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Indirect comparative efficacy and safety of tirzepatide 10 and 15 mg versus semaglutide 2.4 mg for the management of obesity and overweight in patients with type 2 diabetes

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Abstract

Aims: This indirect treatment comparison (ITC) compared the efficacy and safety of tirzepatide with semaglutide for managing obesity or overweight in participants with type 2 diabetes (T2D), informed by the pivotal trials SURMOUNT-2 and STEP 2.

Materials and Methods: Participants had body mass index (BMI) ≥ 27 kg/m^2, with ≥1 unsuccessful prior dietary weight reduction effort and glycated haemoglobin (HbA1c) 7%–10% on stable therapy. A heterogeneity assessment confirmed that study and patient baseline characteristics were similar. Bucher ITCs compared tirzepatide 10 and 15 mg once-weekly (QW) to semaglutide 2.4 mg QW via placebo, all adjunct to a reduced-calorie diet and increased physical activity.

Results: Tirzepatide 10 and 15 mg were associated with statistically significant greater reductions in weight, BMI and HbA1c versus semaglutide. Tirzepatide 15 mg was associated with statistically significant greater odds versus semaglutide of ≥5% and ≥15% weight reduction and statistically significant improvements in several cardiometabolic risk factors, including waist circumference, fasting plasma glucose and triglycerides. Both tirzepatide doses showed non-significant trends of greater improvements in high-density lipoprotein, low-density lipoprotein, systolic blood pressure and diastolic blood pressure versus semaglutide as well as a generally comparable safety profile to semaglutide.

Conclusions: In this ITC versus semaglutide 2.4 mg, tirzepatide 10 and 15 mg were associated with statistically significant greater weight, BMI and HbA1c reduction and tirzepatide 15 mg with statistically significant improvements in multiple cardiometabolic risk factors crucial in managing obesity or overweight among patients with T2D. Both tirzepatide doses also had a generally similar safety profile to semaglutide.

Plain Language Summary

What is the context and purpose of this research study? Excess weight and type 2 diabetes (T2D) are strongly connected, where most patients with T2D have obesity or overweight. Weight management is crucial for improving T2D outcomes and preventing its progression. Weight management comprises behavioural interventions, psychological support, dietary changes and physical activity programmes. Medications may also be prescribed or surgical options may also be considered. Two such medications for weight management are tirzepatide (up to 15 mg) and semaglutide (up to 2.4 mg), which are injected subcutaneously once per week to help control appetite by prolonging patients' feeling of fullness. These medications are also used at different doses to treat T2D.

Because there were no clinical trials directly comparing tirzepatide and semaglutide, particularly in patients with both T2D and either obesity or overweight, this study aimed to indirectly compare the effectiveness and safety of tirzepatide and semaglutide for weight management in patients with overweight or obesity and T2D.

What was done? We indirectly compared the efficacy and safety of two doses of tirzepatide (10 and 15 mg per week) versus semaglutide 2.4 mg per week for weight management in adults with both T2D and either obesity or overweight. We used data from two large clinical trials, SURMOUNT-2 and STEP 2, which tested tirzepatide and semaglutide, respectively, against a placebo, all adjunct to diet and exercise. An indirect treatment comparison of tirzepatide and semaglutide was then possible via the placebo arm acting as the common comparator. The similarity of study design and patient populations in the two trials was evaluated and found to be sufficiently close to allow meaningful comparisons. Appropriate statistical methodology was used to facilitate comparisons of the two trials.

What were the main results? Compared to semaglutide 2.4 mg, the higher dose of tirzepatide (15 mg) was associated with a statistically significant improvement in several outcomes such as weight reduction, glycaemic outcomes and triglycerides, while the lower dose of tirzepatide (10 mg) was associated with some statistically significant improvements (e.g., weight reduction and HbA1c) and had otherwise comparable outcomes to semaglutide. However, both doses of tirzepatide were associated with statistically significant greater reductions in glycated haemoglobin A1c (HbA1c) compared to semaglutide, which is a key target of T2D treatment. Both doses of tirzepatide had a generally similar safety profile compared to semaglutide.

What is the originality and relevance of this study? Currently, there are no clinical trials that compare tirzepatide and semaglutide directly for the management of obesity and overweight in patients with T2D. Previous studies have compared tirzepatide and semaglutide results from different clinical trials for weight management in patients without T2D, not specifically focusing on patients with T2D.

This is the first study to indirectly compare tirzepatide and semaglutide for weight management in people with T2D who also have obesity or overweight. The findings of this study suggest that higher doses of tirzepatide may be more effective than semaglutide for weight reduction and improving other health-related outcomes in these patients.

KEYWORDS

GIP, GLP-1, type 2 diabetes, weight management

1 | INTRODUCTION

Obesity and type 2 diabetes (T2D) are correlated; 80%–90% of patients with T2D have obesity or overweight.[1–3] Additionally, obesity is associated with a 7-fold higher risk of developing T2D, while overweight is associated with a 3-fold higher risk of developing T2D compared to those with normal weight.[4] Obesity management has been shown to improve glycaemic control, metabolic outcomes, cardiovascular health, high-density lipoprotein (HDL) levels and triglyceride concentration levels in patients with T2D and delay or prevent progression from prediabetes to T2D.[5–10]

Obesity management and weight reduction are the cornerstones for the prevention and management of T2D, as evidenced by the current Diabetes UK guidelines and the European Association for the Study of Diabetes (EASD)-American Diabetes Association (ADA) consensus guidelines.[6,11] Recent European Association for the Study of Obesity (EASO) guidelines recommend a shift from a sole emphasis on weight reduction to a broader focus on improving overall health outcomes.[12] This includes not only weight reduction but also addressing obesity-related complications and enhancing the quality of life, mental well-being, physical functioning and social functioning, reflecting the need for sustained health improvements and a multifaceted management strategy.[12]

Management of obesity varies depending on factors including the patient's body mass index (BMI), degree of adiposity, waist circumference and associated risk factors, while taking into account the patient's complications and personalised therapy goals.[12,13] For patients with BMI ≥ 27 kg/m^2, obesity management medications (OMMs) may be considered and for those with BMI ≥ 30 kg/m^2, bariatric or metabolic surgery may be considered, provided there is at least one weight-related comorbidity.[13–15]

Among such OMMs, semaglutide 2.4 mg once-weekly (QW) is an injectable glucagon-like peptide-1 (GLP-1) receptor agonist (RA) approved in several regions for weight management adjunct to diet and physical activity in adults with obesity (BMI ≥ 30 kg/m^2) and overweight (BMI ≥ 27 kg/m^2) in the presence of at least one obesity-related complication (i.e., diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea [OSA] or cardiovascular disease [CVD]).[16–18] Lower doses of semaglutide are also approved for T2D treatment.[19–21] STEP 2, a double-blind randomised control trial (RCT), demonstrated that semaglutide 2.4 mg QW can substantially reduce body weight in participants with both T2D and either obesity or overweight.[22]

Tirzepatide is a once-weekly injectable glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA; representing a new class of OMM indicated for obesity management and T2D treatment in several regions globally.[23–26]

SURMOUNT-2 is the pivotal trial of tirzepatide for obesity and overweight management in participants with T2D.[27] This trial demonstrated substantial and clinically meaningful reductions in body weight for participants receiving tirzepatide 10 or 15 mg over a 72-week period, adjunct to a reduced-calorie diet and increased physical activity.[27]

Currently, there is no direct comparative evidence of tirzepatide versus semaglutide for the management of obesity and overweight in patients with T2D. SURMOUNT-5, a head-to-head trial, demonstrated statistically significant improvements for tirzepatide versus semaglutide regarding weight reduction and key secondary endpoints in adults with obesity or overweight without T2D. Although this trial directly compared tirzepatide to semaglutide, it was conducted in a population without T2D and therefore does not align with the objectives of this ITC.[28]

A recent cohort study found that tirzepatide was significantly more effective than semaglutide for weight management in participants with T2D; however, the study pooled results across treatment doses.[29] Additionally, for patients without T2D, indirect comparisons have shown tirzepatide 10 and 15 mg to be associated with improvements in weight reduction outcomes versus semaglutide 2.4 mg.[30,31]

For the treatment of T2D, tirzepatide has been compared directly in an RCT to semaglutide 1 mg,[32] and indirectly in an indirect treatment comparison (ITC) and a network meta-analysis (NMA) to semaglutide 0.5, 1 and 2 mg.[33,34] However, these comparisons did not focus only on participants with obesity or overweight, and the semaglutide doses were lower than the 2.4 mg dose indicated for obesity management.[16–18]

Therefore, here an ITC was performed to compare the efficacy and safety of tirzepatide 10 and 15 mg with semaglutide 2.4 mg, exclusively for the management of obesity and overweight in participants with T2D, at the primary timepoint of the pivotal trials SURMOUNT-2 and STEP 2.

2 | MATERIALS AND METHODS

2.1 | Data sources

Reported outcomes (weight reduction, lipid, blood pressure parameters, glycaemic and safety outcomes) from the entire trial population of the two pivotal trials, SURMOUNT-2 and STEP 2, were used to inform the ITC.[22,27]

The participant population of interest was aligned with SURMOUNT-2 and STEP 2: participants with obesity or overweight (BMI ≥ 27 kg/m^2) with ≥1 self-reported unsuccessful dietary weight reduction effort and a T2D diagnosis (HbA1c of 7%–10%) on stable therapy (diet and physical activity alone or with oral antihyperglycaemic medication) for ≥3 months before screening.[22,27]

2.2 | Heterogeneity assessment

The feasibility of conducting an ITC for SURMOUNT-2 and STEP 2 was assessed by evaluating heterogeneity in study design and baseline characteristics and considering the interventions, analysis timepoints and outcome and estimand definitions for both studies. This was to ensure the two studies were similar enough to compare robustly without the use of population-adjustment methods. Both

studies employed two estimands for efficacy outcomes: the treatment regimen estimand (SURMOUNT-2) or treatment policy estimand (STEP 2), which captured outcomes regardless of a participant's adherence to the assigned treatment; and the efficacy estimand (SURMOUNT-2) or trial product estimand (STEP 2), which reflected outcomes only for participants who remained on their assigned treatment for the entire study, without use of rescue medication.[22,27] These definitions aligned with the European Medicines Agency (EMA) definitions of estimands (treatment policy and on-treatment, respectively).[35]

Treatment effect modifiers (TEMs) were considered and compared for clinically relevant differences between both trials.[36]

The primary timepoints of each trial were used (Week 72 SURMOUNT-2, Week 68 STEP 2) and were considered comparable given the plateau observed across key outcomes prior to Week 68.[22,27] These timepoints also ensured that participants had a similar exposure duration to the maximum dose due to differences in dose escalation: 20 weeks for tirzepatide 15 mg compared to 16 weeks for semaglutide 2.4 mg.

2.3 | ITCs

Bucher ITCs were conducted to compare tirzepatide 10 and 15 mg QW versus semaglutide 2.4 mg QW via placebo (all adjunct to a reduced-calorie diet and increased physical activity) for several key efficacy and safety outcomes. Standard Bucher ITC methodology for between-trial comparisons was used (see Supporting Information for detailed methodology)[37] in line with key methodological guidance documents[38,39] using the statistical software R version 4.3.0.[40] Analyses of efficacy outcomes were conducted separately for the efficacy estimand and the treatment regimen estimand. Analyses of safety outcomes used the safety population.

3 | RESULTS

3.1 | Heterogeneity assessment

Both SURMOUNT-2 and STEP 2 were considered to have comparable study designs as they were both double-blind, parallel-group, randomised, placebo-controlled, phase 3, multinational trials, with similar inclusion criteria for participants with both T2D and either obesity or overweight. The background treatment was also comparable across both trials, with participants receiving regular lifestyle counselling, completing ≥150 min of physical activity per week and remaining on a diet amounting to total estimated energy requirements minus 500 kcal/day. The semaglutide 1 mg arm of STEP 2 was excluded from the heterogeneity assessment and ITC as this dose is not licensed for weight management.

Baseline use of oral antihyperglycaemic drugs was generally similar for both trials. SURMOUNT-2 did not report insulin use at baseline, but it was later noted that one participant who was receiving insulin was unintentionally enrolled in the trial. STEP 2 allowed basal insulin use; however, only one patient in the placebo arm reported using this. Therefore, the impact on glycaemic outcomes is negligible.[22,27] Biguanides were the most commonly used drug class in both studies, with 89% in SURMOUNT-2 and 91% in STEP 2 (Table S1).

Studies have identified key TEMs that significantly influence the effectiveness of treatments for weight management and T2D. A previous ITC of liraglutide and semaglutide via placebo in the non-T2D population noted that sex, baseline HbA1c and weight were likely TEMs, and therefore were considered of primary importance for this ITC.[41] Neither BMI nor waist circumference were considered as TEMs given their likely correlation with body weight. In addition to sex, baseline HbA1c and baseline weight, race/ethnicity (primarily the proportion of Hispanic participants) and OSA were also considered potential TEMs of secondary importance based on our clinical opinion, with agreement on these factors reached before conducting the analyses.[42]

Patient baseline characteristics across SURMOUNT-2 and STEP 2 were considered to be generally comparable (Table 1). Of particular interest for T2D, HbA1c (%) was very similar across trials. Similarly, baseline weight, waist circumference and BMI were comparable across both studies. The age, race and sex of participants were generally comparable across studies. Despite differences in the percentage of Asian, White and particularly Hispanic participants, a clinical assessment (conducted in accordance with ISPOR guidelines)[36] suggested relative homogeneity in the summary statistics of the TEMs of primary importance (sex, HbA1c and weight) across both SURMOUNT-2 and STEP 2, allowing Bucher ITCs to be conducted. Placebo was used as the common comparator, and results across placebo arms were generally similar for SURMOUNT-2 and STEP 2 across both estimands for efficacy outcomes (Table S2), with some differences found in lipid outcomes (triglycerides, low-density lipoprotein [LDL], HDL and total cholesterol). For safety outcomes, while rates of nausea adverse events (AEs) and discontinuation were similar across placebo arms, there were discrepancies in total gastrointestinal (GI) AEs (Table S2).

3.2 | ITC results

Results for the efficacy estimand and the safety population are presented below and summarised in Table 2. The efficacy estimand results highlight the maximum potential benefit of the treatment under ideal conditions, providing a benchmark for evaluating its effectiveness. Given the similarities observed between the efficacy and treatment regimen estimands for key weight reduction outcomes, efficacy estimand results are given here, while treatment regimen estimand results are given in Table S3.

3.2.1 | Efficacy outcomes

Tirzepatide 10 and 15 mg were associated with statistically significant greater reductions in body weight (kg) (mean difference [MD] [95%

TABLE 1 Patient baseline characteristics for the trial populations which were included in the analysis.

Characteristic		SURMOUNT-2 ($N = 938$)	STEP 2 ($N = 807$)[a]
Age (years), mean (SD)		54.2 (10.6)	55.0 (11.0)
Female (%)		50.7	51.2
Race/ethnicity[b] (%)	American Indian or Alaska Native	-	-
	Asian	13.3	27.3
	Black or African American	8.2	8.9
	White	75.7	59.3
	Native Hawaiian or other Pacific Islander	0.3	-
	Other	-	4.5
	Hispanic	59.8	11.9
Waist circumference (cm), mean (SD)		114.9 (14.4)	115.0 (14.1)
Body weight (kg), mean (SD)		100.7 (21.1)	100.2 (21.7)
BMI (kg/m^2), mean (SD)		36.1 (6.6)	35.9 (6.5)
HbA1c (%), mean (SD)		8.0 (0.9)	8.1 (0.8)
T2D (%)		100.0	100.0
OSA (%)		8.3	15.1

Note: Patient baseline characteristics for the whole trial population in SURMOUNT-2 and STEP 2. Continuous outcomes are shown as mean with SD, and binomial outcomes are given as the percentage of participants.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; N, the total number of individuals; OSA, obstructive sleep apnoea; SD, standard deviation; T2D, type 2 diabetes mellitus.

[a]The semaglutide 1 mg QW arm of the STEP 2 trial has been excluded from this summary.

[b]Participants could report on more than one race or ethnicity category, meaning that the total reported percentages can sum to >100%.

CI]: −2.80 kg [−4.56, −1.04], −4.90 kg [−6.62, −3.18]), body weight (%) (MD [95% CI]: −2.53% [−4.20, −0.86], −4.83% [−6.50, −3.16]) and BMI (MD [95% CI]: −1.00 kg/m^2 [−1.61, −0.39], −1.80 kg/m^2 [−2.41, −1.19]) versus semaglutide, with tirzepatide 15 mg comparisons having larger mean differences than tirzepatide 10 mg comparisons (Table 2, Figure 1). These results align with the arm-level results from each trial, where tirzepatide 10 and 15 mg demonstrated greater reductions in body weight (−13.43% and −15.65%, respectively) compared to semaglutide 2.4 mg (−10.64%) (Table S4).

Tirzepatide 15 mg was associated with statistically significant greater odds of participants achieving ≥5% and ≥15% weight reduction versus semaglutide, while tirzepatide 10 mg was associated with a non-significant trend of greater odds of participants achieving ≥5% and ≥15% weight reduction (Table 2, Figure S1). Both tirzepatide doses were associated with non-significant trends of greater odds of participants achieving ≥10% weight reduction (Table 2, Figure S1).

Tirzepatide 15 mg was associated with a statistically significant greater reduction in waist circumference versus semaglutide (MD [95% CI]: −3.76 cm [−5.50, −2.02]), while tirzepatide 10 mg was associated with a non-significant trend of greater reduction in waist circumference versus semaglutide (MD [95% CI]: −1.20 cm [−2.92, 0.52]) (Table 2, Figure 1).

For diabetes and glucose outcomes (Table 2, Figure 2), tirzepatide 10 and 15 mg were associated with statistically significant greater reductions in HbA1c versus semaglutide (MD [95% CI]: −0.47% [−0.70, −0.24], −0.56% [−0.79, −0.33]). Tirzepatide 15 mg was associated with a statistically significant greater reduction in fasting plasma glucose (FPG) versus semaglutide (MD [95% CI]: −0.46 mmol/L [−0.91, −0.01]), while tirzepatide 10 mg was associated with a non-significant trend of greater reduction versus semaglutide (MD [95% CI]: −0.33 mmol/L [−0.78, 0.12]).

For lipids, tirzepatide 15 mg was associated with a statistically significant greater reduction in triglycerides versus semaglutide, and tirzepatide 10 mg was associated with a non-significant trend of greater reduction versus semaglutide (Table 2). Tirzepatide 10 and 15 mg were associated with non-significant trends of greater improvements in total cholesterol, HDL and LDL versus semaglutide (Table 2). For blood pressure, both tirzepatide doses were associated with non-significant trends of greater reductions in diastolic blood pressure (DBP) and systolic blood pressure (SBP) versus semaglutide (Table 2).

3.2.2 | Safety outcomes

For safety outcomes (Table 2), tirzepatide 10 mg was associated with statistically significant smaller odds of participants experiencing total GI AEs versus semaglutide, and tirzepatide 15 mg was associated with a non-significant trend of smaller odds versus semaglutide. Both tirzepatide doses were associated with non-significant trends of smaller odds of participants experiencing nausea AEs versus semaglutide. Tirzepatide 10 mg was associated with non-significant trends of smaller odds of all-cause discontinuations and participants discontinuing due to AEs versus semaglutide, and tirzepatide 15 mg was associated with

TABLE 2 ITC results summary, efficacy estimand (weight reduction and cardiometabolic risk factors) and safety population (MDs or ORs with 95% CIs).

			Tirzepatide versus Semaglutide 2.4 mg QW	
Category	**Outcome**	**Outcome Measure**	**Tirzepatide 10 mg QW**	**Tirzepatide 15 mg QW**
Weight reduction	Weight CfB, kg	MD	−2.80 (−4.56, −1.04)	−4.90 (−6.62, −3.18)
	Weight CfB, %	MD	−2.53 (−4.20, −0.86)	−4.83 (−6.50, −3.16)
	≥5% weight reduction	OR	1.36 (0.82, 2.24)	1.96 (1.17, 3.31)
	≥10% weight reduction	OR	1.42 (0.74, 2.72)	1.85 (0.96, 3.57)
	≥15% weight reduction	OR	1.87 (0.68, 5.18)	2.85 (1.03, 7.88)
	BMI CfB, kg/m^2	MD	−1.00 (−1.61, −0.39)	−1.80 (−2.41, −1.19)
Cardiometabolic risk factors	Waist circumference CfB, cm	MD	−1.20 (−2.92, 0.52)	−3.76 (−5.50, −2.02)
	HbA1c CfB, %	MD	−0.47 (−0.70, −0.24)	−0.56 (−0.79, −0.33)
	FPG CfB, mmol/L	MD	−0.33 (−0.78, 0.12)	−0.46 (−0.91, −0.01)
	Triglycerides CfB, %	MD	−4.20 (−11.44, 3.04)	−8.30 (−15.38, −1.22)
	LDL CfB, %	MD	−1.74 (−8.21, 4.73)	−0.95 (−7.50, 5.60)
	HDL CfB, %	MD	0.69 (−2.91, 4.29)	3.41 (−0.29, 7.11)
	Total cholesterol CfB, %	MD	−2.98 (−6.80, 0.84)	−2.20 (−6.07, 1.67)
	SBP CfB, mmHg	MD	−0.40 (−3.20, 2.40)	−2.50 (−5.30, 0.30)
	DBP CfB, mmHg	MD	−0.80 (−2.53, 0.93)	−1.50 (−3.23, 0.23)
Safety	Total GI AEs	OR	0.64 (0.41, 0.99)	0.71 (0.46, 1.10)
	Nausea AEs	OR	0.74 (0.38, 1.44)	0.82 (0.42, 1.59)
	All-cause discontinuations	OR	0.72 (0.38, 1.36)	1.12 (0.61, 2.06)
	Discontinuations due to AEs	OR	0.55 (0.19, 1.58)	1.10 (0.41, 2.93)

Note: ITC results comparing tirzepatide (10 and 15 mg QW) versus semaglutide 2.4 mg QW for the efficacy estimand and safety population. MDs with 95% CIs are reported for continuous outcomes and ORs with 95% CIs for binomial outcomes. Green indicates where tirzepatide was associated with a statistically significant improvement compared to semaglutide.

Abbreviations: AE, adverse event; BMI, body mass index; CfB, change from baseline; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GI, gastrointestinal; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; OR, odds ratio; QW, once per week; SBP, systolic blood pressure.

non-significant trends of higher odds of all-cause discontinuations and participants discontinuing due to AEs versus semaglutide.

4 | DISCUSSION

4.1 | Key study findings

For efficacy outcomes based on the efficacy estimand, tirzepatide 10 and 15 mg were associated with statistically significant improvements in change from baseline (CfB) for weight (kg), weight (%), BMI and HbA1c when compared to semaglutide 2.4 mg, with tirzepatide 15 mg also associated with consistent statistically significant improvements across various other efficacy outcomes, such as ≥5% and ≥15% weight reduction, and CfB in waist circumference, FPG and triglycerides. While the estimated odds ratio (OR) for tirzepatide 15 mg versus semaglutide was similar for ≥5% and ≥10% weight reduction, the latter estimate was not statistically significant due to the greater variance associated with the small proportion of participants achieving ≥10% weight reduction in the placebo arms. Both tirzepatide doses were associated with non-significant trends of improvements for all other efficacy outcomes compared to semaglutide 2.4 mg. For ≥15% weight reduction, the greater magnitude of the estimated effect led to a statistically significant OR for tirzepatide 15 mg versus semaglutide despite the increased uncertainty.

The treatment regimen estimand and efficacy estimand ITCs arrived at similar conclusions regarding relative differences between tirzepatide and semaglutide. In terms of safety outcomes, tirzepatide was also associated with a generally similar safety profile to that of semaglutide or better for tirzepatide 10 mg regarding total GI AEs.

While tirzepatide was associated with improved efficacy versus semaglutide, optimising dose escalation is key to improving patient adherence. Balancing efficacy with tolerability and tailoring treatment to individual health profiles is essential for optimal outcomes.

This ITC is the first published evidence of the indirect comparative efficacy and safety of tirzepatide 10 and 15 mg versus semaglutide 2.4 mg in patients with both T2D, and either obesity or overweight, which evaluated outcomes beyond weight reduction. The findings of this study in patients with both T2D and either obesity or overweight align with those from other direct and indirect comparisons of tirzepatide and semaglutide in other target populations or with other treatment doses. SURPASS-2 reported on patients with

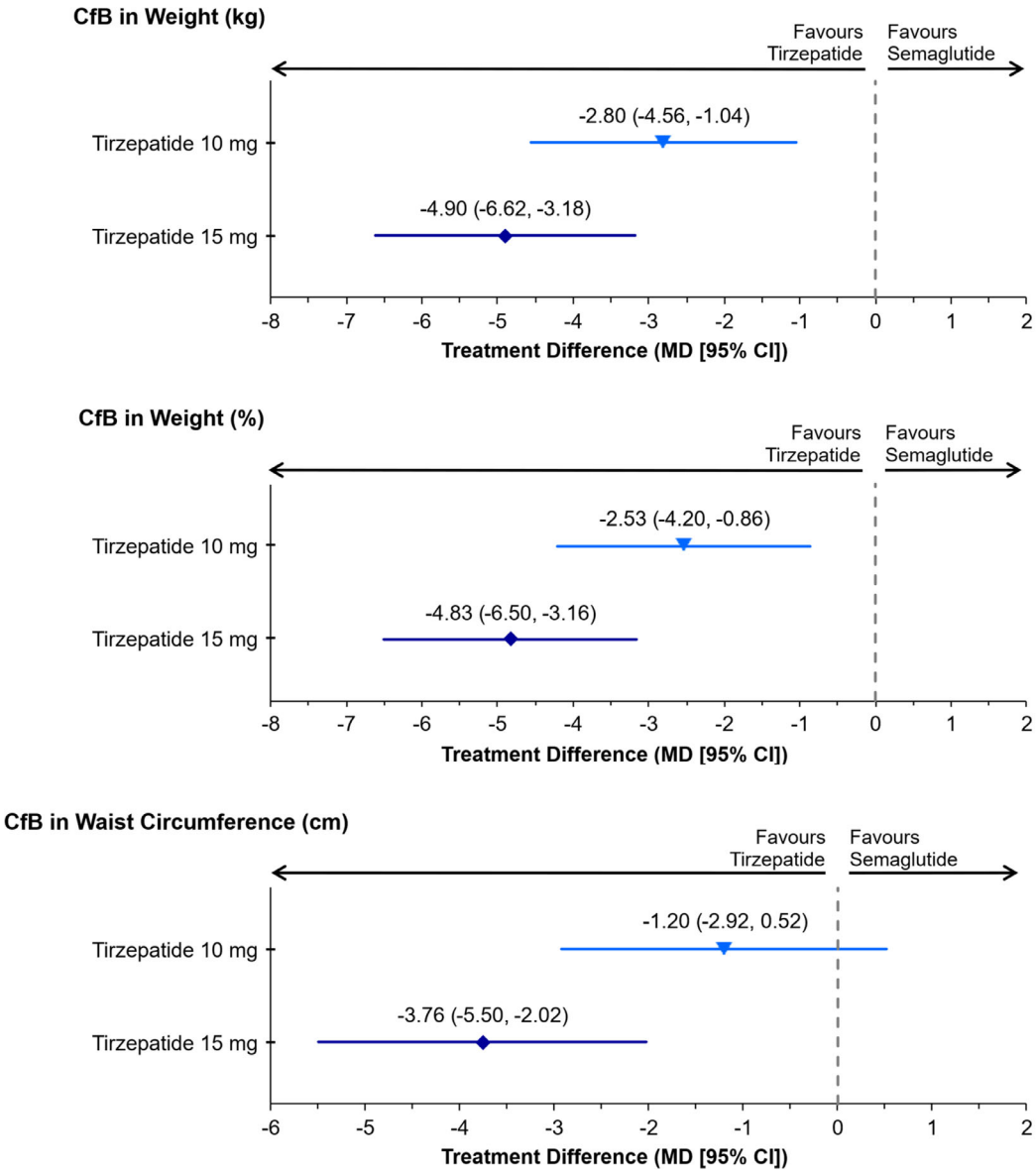

FIGURE 1 Weight and waist reduction efficacy estimand indirect treatment comparison (ITC) results. Forest plots for efficacy estimand ITC results comparing tirzepatide (10 and 15 mg once per week [QW]) versus semaglutide 2.4 mg QW for change from baseline (CfB) in weight (kg), CfB in weight (%) and CfB in waist circumference (cm). The point indicates the mean difference (MD) and the lines indicate the 95% confidence intervals (CIs). Point estimates to the left of the dotted line indicate where tirzepatide was associated with an improvement over semaglutide, and statistical significance is indicated where the 95% CIs do not overlap the dotted line.

T2D receiving tirzepatide 5, 10 and 15 mg and semaglutide 1 mg.[32] In a secondary endpoint of SURPASS-2, tirzepatide 10 and 15 mg showed statistically significant greater weight reduction versus semaglutide 1.0 mg (−3.6 and −5.5 kg, respectively).[32] An ITC comparing tirzepatide 5, 10 and 15 mg to semaglutide 2 mg via semaglutide 1 mg for the treatment of T2D using SURPASS-2 and SUSTAIN FORTE also showed an association with statistically significant greater weight reduction for tirzepatide 10 and 15 mg versus semaglutide 2 mg (−3.2 and −5.2 kg, respectively).[33] An NMA comparing tirzepatide 5, 10 and 15 mg to semaglutide 0.5, 1 and 2 mg, and a cohort study comparing pooled tirzepatide doses to pooled semaglutide doses, both in patients with T2D, reached similar conclusions, demonstrating that tirzepatide was consistently associated with greater or similar efficacy compared with semaglutide across all doses.[29,34] However, it is important to note that the semaglutide doses included in these analyses were unclear or lower than those indicated for the management of obesity and overweight. Additionally, not all participants in these studies had obesity or overweight. Nonetheless, the results from the aforementioned direct and indirect comparisons align with the results of this ITC, where tirzepatide 10 and 15 mg were associated with statistically significant greater weight reduction compared to semaglutide 2.4 mg (−2.80 and −4.90 kg, respectively). Given the lower semaglutide doses in the previous studies, the treatment differences between tirzepatide and semaglutide in these previous studies were more

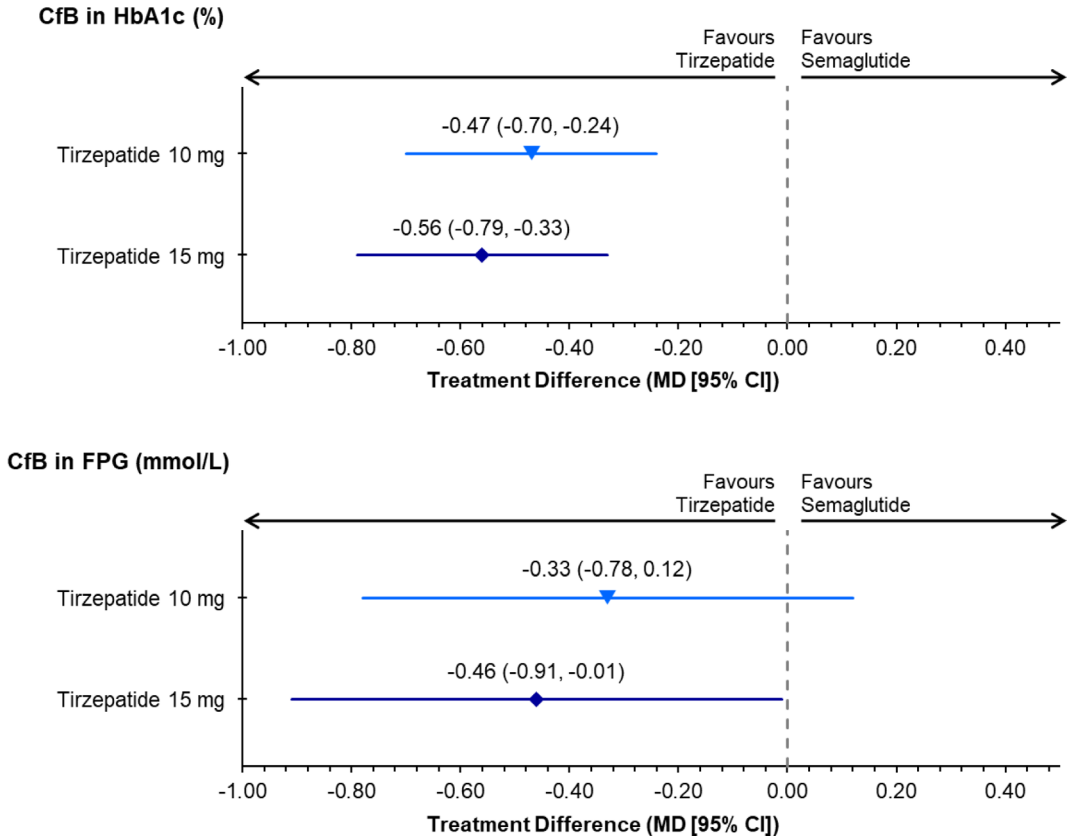

FIGURE 2 Diabetes and glycaemic parameters efficacy estimand indirect treatment comparison (ITC) results. Forest plots for efficacy estimand ITC results comparing tirzepatide (10 and 15 mg once per week [QW]) versus semaglutide 2.4 mg QW for change from baseline (CfB) in glycated haemoglobin (HbA1c) (%) and CfB in fasting plasma glucose (FPG) (mmol/L). The point indicates the mean difference (MD) and the lines indicate the 95% confidence intervals (CIs). Point estimates to the left of the dotted line indicate where tirzepatide was associated with an improvement over semaglutide, and statistical significance is indicated where the 95% CIs do not overlap the dotted line.

pronounced compared to this ITC; however, the results of this ITC underscore the substantial impact of tirzepatide on weight management across diverse patient populations and dosage comparisons.

Going beyond weight reduction, in patients with T2D tirzepatide 10 and 15 mg showed statistically significant greater reductions in HbA1c versus semaglutide 1 mg in SURPASS-2 (−0.39% and −0.45%, respectively),[32] and versus semaglutide 2 mg in an ITC (−0.36% and −0.40%, respectively).[33] These results are aligned with the statistically significant reductions in HbA1c demonstrated in this ITC (−0.47% and −0.56%).

It should be noted that the observed improvements in HbA1c for tirzepatide 10 and 15 mg versus semaglutide (−0.47% and −0.56%) represent a clinically meaningful difference for tirzepatide 15 mg for participants with T2D in line with previous clinical studies and guidelines, where a reduction of 0.5% is considered significant.[43–45] Since patients with T2D typically struggle with both weight management and glycaemic control, which are intricately linked and challenging to address simultaneously, a modest reduction in HbA1c can lead to significant long-term benefits, including reduced risk of T2D-related complications such as cardiovascular disease and microvascular complications including neuropathy and nephropathy.[46] Thus, the clinically and statistically significant greater reduction in HbA1c with tirzepatide 15 mg compared to semaglutide 2.4 mg highlights its potential as an effective treatment option for improving glycaemic control in patients with both T2D and either obesity or overweight.

4.2 | Strengths and generalisability

Two pivotal RCTs, SURMOUNT-2 (tirzepatide) and STEP 2 (semaglutide) were identified for the ITC. Within-trial bias was reduced as both were randomised placebo-controlled trials, and randomisation was preserved in the analysis.

To ensure comparability between SURMOUNT-2 and STEP 2, a thorough heterogeneity assessment was conducted. The two trials were found to be comparable in terms of study design, patient populations and reported outcomes. Both trials were multinational, with representation from North America, South America and Asia, implying that the ITC findings are generalisable across multiple geographies.

Standard Bucher ITC analyses were conducted[37] adhering to key methodological guidance.[38,39] Results for efficacy outcomes were produced across both efficacy and treatment regimen estimands, and the direction of results was generally consistent across both estimands.

4.3 | Limitations

The focus on two pivotal trials, SURMOUNT-2 and STEP 2, resulted in a robust evidence base, but ultimately restricted the study to comparisons informed exclusively by these two trials. Treatment comparisons were, therefore, only possible for outcomes reported by both trials. The absence of data reported in STEP 2 for the percentage of participants achieving ≥20% weight reduction and severe GI AEs for the safety population precluded the analysis for these outcomes.

While the study characteristics of SURMOUNT-2 and STEP 2 were generally very similar, there may be differences in the reporting of AEs, which may impact the interpretations of the safety analysis results. Differences may be caused by variations in collection methods being used, such as questionnaires with checkboxes, open format or investigator team verbal questioning. In addition, STEP 2 was conducted before the COVID-19 pandemic, while SURMOUNT-2 was conducted during the COVID-19 pandemic. Therefore, the results of the safety analyses should be interpreted with care.

Finally, although the two trials were generally well-balanced in their TEMs, facilitating a robust comparison, some differences were found in the demographic characteristics. Notably, the studies differed in the percentage of Asian, White and Hispanic participants and only STEP 2 included European participants. To what extent this heterogeneity influences the comparisons between tirzepatide and semaglutide remains unclear.

5 | CONCLUSION

This indirect comparison study provides evidence for the clinical efficacy and safety of tirzepatide 10 and 15 mg relative to semaglutide 2.4 mg in the management of obesity and overweight in patients with T2D. By comparing the pivotal trials SURMOUNT-2 and STEP 2 based on a comprehensive heterogeneity assessment and appropriate statistical methodology, a rigorous indirect comparison was produced.

With tirzepatide 15 mg showing the largest improvements, tirzepatide 10 and 15 mg showed improvements across efficacy outcomes compared to semaglutide 2.4 mg. Furthermore, the safety profile of tirzepatide 10 and 15 mg was found to be generally similar to that of semaglutide 2.4 mg.

AUTHOR CONTRIBUTIONS

All authors provided critical revision of the manuscript for important intellectual content and have participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have given their final approval of the manuscript to be published. In addition, AC and EJ were involved in the conception of the work and the interpretation of the data. SZR was involved in the analysis and interpretation of the data, and the drafting of the work. GKD was involved in the interpretation of the data. MB and LF were involved in the analysis and interpretation of the data. TC and LJC were involved in the conception and design of the work, the acquisition, analysis and interpretation of the data, and the drafting of the work. HS was involved in the acquisition, analysis and interpretation of the data. JFB was involved in the conception and design of the work, and the interpretation of the data.

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CONFLICT OF INTEREST STATEMENT

AC: Honoraria from AstraZeneca, Boehringer Ingelheim, Lilly, Novo Nordisk; Member of the DMC of Boehringer Ingelheim clinical trials–SYNCRONIZE program; EJ, SZR, GKD, MB, LF, HS: Employee and shareholder of Eli Lilly and Company; TC, LJC: Employees of Costello Medical, which received payment from Eli Lilly and Company for analytical services for this study; JFB: Received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Gilead, GSK, IQVIA, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, Takeda.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16508.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date for data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after a receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

REFERENCES

1. Nianogo RA, Arah OA. Forecasting obesity and type 2 diabetes incidence and burden: the ViLA-obesity simulation model. *Front Public Health*. 2022;10:818816.
2. Andréasson K, Edqvist J, Adiels M, et al. Body mass index in adolescence, risk of type 2 diabetes and associated complications: a nationwide cohort study of men. *EClinicalMedicine*. 2022;46:101356.
3. Ruze R, Liu T, Zou X, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Front Endocrinol*. 2023;14:1161521.
4. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract*. 2010;89(3):309-319. doi:10.1016/j.diabres.2010.04.012

5. Khavandi K, Amer H, Ibrahim B, Brownrigg J. Strategies for preventing type 2 diabetes: an update for clinicians. *Therap Adv Chronic Dis*. 2013;4(5):242-261.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;65(12):1925-1966.
7. Jiménez JM, Carbajo MA, López M, et al. Changes in lipid profile, body weight variables and cardiovascular risk in obese patients undergoing one-anastomosis gastric bypass. *Int J Environ Res Public Health*. 2020;17(16):5858. doi:10.3390/ijerph17165858
8. Shinde S, Thieu VT, Kwan AY, Houghton K, Meyers J, Schapiro D. Impact of weight change on glycemic control and metabolic parameters in T2D: a retrospective US study based on real-world data. *Diabetes Ther*. 2024;15(2):409-426.
9. Silitonga HA, Siahaan JM, Anto EJ. Correlation between obesity and lipid profile in type 2 diabetes mellitus patients at the endocrine and metabolic polyclinic in general hospital Pirngadi Medan. *Open Access Maced J Med Sci*. 2019;7(8):1309-1313. doi:10.3889/oamjms.2019.312
10. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481-1486. doi:10.2337/dc10-2415
11. NHS England. NHS Diabetes Prevention Programme (NHS DPP). Accessed January 29, 2025, https://www.england.nhs.uk/diabetes/diabetes-prevention/
12. Busetto L, Dicker D, Frühbeck G, et al. A new framework for the diagnosis, staging and management of obesity in adults. *Nat Med*. 2024;30:1-5.
13. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-e891. doi:10.1503/cmaj.191707
14. Yumuk V, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. *Obes Facts*. 2015;8(6):402-424. doi:10.1159/000442721
15. Dietz WH, Belay B, Bradley D, et al. A model framework that integrates community and clinical systems for the prevention and management of obesity and other chronic diseases. *NAM Perspectives*. 2017.
16. European Medicines Agency (EMA). Wegovy (semaglutide) Summary of Product Characteristics. Accessed January 29, 2025. https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf
17. U.S. Food and Drug Administration (FDA). Wegovy (semaglutide) injection, for subcutaneous use. Accessed April 2, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215256s007lbl.pdf
18. Medicines and Healthcare products Regulatory Agency (MHRA). Wegovy 2.4 mg Solution for Injection in Pre-filled Pen – PLGB 04668/0433. Public Assessment Report. Accessed May 30. 2024, https://mhraproducts4853.blob.core.windows.net/docs/beebbeb97c4051a1d965fe7050835904f621122c
19. European Medicines Agency (EMA). Ozempic (semaglutide) Summary of Product Characteristics. Accessed January 29, 2025. https://www.ema.europa.eu/en/documents/product-information/ozempic-epar-product-information_en.pdf
20. U.S. Food and Drug Administration (FDA). Ozempic (semaglutide) injection, for subcutaneous use. Accessed January 29, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf
21. Medicines and Healthcare products Regulatory Agency (MHRA). Ozempic 2 mg Solution for Injection in Pre-Filled Pen – PLGB 04668/0435. Public Assessment Report. Accessed January 29, 2025. https://mhraproducts4853.blob.core.windows.net/docs/851066223f7ec7aab00effba53bc55a922cb772e
22. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2· 4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *The Lancet*. 2021;397(10278):971-984.
23. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *New Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
24. European Medicines Agency (EMA). Mounjaro (tirzepatide) Summary of Product Characteristics. Accessed January 29, 2025. https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf
25. Medicines and Healthcare products Regulatory Agency (MHRA). Mounjaro 15 mg Solution for Injection in Pre-filled Pen – PLGB 14895/0323. Public Assessment Report. Accessed January 29, 2025. https://mhraproducts4853.blob.core.windows.net/docs/74a8638b13b81668c1f35bf5b2bd68bf433c7d05
26. U.S. Food and Drug Administration. Mounjaro Full Prescribing Information. Accessed January 29, 2025. https://www.accessdata.fda.gov/spl/data/b597917f-9673-4331-809d-79a538bb943c/b597917f-9673-4331-809d-79a538bb943c.xml
27. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *The Lancet*. 2023;402:613-626.
28. Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *New England J Med*. 2025. doi:10.1056/NEJMoa2416394
29. Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, et al. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. *JAMA Intern Med*. 2024;184(9):1056-1064. doi:10.1001/jamainternmed.2024.2525
30. Azuri J, Hammerman A, Aboalhasan E, Sluckis B, Arbel R. Tirzepatide versus semaglutide for weight loss in patients with type 2 diabetes mellitus: a value for money analysis. *Diabetes Obes Metab*. 2023;25(4):961-964.
31. le Roux CW, Hankosky ER, Wang D, et al. Tirzepatide 10 and 15 mg compared with semaglutide 2.4 mg for the treatment of obesity: an indirect treatment comparison. *Diabetes Obes Metab*. 2023;25(9):2626-2633.
32. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *New Engl J Med*. 2021;385(6):503-515.
33. Vadher K, Patel H, Mody R, et al. Efficacy of tirzepatide 5, 10 and 15 mg versus semaglutide 2 mg in patients with type 2 diabetes: an adjusted indirect treatment comparison. *Diabetes Obes Metab*. 2022;24(9):1861-1868. doi:10.1111/dom.14775
34. Karagiannis T, Malandris K, Avgerinos I, et al. Subcutaneously administered tirzepatide vs semaglutide for adults with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Diabetologia*. 2024;67(7):1206-1222. doi:10.1007/s00125-024-06144-1
35. European Medicines Agency (EMA). ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Accessed 29 January 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
36. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR task force on indirect treatment comparisons good research practices: part 2. *Value Health*. 2011;14(4):429-437. doi:10.1016/j.jval.2011.01.011
37. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683-691. doi:10.1016/s0895-4356(97)00049-8

38. Dias S, Sutton AJ, Welton NJ, Ades A. NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, Meta-Regression, Bias and Bias-Adjustment. Report by the Decision Support Unit. 2011.
39. Health Technology Assessment Coordination Group (HTA CG). Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024.
40. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2023.
41. National Institute for Health and Care Excellence (NICE). Semaglutide for managing overweight and obesity (GID-TA10765). 2022.
42. Nunes AP, Loughlin AM, Qiao Q, et al. Tolerability and effectiveness of exenatide once weekly relative to basal insulin among type 2 diabetes patients of different races in routine care. *Diabetes Ther*. 2017;8(6):1349-1364. doi:10.1007/s13300-017-0314-z
43. Lameijer A, Fokkert M, Edens M, Slingerland R, Bilo H, van Dijk P. Determinants of HbA1c reduction with FreeStyle libre flash glucose monitoring (FLARE-NL 5). *J Clin Transl Endocrinol*. 2020;22:100237.
44. Lenters-Westra E, Weykamp C, Schindhelm RK, Siebelder C, Bilo HJ, Slingerland RJ. One in five laboratories using various hemoglobin A1c methods do not meet the criteria for optimal diabetes care management. *Diabetes Technol Ther*. 2011;13(4):429-433.
45. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. NICE guideline [NG28]2015.
46. Blüher M, Ceriello A, Davies M, et al. Managing weight and glycaemic targets in people with type 2 diabetes-how far have we come? *Endocrinol Diabetes Metab*. 2022;5(3):e00330. doi:10.1002/edm2.330

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