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Tirzepatide 10 and 15 mg compared with semaglutide 2.4 mg for the treatment of obesity: An indirect treatment comparison

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Abstract

Aim: To compare the efficacy of tirzepatide 10 and 15 mg with semaglutide 2.4 mg using an indirect treatment comparison.

Materials and Methods: Using SURMOUNT-1 and STEP 1 trial data, mean percentage change in body weight from baseline and odds ratio (OR) of achieving 5% or greater weight loss were compared between tirzepatide 10 and 15 mg at week 72 and semaglutide 2.4 mg at week 68 using matching-adjusted indirect comparison of the efficacy estimand. Sensitivity analyses were completed using different methods, including the Bucher method, also using different estimands and/or time points.

Results: Greater reductions in percentage change in body weight were observed with tirzepatide 10 and 15 mg versus semaglutide 2.4 mg (tirzepatide 10 mg mean difference: −4.67% [95% CI −5.91%, −3.43%]; tirzepatide 15 mg mean difference: −5.92% [95% CI −7.16%, −4.68%]; both $P < .001$). Similarly, more participants achieved 5% or greater weight loss with tirzepatide 10 mg (OR 2.61 [95% CI 1.48, 4.57]; $P < .001$) and 15 mg (OR 2.75 [95% CI 1.57, 4.81]; $P < .001$) compared with semaglutide 2.4 mg. All sensitivity analyses were consistent, except for an OR of achieving 5% or greater weight loss with tirzepatide 10 mg using the Bucher method to analyse the treatment regimen estimand ($P = .074$).

Conclusions: Currently there are no direct comparisons of tirzepatide and semaglutide for weight management. Using the matching-adjusted indirect treatment comparison method to compare the efficacy of tirzepatide and semaglutide for chronic weight management, this analysis showed greater weight loss with tirzepatide 10 and 15 mg versus semaglutide 2.4 mg.

KEYWORDS
incretin-based therapies, obesity, semaglutide, tirzepatide, weight loss

1 | INTRODUCTION

In the last 50 years, obesity has increased to pandemic levels.[1] The pathogenesis of obesity is complex, involving sociocultural, environmental, genetic, physiological and behavioural factors. Obesity is now recognized as a disease[2] and treatments that induce short-term weight loss often fail over time. Effective treatments are needed to address the complex and persistent hormonal, metabolic and neurochemical adaptations; poor adherence; and persistence experienced by those living with obesity.[1]

Semaglutide 2.4 mg is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist (RA) that was approved for chronic weight management in June 2021.[3] The phase 3 STEP 1 trial showed that, in people with obesity or overweight (without diabetes), semaglutide 2.4 mg treatment resulted in 16.9% or 14.9% body weight loss using the efficacy and treatment regimen estimands, respectively, after 68 weeks of treatment with mostly mild or moderate adverse events (the most frequently reported adverse events were gastrointestinal).[4] Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA that was recently approved in the United States for the treatment of people with type 2 diabetes (T2D) and is in development for chronic weight management.[5] In the phase 3 SURMOUNT-1 study of people with obesity or overweight (without diabetes), tirzepatide treatment resulted in mean body weight reductions of up to 22.5% or 20.9% using the efficacy and treatment regimen estimands, respectively, at week 72, with mostly mild or moderate adverse events (the most frequently reported adverse events were gastrointestinal).[6]

Currently, there are no head-to-head studies comparing tirzepatide with semaglutide for chronic weight management. This study aimed to use indirect treatment comparisons (ITCs)[7,8] using placebo as the common comparator to provide evidence on the comparative efficacy of tirzepatide 10 and 15 mg versus semaglutide 2.4 mg. As baseline characteristics such as gender, baseline body weight and prediabetes were hypothesized to be potential effect modifiers,[9] a population-adjusted indirect comparison was used to account for differences in the study populations.

2 | METHODS

2.1 | Primary analysis

A systematic literature review was used to identify trials eligible for inclusion in the ITC network comparing tirzepatide with semaglutide 2.4 mg with placebo as the common comparator. The PICOS criteria and PRISMA diagram are provided in Table **S1** and Figure **S1**, respectively. The systematic literature review identified three studies eligible for inclusion: SURMOUNT-1, STEP 1 and STEP 8. STEP 8 was excluded from the analysis based on the pooled placebo arm, which included two placebo arms with different administration schedules.[10] By design, the pooling of placebo arms with different administration schedules, as in STEP 8, may not be comparable with the SURMOUNT-1 and STEP 1 placebo arms.

Matching-adjusted indirect comparison (MAIC) was conducted according to Signorovitch et al.[11] To reduce bias and enable valid treatment comparison across trials, we weighted the individual SURMOUNT-1 patient data to match the aggregate data in STEP 1. Individual patient data were not available for STEP 1, but were available for SURMOUNT-1. Aggregate published data were used for STEP 1. The key baseline characteristics of the participants enrolled in SURMOUNT-1 and STEP 1 are summarized in Table 1. The baseline characteristics of patients enrolled in SURMOUNT-1 and STEP 1 were assessed for differences, especially in variables that are possible effect modifiers, including gender, prediabetes and baseline body weight. MAIC weights individual patient data to match the characteristics of the comparator's patient population to weight treatment effect modifiers that differ between the studies. For the primary analysis, we matched for gender because of it being considered the only variable to have differed meaningfully between the trials with a standardized difference of 0.15. The rest of the baseline characteristics were quite balanced between the two studies, with standardized differences of less than 0.1. Baseline data for SURMOUNT-1 were reweighted using the method of moments to balance gender differences with semaglutide aggregate data.[9] The MAIC was anchored to the common placebo arm. Figure 1 shows the ITC network used in the primary and secondary analyses.

TABLE 1 Key baseline characteristics in the SURMOUNT-1, STEP 1 and weighted SURMOUNT-1 trials

	SURMOUNT-1 ($N = 2539$)	STEP 1 ($N = 1961$)	Weighted[a] SURMOUNT-1 ($N = 2490$)
Mean age (SD), y	44.9 (12.5)	46 (13)	44.9 (12.4)
Female proportion	67.5%	74.1%	74.1%
Mean body weight (SD), kg	104.8 (22.1)	105.3 (21.9)	103.8 (21.7)
Mean BMI (SD), kg/m^2	38.0 (6.8)	37.9 (6.7)	38.0 (6.8)
Mean waist circumference (SD), cm	114.1 (15.2)	114.7 (14.6)	113.5 (14.9)
Prediabetes proportion at randomization	40.6%	43.7%	40.2%

Note: Prediabetes defined as fasting blood glucose 100-125 mg/dL (5.6-6.9 mmol/L), 2-hour blood glucose 140-199 mg/dL (7.8-11.0 mmol/L) during oral glucose tolerance test and/or HbA1c 5.7%-6.4% (39-47 mmol/mol).
Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Patient data weights to balance the gender are 1.1 for female and 0.8 for male.

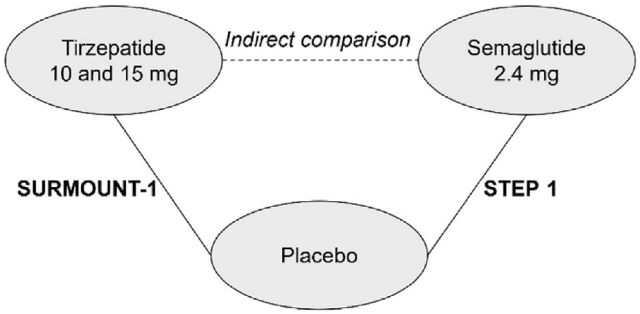

FIGURE 1 Matching-adjusted indirect treatment comparison of tirzepatide 10 and 15 mg versus semaglutide 2.4 mg using placebo as the common comparator

2.1.1 | Study and participant characteristics

Study characteristics and key inclusion criteria of the SURMOUNT-1 and STEP 1 trials are detailed in Table 1. Both trials were double-blind, parallel-group, randomized, placebo-controlled, phase 3, multinational trials with the same key inclusion criteria of a body mass index (BMI) of 30 kg/m^2 or greater, or a BMI of 27 kg/m^2 or greater with at least one weight-related complication, excluding diabetes.[4,6] In SURMOUNT-1 and STEP 1, background therapy to the treatment and placebo arms involved lifestyle interventions, including regular lifestyle counselling sessions, a deficit of 500 calories per day and at least 150 minutes of physical activity per week. There was a difference between the studies regarding the timing of the primary endpoint (72 vs. 68 weeks for SURMOUNT-1 and STEP 1, respectively) (Table 2). The titration of tirzepatide to 15 mg per week was 4 weeks longer than the titration to semaglutide 2.4 mg per week. For the primary analyses, the endpoints were compared at these two time points, consistent with the primary endpoints for these studies.

Primary outcomes were based on the efficacy estimand (referred to as the 'trial product estimand' in the STEP programme). The efficacy estimand represented the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, if the treatment was administered as intended (according to the hypothetical strategy in the ICH E9 [R1] addendum14). For continuous outcomes, the relative treatment effect was evaluated with the mean difference. For binary outcomes, the relative treatment effect was evaluated with the odds ratio (OR).

MAIC was performed using R version 4.1.2.

2.2 | Outcomes

The co-primary endpoints were the percentage change in body weight from baseline to week 72 (SURMOUNT-1) or week 68 (STEP 1) and the percentage of participants achieving at least 5% weight reduction at week 72 (SURMOUNT-1) or week 68 (STEP 1). The predetermined primary outcomes for SURMOUNT-1 were with tirzepatide 10 and 15 mg; the outcomes of the 5 mg dose were considered secondary endpoints. The co-primary endpoints were controlled for type 1 error rate in both trials. Mean treatment difference (95% CI) and OR (95% CI) are reported.

TABLE 2 Overview of the study characteristics and key inclusion criteria of the SURMOUNT-1 and STEP 1 trials

Trial name	SURMOUNT-1	STEP 1
Study design	Double-blind, parallel-group, randomized, placebo-controlled, phase 3, multinational	Double-blind, parallel-group, randomized, placebo-controlled, phase 3, multinational
Key inclusion criteria	BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with ≥ 1 weight-related complication, excluding diabetes	BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with ≥ 1 weight-related complication, excluding diabetes
Time of primary endpoint	72 wk	68 wk
Randomized treatment	Tirzepatide 5, 10 and 15 mg	Semaglutide 2.4 mg
No. of randomized patients (ratio)	2539 (1:1:1:1)	1961 (2:1)
Key regions of enrolment	United States, Argentina, Mexico, Brazil	United States, France, Germany, India, UK
Time of study conduct	2019-2022	2018-2021
Co-primary endpoint	Percentage change in body weight from baseline to week 72 and a weight reduction of 5% or more at week 72 for 10- and 15-mg doses	Percentage change in body weight from baseline to week 68 and a weight reduction of 5% or more at week 68

Abbreviation: BMI, body mass index.

2.3 | Sensitivity analysis

Six different sensitivity analyses were conducted to assess the robustness of the findings of the primary analysis, as detailed in Table 3. The efficacy estimand was the base case, whereas the treatment regimen estimand was specifically evaluated in two sensitivity analyses. The treatment regimen estimand (termed 'treatment policy estimand' in STEP 1) assessed the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, regardless of treatment discontinuation. Week 72 (SURMOUNT-1) and week 68 (STEP 1) time points were the base case and other time points were specifically evaluated in some sensitivity analyses. As with the primary analysis, sensitivity analyses 1 and 2 were conducted with the MAIC method. Sensitivity analysis 1 used the treatment regimen estimand, while sensitivity analysis 2 compared 68-week data from SURMOUNT-1 with 68-week data for STEP 1. To test the robustness of the primary analysis and sensitivity analyses 1 and 2, sensitivity analyses 3, 4 and 5 were conducted using the Bucher method,[12] where the relative treatment effect was directly calculated with the aggregate data. Sensitivity analyses 3 and 5 used

TABLE 3 Details of primary and sensitivity analyses

Analysis	Method	Estimand	Analysis time
Primary analysis	MAIC (reweight gender)	Efficacy estimand	Tirzepatide data at week 72 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 1	MAIC (reweight gender)	Treatment regimen estimand	Tirzepatide data at week 72 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 2	MAIC (reweight gender)	Efficacy estimand	Tirzepatide data at week 68 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 3	Bucher method	Efficacy estimand	Tirzepatide data at week 72 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 4	Bucher method	Treatment regimen estimand	Tirzepatide data at week 72 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 5	Bucher method	Efficacy estimand	Tirzepatide data at week 68 versus semaglutide 2.4 mg data at week 68
Sensitivity analysis 6	MAIC (reweight gender, prediabetes status and baseline weight)	Efficacy estimand	Tirzepatide data at week 72 versus semaglutide 2.4 mg data at week 68

Abbreviation: MAIC, matching-adjusted indirect comparison.

SURMOUNT-1 week-72 data (sensitivity analysis 3) and week-68 data (sensitivity analysis 5). Sensitivity analysis 4 accounted for the treatment regimen estimand. Sensitivity analysis 6 used the same method (MAIC), estimand and analysis time as the primary analysis, reweighted for gender, prediabetes status and baseline weight. All sensitivity analyses used week-68 data from STEP 1. Individual patient weight data of SURMOUNT-1 at week 68 were imputed by linear interpolation between individual weight data at week 60 and week 72.

3 | RESULTS

There were 1909 participants included in this analysis from the tirzepatide 10 and 15 mg and placebo arms from the SURMOUNT-1 study (tirzepatide 10 mg, $N = 636$; tirzepatide 15 mg, $N = 630$; placebo, $N = 643$). There were 1961 participants included from STEP 1 (semaglutide 2.4 mg, $N = 1306$; placebo, $N = 655$).

After matching, baseline characteristics such as age, gender, body weight, BMI, prediabetes and waist circumference were balanced between the reweighted SURMOUNT-1 and STEP 1 populations with standardized differences of less than 0.1 (Table 1).

Results of the comparison with placebo for percentage change from baseline in body weight and percentage of participants achieving 5% or greater body weight reduction from baseline at endpoint, as reported in SURMOUNT-1 and STEP 1, are shown in Table S2.[4,6]

3.1 | ITC for percentage change in body weight

Primary analysis results showed tirzepatide 10 and 15 mg both resulted in significantly greater reductions in percentage change in body weight compared with semaglutide 2.4 mg (tirzepatide 10 mg mean difference: −4.67% [95% CI −5.91% to −3.43%]; tirzepatide 15 mg mean difference: −5.92% [95% CI −7.16% to −4.68%]; $P < .001$ for both) (Figure 2A).

The results from the sensitivity analyses (detailed in Table 3) accounting for the treatment regimen estimand, SURMOUNT-1 data at week 68, the Bucher method and/or adjusting for gender, baseline prediabetes status and baseline body weight, were consistent with those of the primary analysis (Figure 2A). In particular, sensitivity analysis 1, which examined the treatment regimen estimand, showed a mean difference of −5.56% (95% CI −6.90% to −4.22%; $P < .001$) between tirzepatide 10 mg and semaglutide 2.4 mg and a mean difference of −6.80% (95% CI −8.14% to −5.46%; $P < .001$) between tirzepatide 15 mg and semaglutide 2.4 mg.

3.2 | ITC for participants achieving 5% or greater reduction in body weight from baseline

Primary analysis results showed that significantly more participants achieved 5% or greater weight loss with tirzepatide 10 mg (OR 2.61, 95% CI 1.48 to 4.57; $P < .001$) and 15 mg (OR 2.75, 95% CI 1.57 to 4.81; $P < .001$) compared with semaglutide 2.4 mg (Figure 2B).

The results from the sensitivity analyses (detailed in Table 3) accounting for the treatment regimen estimand, SURMOUNT-1 data at week 68, the Bucher method and/or adjusting for gender, baseline prediabetes status and baseline body weight, were consistent with those of the primary analysis (Figure 2B). Sensitivity analysis 1, which examined the treatment regimen estimand, showed ORs of 3.71 (95% CI 2.39 to 5.70; $P < .001$) and 4.14 (95% CI 2.66 to 6.49; $P < .001$) between tirzepatide 10 and 15 mg, respectively, compared with semaglutide 2.4 mg. The only sensitivity analysis that did not show a significant OR of participants achieving 5% or greater weight loss was sensitivity analysis 4, which accounted for the treatment regimen estimand using the Bucher method between tirzepatide 10 mg and semaglutide 2.4 mg using week-72 SURMOUNT-1 data ($P = .074$).

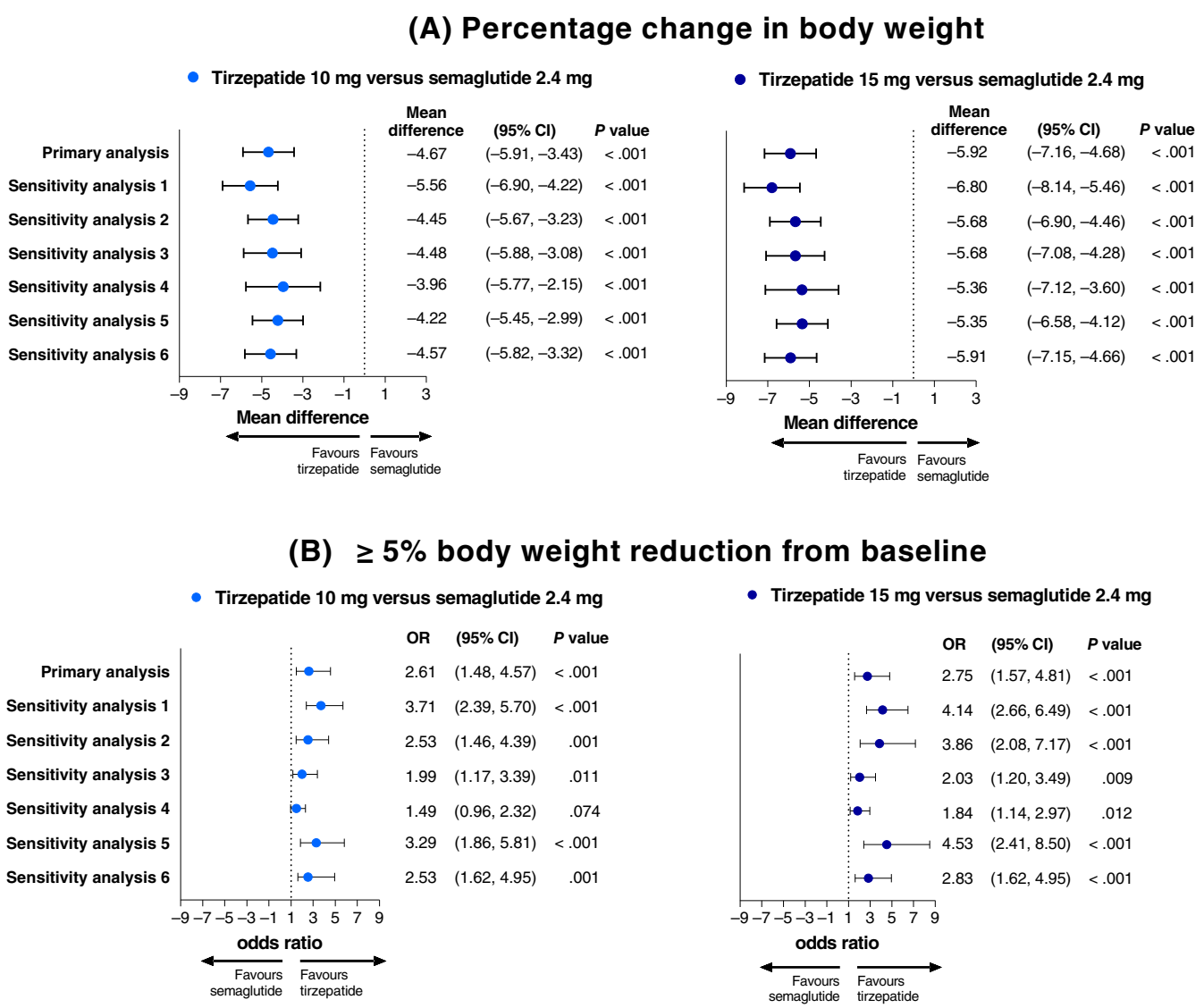

FIGURE 2 Indirect treatment comparison of tirzepatide 10 and 15 mg versus semaglutide 2.4 mg in the change from baseline in A, Percentage change in body weight, and B, ≥ 5% body weight reduction from baseline at endpoint. Primary and sensitivity analyses

4 | DISCUSSION

Semaglutide 2.4 mg and tirzepatide represent new classes of antiobesity medications with powerful efficacy, with weight loss of 15% or greater.[13] This is the first comparison of tirzepatide 10 and 15 mg with semaglutide 2.4 mg on percentage change in body weight and participants achieving 5% or greater reduction in body weight from baseline in patients with obesity and overweight and no diabetes. Across analyses, additional weight reduction of 4.0%-5.6% and 5.4%-6.8% was observed for tirzepatide 10 and 15 mg, respectively, compared with semaglutide 2.4 mg. Consistent with this, participants were more probable to achieve 5% or greater body weight loss with either tirzepatide 10 or 15 mg than semaglutide 2.4 mg. In the absence of a head-to-head trial, data on comparative efficacy can help providers make relevant clinical decisions to support individualized care once tirzepatide is approved for chronic weight management[14] and inform pharmacoeconomic assessments.

Intentional weight loss has been shown to improve clinical outcomes in people with obesity and additional benefits are observed with greater weight loss. For example, sustained weight loss ranging from 5% to 16% can result in clinically meaningful improvements in metabolic health and weight-related complications, such as cardiovascular risk factors as well as quality of life, depression, genitourinary function and fertility, among others.[15,16] Given the relationship between weight loss magnitude and clinical outcomes benefit, it could be expected that the difference in the magnitude of weight loss observed for semaglutide 2.4 mg (16.9%) and tirzepatide 15 mg (20.9%) in their respective clinical trials could result in differential clinical benefits, although this will require future research. In this ITC, the magnitude of difference in body weight reduction was 4.7% and 5.9% with tirzepatide 10 and 15 mg, respectively, compared with semaglutide 2.4 mg. The best evidence for the impact of weight loss on mortality and long-term outcomes will come from appropriately powered randomized controlled trials.

The mechanism(s) through which tirzepatide results in greater body weight reduction than semaglutide 2.4 mg are not known. It is known that semaglutide is a GLP-1 RA[17] and tirzepatide shares this property, while also activating GIP receptors.[18] GLP-1 acts both centrally[19] and peripherally[20] to regulate body weight. Similarly, GIP receptors are thought to regulate body weight by modulating appetite and food intake based on their distribution and signalling in the central nervous system.[21–24] Tirzepatide has also been shown to delay gastric emptying, although the effect wanes with chronic treatment and is not thought to be the key driver of weight loss.[25] For semaglutide, findings on gastric emptying have been mixed.[26–28] Although the exact properties of the medications that confer the differences in efficacy seen here are unknown, the different mechanisms of action are one potential driver that can be considered in future research.

Studies in people with T2D are consistent with the results observed here. In an open-label randomized clinical trial of participants with T2D, all doses of tirzepatide (5, 10, 15 mg) resulted in greater reductions in body weight and HbA1c than semaglutide 1 mg.[29] Similarly, an ITC leveraging data from the SURPASS-2 and SUSTAIN FORTE trials showed that tirzepatide 10 and 15 mg resulted in significantly greater reductions in body weight and HbA1c than semaglutide 2.0 mg, while no significant differences were observed between tirzepatide 5 mg and semaglutide 2.0 mg.[14] Although the trials presented and compared here were not designed as weight loss trials and the doses of semaglutide differ, the results are largely consistent that tirzepatide confers larger reductions in body weight than semaglutide.

Because of intrinsic difficulties in using ITCs to compare safety and tolerability data arising from differences in the collection of safety data, adverse events were not analysed. For example, safety data can be collected using questionnaires with check boxes, open format, or investigator team verbal questioning. Moreover, the majority of the SURMOUNT-1 trial was conducted during the COVID-19 pandemic (2019-2022), while STEP 1 was completed in early 2021. From the main study publications, similar percentages of participants reported any adverse event for tirzepatide 10 mg (81.8%), tirzepatide 15 mg (78.9%) and semaglutide 2.4 mg (89.7%), with gastrointestinal (nausea, diarrhoea and constipation) being the most common.[4,6] Although recent work has established a link between gastrointestinal adverse events and weight loss among GLP-1 RAs,[30] in both trials used in the current analysis the gastrointestinal events were transient, mild to moderate in severity, and occurred during the dose escalation period of both studies, suggesting that they are not a key driver of weight loss. Specifically, the rates of nausea, diarrhoea and constipation for the tirzepatide doses were 31.0%-33.3%, 21.2%-23.0% and 11.7%-17.1%, respectively, whereas the rates of nausea, diarrhoea and constipation for semaglutide 2.4 mg were 44.2%, 31.5% and 23.4%, respectively.

This study had several strengths. A systematic literature review was used to identify eligible studies. Two comparison methods—MAIC and Bucher—were used to leverage similarities between the two placebo-controlled study designs, inclusion criteria and populations. MAIC specifically accounts for any differences in baseline characteristics of potential effect modifiers. The placebo group of both studies was designed similarly with a prescribed 500-calorie deficit and 150-minute activity per week interventions. Notably, the impact of the lifestyle intervention in both trials resulted in similar body weight reductions of 2.4%. The similar results in the placebo groups of both studies indicate that the lifestyle interventions prescribed resulted in similar outcomes. Similar baseline characteristics were observed between the SURMOUNT-1 and STEP 1 populations, and the population sizes were also similar. Sensitivity analyses 1 and 4 used the treatment regimen estimand to account for the impact of treatment discontinuation or the use of rescue therapy.

This study also had limitations. Only two studies were eligible for inclusion in the analysis. Moreover, there was no access to the individual participant data for STEP 1 so aggregate data were used. SURMOUNT-1 and STEP 1 had different study durations (72 vs. 68 weeks), although sensitivity analyses 2 and 5 were conducted to address this. No safety outcomes were formally compared because of differences in the collection of such events across trials. The primary outcomes for both SURMOUNT-1 and STEP 1 were related to the regulatory framework of achieving greater than 5% weight loss. This amount of weight loss may no longer be clinically relevant, but analysis of the secondary outcomes of greater than 10%, greater than 15%, and greater than 20% weight loss was beyond the remit of our analysis. The present results do not provide information on the lower dose of tirzepatide 5 mg versus semaglutide 2.4 mg as the 5 mg dose was not included in the co-primary endpoint of the SURMOUNT-1 trial. ITCs will not account for unmeasured confounders and other unobserved differences between trials. As a result, findings cannot replace a direct head-to-head trial.

In conclusion, in this ITC, greater weight loss and better odds of achieving 5% or greater body weight reduction were seen with tirzepatide 10 and 15 mg versus semaglutide 2.4 mg. Primary analysis results were supported by the sensitivity analysis results, which accounted for different estimands, study endpoints and analytical approaches to minimize bias. In the absence of a direct head-to-head comparison, these findings may guide clinical decisions and pharmacoeconomic assessment of the most appropriate therapies for chronic weight management in patients without diabetes once both treatments are approved for chronic weight management.

AUTHOR CONTRIBUTIONS

SW, ERH, DW, MY, HK, MCB and L-EG-P designed the study. DW and AS collected the data. SW, ERH, DW, RM, MY, AH, HK, MCB, L-EG-P and CWIR analysed and interpreted the data. All authors were involved in writing the paper and had final approval of the submitted version.

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during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of 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 receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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. Open access funding provided by IReL.

FUNDING INFORMATION

Eli Lilly and Company.

CONFLICT OF INTEREST

SW reports receiving honoraria and travel expenses and has participated in academic advisory boards for Novo Nordisk, Bausch Health, Eli Lilly and Janssen. SW is also the medical director of a medical clinic specializing in weight management and diabetes. CWIR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio and the Health Research Board. He serves on advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Keyron and Boehringer Ingelheim. CWIR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. ERH, RM, MY, AH, HK, MCB, AS and L-EG-P are employees and shareholders of Eli Lilly and Company. DW is a previous employee and shareholder of Eli Lilly and Company.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15148.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, 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 of 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 receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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