the SURPASS program include six international study groups: SURPASS-1 (NCT03954834) [31], SURPASS-2 (NCT03987919) [12], SURPASS-3 (NCT03882970) [22], SURPASS-4 (NCT03730662) [5],SURPASS-5 (NCT04039503) [4], SURPASS-6 (NCT04537923) [31]. Additionally, there are two studies among the Japanese population: SURPASS-J mono (NCT03861052) [17] and SURPASS-J combo (NCT03861039) [19], one study in the Asia-Pacific region: SURPASS-AP combo (NCT04093752) [13] and the SURPASS-CVOT (NCT04255433), which is currently ongoing [26]. The analyses included both a cohort of diabetic patients who had not been pharmacologically treated before (only with diet and lifestyle modifications) and a group of patients taking various oral antidiabetic drugs (such as metformin, sulfonylurea derivatives, pioglitazone, SGLT2 inhibitors, and/or insulin).

Some studies were conducted with a placebo control group, while others included active comparisons, such as dulaglutide and semaglutide, long-acting insulin analogs (glargine and degludec), or short-acting insulin analogs (lispro). The research within the SURPASS program aimed to evaluate TZP administered once weekly at doses of 5 mg, 10 mg, and 15 mg. Across all SURPASS studies, the primary outcome measure was the change from baseline in HbA1c. However, a secondary outcome measure in these studies was the change in body weight. Details of the methodology of the SURPASS studies are provided in Table 3.

All participants were adults aged > 18 years. Protocols were approved by local ethics committees, and the studies were conducted in accordance with the principles outlined in the Helsinki Declaration, Guidelines of International Medical Organizations for Human Research, and Good Clinical Practice

Fig. 2. Changes in body weight in the SURPASS 1-5 studies in populations of patients treated with TZP 5 mg, 10 mg, 15 mg, and in comparator groups.

*Comparative groups for SURPASS 1 and 5: individuals receiving placebo; for SURPASS-2: individuals receiving semaglutide; for SURPASS-3: individuals receiving insulin Degludec; for SUPRASS-4 and SURPASS-AP combo: individuals receiving Insulin Glargine; for SUPRASS-4: insulin lispro; for SURPASS-J mono: dulaglutide; for SURPASS-J combo: no comparative group was included.

guidelines. All participants provided written consent to participate in the studies [3].

A total of 9200 participants were enrolled across five studies. More men (65.7%) than women (44.3%) participated in the studies. The mean BMI ranged from 27.9 kg/m^2 to 34.2 kg/m^2. The highest mean body weight was observed in the SURPASS-5 study at 95.2 kg, while the lowest was in the SURPASS-AP combo study at 76.6 kg. The SURPASS-4 study recorded the highest mean ± SD age of 63.6±8.6, while the SURPASS-AP combo and SURPASS-1 studies recorded the lowest at 54.1±11.9. The key demographic and clinical data of the participants in the SURPASS studies are detailed in Table 4.

Within the SURPASS-1 study, a significant reduction in body weight was observed, showing a decrease ranging from -7.0 kg to -9.5 kg under TZP therapy, compared to -0.7 kg in the placebo group. The percentage of participants achieving weight reduction of 5% or more, 10% or more, and 15% or more was 67-78%, 31-47%, and 13-27%, respectively, among those receiving TZP therapy, compared to 14%, 1%, and 0% in the placebo group [31]. In the SURPASS-2 study, differences in weight reduction between groups receiving different doses of TZP (5 mg, 10 mg, and 15 mg) and the group receiving semaglutide were observed. The results showed the following values: -1.9 kg (95% CI, -2.8 to -1.0) with a dose of 5 mg TZP, -3.6 kg (95% CI, -4.5 to -2.7) with a dose of 10 mg TZP, and -5.5 kg (95% CI, -6.4 to -4.6) with a dose of 15 mg TZP (P<0.001 for all comparisons). Greater weight loss was observed with TZP compared to

semaglutide [12]. In the SURPASS-3 study, after 52 weeks, with a mean baseline body weight of 94.3 kg (standard deviation 20.1), weight reduction was observed in all three TZP dose groups (-7.5 kg to -12.9 kg). In contrast, patients using insulin degludec experienced an increase in body weight by 2.3 kg [22]. In the SURPASS-4 study, the following changes in body weight were observed: -7.1 kg with TZP 5 mg, -9.5 kg with 10 mg dose, -11.7 kg with 15 mg dose, and +1.9 kg with glargine [5]. In the SURPASS-5 study, compared to baseline, mean changes in body weight were: -5.4 kg with TZP 5 mg, -7.5 kg with 10 mg dose, -8.8 kg with 15 mg dose, and +1.6 kg with placebo [4]. In the SURPASS-6 study, the average change in body weight from baseline was -9.0 kg for TZP and 3.2 kg for insulin lispro, resulting in an estimated treatment difference of -12.2 kg (95% confidence interval, from -13.4 to -10.9) [30].

The results of the other SURPASS studies, SURPASS-J mono, SURPASS-J combo, SURPASS-AP combo, are depicted in Figure 2.

Drug safety

The safety assessment of TZP was conducted throughout the entire SURMOUNT and SURPASS clinical trials. It included the analysis of physical parameters, laboratory test results, and reported adverse events, including serious adverse events (SAEs), adverse events leading to therapy discontinuation, and deaths.

In the SURPASS clinical trials, the occurrence of SAEs ranged from 2.3% to 16.84%, depending on the specific study. Patients presenting at least one treatment-emergent adverse event ranged from 4.2% to 86.66%. Furthermore, adverse events leading to treatment discontinuation occurred in the range of 1.58% to 8.16%.

In the SURMOUNT 1-5 studies, cases of any SAE were reported in the range of 2.55% to 6.3%. Meanwhile, patients experiencing at least one treatment-emergent adverse event ranged from 49.68% to 78.38%. Adverse events leading to treatment discontinuation in the SURMOUNT 1-5 studies occurred in the range of 1.15% to 5.04%.

The most commonly observed adverse events were gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain, which were characterized by moderate severity. Gastrointestinal-related events occurred more frequently in the TZP group than in the placebo group.

CONCLUSIONS

Despite concerning epidemiological trends regarding obesity and pessimistic forecasts for the future, there is hope for effective and safe therapeutic options for individuals affected by this disease. The newly introduced TZP, a dual GIP/GLP-1 receptor agonist, presents itself as a promising treatment method for T2DM. Phase III clinical trials, such as SURPASS and SURMOUNT, have demonstrated that TZP not only effectively controls blood glucose levels but also leads to significant weight reduction while maintaining a relatively favorable safety profile. In this review, the effectiveness and safety of TZP based on Phase III clinical trials conducted within the SURPASS and SURMOUNT programs have been summarized. High effectiveness in weight reduction and a favorable safety profile have been demonstrated. It is important to continue research on the impact of TZP on the weight of individuals affected by obesity but without diabetes. Additionally, further studies on the drug's impact on cardiometabolic diseases and the economic viability of therapy will allow for a personalized approach to utilizing this medication. Furthermore, despite promising therapeutic effects, attention should be paid to the occurrence of adverse events, especially those related to the gastrointestinal tract, such as nausea, diarrhea, and abdominal pain. Although most of these symptoms were of moderate severity, further research is necessary to better understand the long-term effects of its use and to minimize the risk of adverse events.

AUTHORS' DECLARATION:

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