

Tirzepatide 10 and 15 mg (SURMOUNT-1) vs. Semaglutide 7.2 mg (STEP UP) in Adults With Obesity Without Type 2 Diabetes: An Indirect Treatment Comparison

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Conflict of Interest: Consultancy/advisory board work contracted via the University of Liverpool for Alnylam, Amgen, AstraZeneca, Boehringer Ingelheim, Cytoki, Eli Lilly and Company, Kailera, Menarini, Napp, Novo Nordisk, Pfizer, Prosciento, Response Pharmaceuticals, Rhythm Pharmaceuticals, Saniona, Shionogi; funding for clinical trials from Amgen, AstraZeneca and Novo Nordisk; personal honoraria/lecture fees from Abbvie, AstraZeneca, Boehringer Ingelheim, Medscape, Menarini and Novo Nordisk.



INTRODUCTION

Objective

- Given the lack of direct evidence, indirect treatment comparisons were used to compare tirzepatide 10 and 15 mg versus semaglutide 7.2 mg in adults with obesity without type 2 diabetes, based on the trials SURMOUNT-1¹ and STEP UP.²

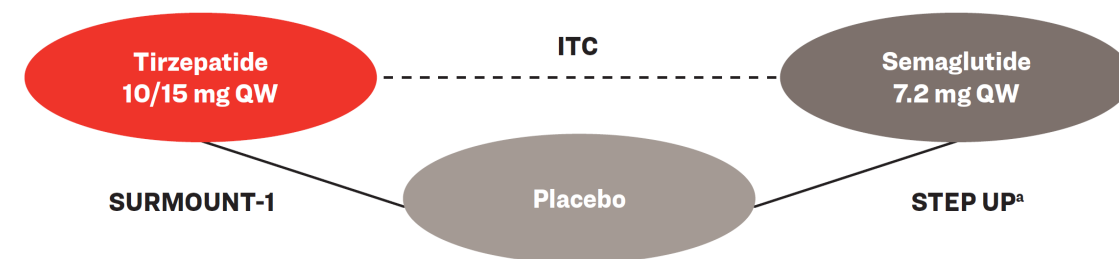
Background

- Tirzepatide QW is a GIP/GLP-1 RA approved for weight management in several regions.³⁻⁵
- Semaglutide 2.4 mg QW is also an injectable GLP-1 RA for weight management approved in several regions.⁶⁻⁸ In SURMOUNT-5, tirzepatide 10 or 15 mg was superior for reduction in body weight and waist circumference after 72 weeks vs. semaglutide 1.7 or 2.4 mg.⁹
- Semaglutide 7.2 mg QW, a new higher dose preparation, has recently been approved for weight management⁴⁻⁶ following the STEP UP trial.²

Comparative evidence

- No head-to-head evidence comparing tirzepatide with semaglutide 7.2 mg QW is currently available.
- This ITC compared weight reduction and glycemic outcomes, alongside safety and discontinuation outcomes, for tirzepatide 10 and 15 mg in SURMOUNT-1 vs. semaglutide 7.2 mg in STEP UP.

Figure 1. ITCs compared tirzepatide 10 and 15 mg with semaglutide 7.2 mg connected via placebo



Footnotes: ^aThe semaglutide 2.4 mg arm from STEP UP was excluded due to not being a treatment of interest in this ITC. Analysis sample sizes (n): STEP UP - 1005 (semaglutide 7.2 mg), 201 (placebo); SURMOUNT-1 - 598 (tirzepatide 10 mg), 590 (tirzepatide 15 mg), 619 (placebo). **Abbreviations:** BMI, body mass index; GIP, dual-glucose dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; ITC, indirect treatment comparison; QW, once weekly; RA, receptor agonist. **References:** 1. Jastreboff AM et al. New Engl J Med. 2022; 387(3), 205–216; 2. Wharton, S et al. The Lancet. 2025; 13(11), 949–963; 3. EMA. Mounjaro. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf [Last accessed 31.03.26]; 4. FDA. Mounjaro Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215866s039lbl.pdf [Last accessed 31.03.26]; 5. MHRA. Mounjaro. Summary of Product Characteristics. Available at: <https://mhraproducts4853.blob.core.windows.net/docs/f92eb92103070f13613b0bbc9d73eea8c746dd06> [Last accessed 30.07.26]; 6. EMA. Wegovy Label. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf [Last accessed 31.03.26]; 7. MHRA. Wegovy. Summary of Product Characteristics. Available at: <https://mhraproducts4853.blob.core.windows.net/docs/3383da93e1311ede9c64642a77bf87b11a3778c5> [Last accessed 15.04.26]; 8. FDA. Wegovy Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s029lbl.pdf [Last accessed 02.04.26]; 9. Aronne, L.J et al. New Engl J Med. 2025; 393(1), 26–36

METHODS

- BMI ≥ 30 kg/m² subgroup data from SURMOUNT-1 (94.5% of participants) were used to align the baseline BMI of the SURMOUNT-1 cohort with that of STEP UP, as SURMOUNT-1 had broader eligibility criteria, including adults with overweight (≥ 27 kg/m²) with ≥ 1 obesity-related complication.
- A heterogeneity assessment identified cross-trial differences in TEMs between the BMI ≥ 30 kg/m² populations, including differences in % female (68.5% SURMOUNT-1; 73.7% STEP UP), % Hispanic/Latino (48.7%; 4.5%, respectively) and baseline BMI (38.5 kg/m²; 39.9 kg/m², respectively). Clinical experts were consulted to identify the outcomes which were likely to be impacted by the identified TEMs.
- Through clinical expert elicitation, weight reduction outcomes were deemed most likely to be impacted by the identified TEMs, therefore ML-NMR¹ analyses adjusting for sex, ethnicity and baseline BMI were conducted. Non-population-adjusted Bucher ITCs¹¹ were also conducted for these outcomes.
- Other outcomes were deemed less likely to be materially impacted by the identified TEMs, therefore non-population-adjusted Bucher ITCs² were conducted for these outcomes.
- Analyses were conducted at the primary timepoint of both trials, Week 72.
- Efficacy outcomes were analysed separately for the efficacy and treatment regimen estimands, with safety and discontinuation outcomes analysed in the safety population.
- Severe gastrointestinal AEs were too rare to conduct an ITC (<2% of participants per arm), however treatment discontinuation due to AEs was included in these analyses.

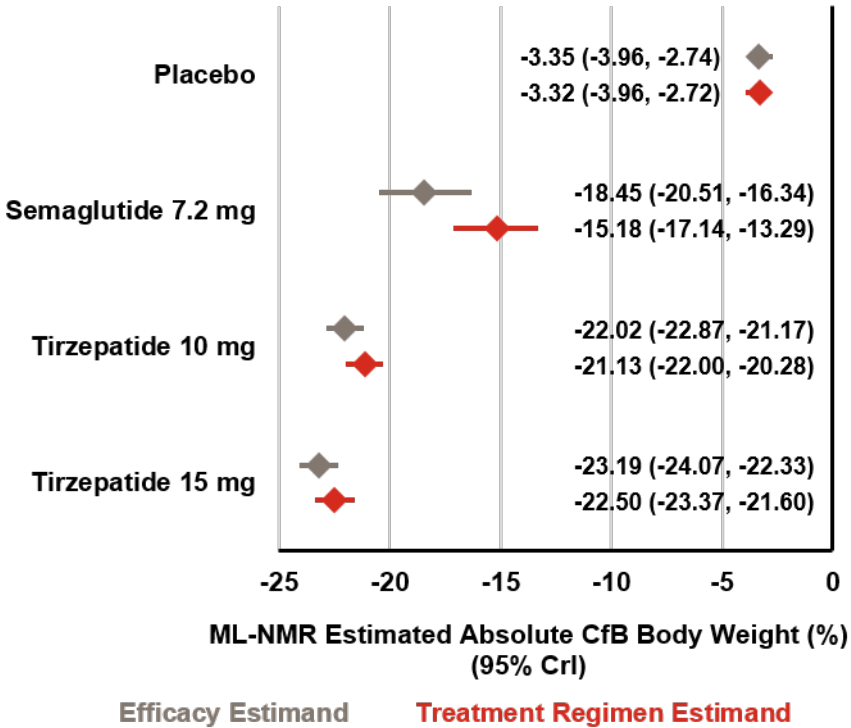
RESULTS

Table 1. Tirzepatide 10 and 15 mg were associated with statistically significant reductions in weight (%) vs. semaglutide 7.2 mg in the TR estimand, and were associated with no statistically significant difference in HbA1c reduction and discontinuation vs. semaglutide 7.2 mg

Outcome	Measure	Analysis	Estimand	Tirzepatide 10 mg vs. Semaglutide 7.2 mg	Tirzepatide 15 mg vs. Semaglutide 7.2 mg
CfB in body weight (%)	MD	ML-NMR: sex, ethnicity, baseline BMI	Treatment regimen	-3.17 (-5.01, -1.40)	-4.51 (-6.31, -2.80)
			Efficacy	-0.66 (-2.58, 1.28)	-1.81 (-3.83, 0.12)
≥20% weight reduction	OR	ML-NMR: sex, ethnicity, baseline BMI	Treatment regimen	2.46 (0.70, 7.75)	3.54 (1.05, 11.05)
			Efficacy	2.84 (0.67, 10.81)	4.15 (1.02, 15.64)
CfB in HbA1c (%) ^a	MD	Bucher ITC	Treatment regimen	-0.05 (-0.12, 0.02)	-0.07 (-0.14, 0.00)
			Efficacy	-0.01 (-0.06, 0.04)	-0.04 (-0.09, 0.01)
Treatment discontinuation due to AEs	OR	Bucher ITC	Safety population	0.45 (0.10, 2.08)	0.36 (0.08, 1.68)

Footnotes: Green indicates where tirzepatide performed statistically better compared to semaglutide 7.2 mg. Results are shown as MD or OR with 95% CIs for Bucher ITC and 95% CrIs for ML-NMR. For the ML-NMR, complete cases of covariates and outcomes of SURMOUNT-1 IPD were used. The treatment regimen (or treatment policy) estimand assessed all participants regardless of discontinuation or initiation of an alternative weight management therapy. The efficacy (or trial product) estimand assessed outcomes as though all participants had remained on treatment and not initiated an alternative weight management therapy. ^aCfB in HbA1c (%) was considered of interest as 40.9% of SURMOUNT-1 and 37.6% of STEP UP participants had prediabetes. ^bAbsolute outcome estimates were calculated from the ML-NMR results using tirzepatide 15 mg as the reference treatment. **Abbreviations:** AE, adverse event; BMI, body mass index; CI, confidence interval; CrI, credible interval; IPD, individual patient data; ITC, indirect treatment comparison; MD, mean difference; ML-NMR, multi-level network meta-regression; OR, odds ratio; TR, treatment regimen.

Figure 2. Tirzepatide 15 mg was associated with the greatest ML-NMR-estimated absolute reduction in percentage body weight, followed by tirzepatide 10 mg, then semaglutide 7.2 mg^b



DISCUSSION

Strengths and Limitations

- This ITC benefits from a robust population-adjusted approach to account for heterogeneity in key TEMs between trials.
- Differences between efficacy and treatment regimen estimand results may reflect differences in intercurrent events, discontinuation and adherence.
- However, the comparison was not direct, and the ITC was based on only two trials and relied on aggregate-level adjustments, therefore residual cross-trial confounding cannot be excluded.
- Due to the low number of safety events occurring, analyses for safety outcomes of interest were not feasible.

Conclusions

- Compared with semaglutide 7.2 mg, in this ITC:
 - Tirzepatide 15 mg was associated with a statistically significant greater reduction in body weight and greater odds of achieving $\geq 20\%$ weight reduction in some analyses and estimands.
 - Tirzepatide 10 mg was associated with a statistically significant greater reduction in body weight in the ML-NMR treatment regimen analysis.
 - Both doses of tirzepatide were associated with no statistically significant differences in HbA1c reduction or treatment discontinuation due to AE.
- Tirzepatide 15 mg was associated with the greatest ML-NMR-estimated absolute reduction in percentage body weight, followed by tirzepatide 10 mg, then semaglutide 7.2 mg.

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Sponsored by Eli Lilly and Company

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- Compared with semaglutide 7.2 mg, in this ITC:
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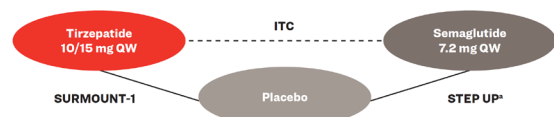
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- No head-to-head evidence comparing tirzepatide with semaglutide 7.2 mg QW is currently available.
- This ITC compared weight reduction and glycemic outcomes, alongside safety and discontinuation outcomes, for tirzepatide 10 and 15 mg in SURMOUNT-1 vs. semaglutide 7.2 mg in STEP UP.

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RESULTS

Weight reduction outcomes (Bucher ITC and ML-NMR)

- In the Bucher ITC, in both estimands tirzepatide 15 mg was associated with a statistically significant difference in weight (%) reduction vs. semaglutide 7.2 mg, while tirzepatide 10 mg was associated with no statistically significant difference.
- After adjusting for sex, ethnicity and baseline BMI, in the treatment regimen estimand tirzepatide 10 and 15 mg were associated with a statistically significant difference in weight (%) reduction vs. semaglutide 7.2 mg. In the efficacy estimand, tirzepatide 10 and 15 mg were associated with no statistically significant difference vs. semaglutide 7.2 mg.
- In the Bucher ITC, in both estimands tirzepatide 10 mg was associated with no a statistically significant difference in odds of achieving ≥20% weight reduction vs. semaglutide 7.2 mg. In the efficacy estimand, tirzepatide 15 mg was associated with a statistically significant difference in odds of achieving ≥20% weight reduction vs. semaglutide 7.2 mg, but was associated with no statistically significant difference in the treatment regimen estimand.
- In the ML-NMR in both estimands, tirzepatide 15 mg was associated with statistically greater odds of ≥20% weight reduction vs. semaglutide 7.2 mg.

CfB in HbA1c (Bucher ITC)

- In both estimands, tirzepatide 10 and 15 mg were associated with no statistically significant difference in HbA1c (%) reduction vs. semaglutide 7.2 mg.

Treatment discontinuation due to AEs (Bucher ITC)

- Tirzepatide 10 and 15 mg were associated with no statistically significant difference in odds of treatment discontinuation due to AEs vs. semaglutide 7.2 mg.

METHODS

- BMI ≥30 kg/m² subgroup data from SURMOUNT-1 (94.5% of participants) were used to align the baseline BMI of the SURMOUNT-1 cohort with that of STEP UP, as SURMOUNT-1 had broader eligibility criteria, including adults with overweight (≥27 kg/m²) with ≥1 obesity-related complication.
- A heterogeneity assessment identified differences in TEMs between the BMI ≥30 kg/m² populations, including differences in % female (68.5% SURMOUNT-1; 73.7% STEP UP), % Hispanic/Latino (48.7%; 4.5%, respectively) and baseline BMI (38.5 kg/m²; 39.9 kg/m², respectively). Clinical experts were consulted to identify the outcomes which were likely to be impacted by the identified TEMs.
- Through clinical expert elicitation, weight reduction outcomes were deemed likely to be impacted by TEMs, therefore ML-NMR¹⁰ adjusting for sex, ethnicity and baseline BMI were conducted. Non-population-adjusted Bucher ITCs¹¹ were also conducted for these outcomes.
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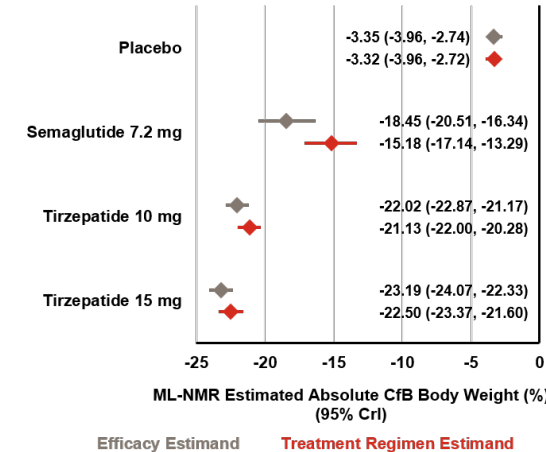
Table 1. Tirzepatide 10 and 15 mg were associated with statistically significant differences for some weight reduction outcomes, and were associated with no statistically significant difference in HbA1c reduction and discontinuation vs. semaglutide 7.2 mg

Outcome	Measure	Analysis	Estimand	Tirzepatide 10 mg	Tirzepatide 15 mg
CfB in body weight (%)	MD	Bucher ITC	Treatment regimen	-1.90 (-4.03, 0.23)	-3.40 (-5.49, -1.31)
			Efficacy	-0.90 (-2.91, 1.11)	-2.10 (-4.11, -0.09)
			ML-NMR: sex, ethnicity, baseline BMI	-3.17 (-5.01, -1.14)	-4.51 (-6.31, -2.80)
		Bucher ITC	Treatment regimen	-0.66 (-2.58, 1.28)	-1.81 (-3.83, 0.12)
			Efficacy	1.21 (0.43, 3.40)	1.67 (0.59, 4.69)
			ML-NMR: sex, ethnicity, baseline BMI	2.61 (0.78, 8.96)	3.69 (1.08, 12.67)
≥ 20% weight reduction	OR	Bucher ITC	Treatment regimen	2.46 (0.70, 7.75)	3.54 (1.05, 11.05)
			Efficacy	2.84 (0.67, 12.81)	4.15 (1.02, 15.64)
			ML-NMR: sex, ethnicity, baseline BMI	2.84 (0.67, 12.81)	4.15 (1.02, 15.64)
		Bucher ITC	Treatment regimen	-0.05 (-0.12, 0.02)	-0.07 (-0.14, 0.00)
			Efficacy	-0.01 (-0.06, 0.04)	-0.04 (-0.09, 0.01)
			ML-NMR: sex, ethnicity, baseline BMI	-0.01 (-0.06, 0.04)	-0.04 (-0.09, 0.01)
CfB in HbA1c (%) ^a	MD	Bucher ITC	Treatment regimen	-0.05 (-0.12, 0.02)	-0.07 (-0.14, 0.00)
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Treatment discontinuation due to AEs	OR	Bucher ITC	Treatment regimen	0.45 (0.10, 2.08)	0.36 (0.08, 1.68)
			Safety population	0.45 (0.10, 2.08)	0.36 (0.08, 1.68)

Footnotes: Green indicates where tirzepatide was associated with a statistically greater improvement compared to semaglutide. Results are shown as mean difference or odds ratio with 95% CIs for Bucher ITC and 95% CIs for ML-NMR. For the ML-NMR, complete cases of covariates and outcomes of SURMOUNT-1 IPD were used. The treatment regimen (or treatment policy) estimand assessed all participants regardless of discontinuation or initiation of an alternative weight management therapy. The efficacy (or trial product) estimand assessed outcomes as though all participants had remained on treatment and not initiated an alternative weight management therapy. The safety population assessed all participants who received ≥1 (SURMOUNT-1) or ≥2 (STEP UP) doses of the trial product. ^aCfB in HbA1c (%) was considered of interest as 40.9% of SURMOUNT-1 and 37.6% of STEP UP participants had prediabetes.

KEY RESULTS

Figure 2. Tirzepatide 15 mg was associated with the greatest ML-NMR-estimated absolute reduction in percentage body weight, followed by tirzepatide 10 mg, then semaglutide 7.2 mg



Footnotes: Diamonds represent MDs and error bars represent 95% CrIs for ML-NMR. Absolute outcome results are generated using ML-NMR results (adjusted for sex, ethnicity and baseline BMI), using tirzepatide 15 mg as the reference.

STRENGTHS AND LIMITATIONS

- This ITC benefits from a robust population-adjusted approach to account for heterogeneity in key TEMs between trials.
- Differences between efficacy and treatment regimen estimand results may reflect differences in intercurrent events, discontinuation and adherence.
- However, the comparison was not direct, and the ITC was based on only two trials and relied on aggregate-level adjustments, therefore residual cross-trial confounding cannot be excluded.
- Due to the low number of safety events occurring, analyses for safety outcomes of interest were not feasible.

Abbreviations: AE, adverse event; BMI, body mass index; CfB, change from baseline; CI, confidence interval; CrI, credible interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin A1c; IPD, individual participant data; ITC, indirect treatment comparison; MD, mean difference; mg, milligram; ML-NMR, multi-level network meta-regression; OR, odds ratio; QW, once-weekly; RA, receptor agonist; T2D, type 2 diabetes; TEM, treatment effect modifier.

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References: 1. Jastreboff AM et al. New Engl J Med. 2022; 387(3): 205-216. 2. Wharton, S et al. The Lancet. 2025; 13(11): 949-963. 3. EMA. Mounjaro. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf [Last accessed 31.03.26]. 4. FDA. Mounjaro Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215866a030bl.pdf [Last accessed 31.03.26]. 5. M-HRA. Mounjaro. Summary of Product Characteristics. Available at: <https://mhra.products4853.blobo.com/windows.net/docs/92be2b62103070f13613b0bbcd73ee8a2746d06> [Last accessed 30.07.26]. 6. EMA. Wegovy Label. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf [Last accessed 31.03.26]. 7. MHRA. Wegovy. Summary of Product Characteristics. Available at: <https://mhra.products4853.blobo.com/windows.net/docs/3383da5e1311ede9c4642a70b7011a3378c5> [Last accessed 15.04.26]. 8. FDA. Wegovy Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215266a020bl.pdf [Last accessed 02.04.26]. 9. Anonme, L.J et al. New Engl J Med. 2025; 393(1): 26-36. 10. Philpott, DM et al. J R Stat Soc Ser A Stat Soc. 2020; 183(3): 1189-1211. Bucher, HC et al. J Clin Epidemiol. 1997; 50(6): 683-91.