Long-Term Care Updates

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GLP-1 receptor agonists for obesity: How does tirzepatide compare?

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Introduction

Tirzepatide (Mounjaro), a dual agonist of glucose-dependent insulinotropic (GIP) and glucagon-like peptide-1 (GLP-1) receptors, was approved by the US Food and Drug Administration (FDA) in May of 2022 for the treatment of type 2 diabetes.[1] In the phase 3 clinical trials that led to tirzepatide's approval, notable weight loss was reported, with 41% to 69% of patients across the SURPASS trials losing 10% or more of their body weight.[2-6] These weight-related findings, along with results from the recently published SURMOUNT-1 trial[7] of tirzepatide in patients with overweight or obesity and without diabetes, made headlines across the country. In October of 2022 the FDA granted "fast track" review status for tirzepatide's use for the treatment of obesity.[8] If tirzepatide receives approval for this indication, it will join once-daily liraglutide (Saxenda) and once-weekly semaglutide (Wegovy) as the only GLP-1 receptor agonists approved for chronic weight management in patients with overweight (with at least one weight-related comorbidity) or obesity.

This article will review clinical research addressing the safety and efficacy of these three medications for chronic weight management to provide an indirect comparison across the agents.

Clinical Research - Efficacy

Details of the clinical trials and specific weight-related outcomes for liraglutide, semaglutide, and tirzepatide are provided in Table 1. Studies that assessed changes in body weight as secondary outcomes in patients with type 2 diabetes regardless of body weight classification are not included. Further, studies in patients with overweight or obesity that assessed adolescent patients, solely Asian populations, or weight maintenance after discontinuation of therapy were also excluded. In all trials liraglutide was given once daily via subcutaneous injection while semaglutide and tirzepatide were given one weekly via subcutaneous injection. No head-to-head studies comparing tirzepatide to the other two agents have been published, while the superiority of semaglutide to liraglutide has been demonstrated in one clinical trial (STEP-8).[9] Semaglutide is generally preferred over liraglutide for weight loss given its superior efficacy, as reflected in Table 1, and less frequent administration.[10]

Table 1. Clinical trials of liraglutide, semaglutide, and tirzepatide in patients with overweight or obesity.

	Study	Patient population and comparator*	Duration (weeks)	Body weight change	≥10% weight loss	≥15% weight loss	≥20% weight loss	≥25% weight loss
LIRAGLUTIDE	SCALE Obesity and Prediabetes (vs. placebo)[13]	Overweight (with at least one weight-related comorbidity) or obesity	56	-8% (3mg)	33% (3mg) NNT=5	14% (3mg) NNT=10	---	---
	SCALE Diabetes (vs. placebo)[14]	T2DM with overweight or obesity	56	-6% (3mg)	25% (3mg) NNT=6	---	---	---
	SCALE Insulin (vs. placebo)[15]	T2DM with overweight or obesity treated with basal insulin All patients received intensive behavioral therapy	56	-6% (3mg)	23% (3mg) NNT=7	---	---	---
	SCALE IBT (vs. placebo)[16]	Obesity All patients received intensive behavioral therapy	56	-7% (3mg)	31% (3mg) NNT=10	18% (3mg) NNT=11	---	---
	STEP-8 (vs. semaglutide 2.4mg)[9]	Overweight (with at least one weight-related comorbidity) or obesity	68	-6% (3mg)	26% (3mg) Inferior to semaglutide	12% (3mg) Inferior to semaglutide	6% (3mg) Inferior to semaglutide	---
SEMAGLUTIDE	STEP-1 (vs. placebo)[11]	Overweight (with at least one weight-related comorbidity) or obesity	68	-15% (2.4mg)	69% (2.4mg) NNT=2	51% (2.4mg) NNT=3	32% (2.4mg) NNT=4	---
	STEP-2 (vs. placebo)[17]	T2DM with overweight or obesity	68	-7% (1.0mg) -10% (2.4mg)	29% (1.0mg) 46% (2.4mg) NNT=3-5	14% (1.0mg) 26% (2.4mg) NNT=5-10	5% (1.0mg) 13% (2.4mg) NNT=9-33	---
	STEP-3 (vs. placebo)[18]	Overweight (with at least one weight-related comorbidity) or obesity All patients received intensive behavioral therapy	68	-16% (2.4mg)	75% (2.4mg) NNT=3	56% (2.4mg) NNT=3	36% (2.4mg) NNT=4	---
	STEP-5 (vs. placebo)[19]	Overweight (with at least one weight-related comorbidity) or obesity	104	-15% (2.4mg)	62% (2.4mg) NNT=3	52% (2.4mg) NNT=3	36% (2.4mg) NNT=3	---
	STEP-8 (vs. liraglutide 3mg)[9]	Overweight (with at least one weight-related comorbidity) or obesity	68	-16% (2.4mg)	71% (2.4mg) NNT=3 vs. liraglutide	56% (2.4mg) NNT=3 vs. liraglutide	38% (2.4mg) NNT=4 vs. liraglutide	---
TIRZEPATIDE	SURMOUNT-1 (vs. placebo)[7]	Overweight (with at least one weight-related comorbidity) or obesity	72	-15% (5mg) -20% (10mg) -21% (15mg)	69% (5mg) 78% (10mg) 84% (15mg) NNT=2-3	48% (5mg) 67% (10mg) 71% (15mg) NNT=2-3	30% (5mg) 50% (10mg) 57% (15mg) NNT=2-4	15% (5mg) 32% (10mg) 36% (15mg) NNT=3-8

*All patients received lifestyle intervention/counseling unless otherwise noted; studies excluded patients with diabetes unless otherwise noted

While indirect comparison between tirzepatide and semaglutide should be done cautiously, results from the two most closely related studies (SURMOUNT-1[7] and STEP-1[11]) suggest that the maintenance dose of 2.4mg for semaglutide is comparable to the lowest dose of tirzepatide (10mg). Around 15% to 20% more patients lost ≥10%, ≥15%, and ≥20% of their body weight with the highest dose of tirzepatide (15mg) when compared with semaglutide 2.4mg. Additionally, a similar proportion of patients lost ≥25% of their body weight with tirzepatide 15mg when compared with those that lost ≥20% with semaglutide 2.4mg.[7,11] Ongoing SURMOUNT trials, all of which are placebo-controlled, are expected to conclude and report findings in mid-to-late 2023. SURMOUNT-2 is assessing the safety and efficacy of tirzepatide 10mg and 15mg doses in patients with type 2 diabetes and overweight or obesity, SURMOUNT-3 is assessing the safety and efficacy of tirzepatide when added to intensive behavioral therapy, and SURMOUNT-4 is assessing the long-term maintenance effects of tirzepatide in patients with overweight or obesity.[12]

Clinical Research – Safety

To provide a closer, yet still indirect, comparison between liraglutide, semaglutide, and tirzepatide with respect to safety outcomes, the following trials will be considered: SCALE Obesity and Prediabetes (liraglutide)[13], STEP-1 (semaglutide)[11], and SURMOUNT-1 (tirzepatide)[7]. Table 2 below lists the most common adverse reactions reported in patients receiving these medications. Event rates were adjusted based on the rate of each reaction reported in patients receiving placebo in each study.

Adverse event data suggest that the rates of adverse gastrointestinal events with tirzepatide are similar to or lower than liraglutide and semaglutide, even at the highest tirzepatide dose. Across these trials, around 6% to 7% of patients discontinued therapy due to adverse reactions.[7,11,13]

Table 2. Placebo-adjusted incidence of adverse reactions with liraglutide, semaglutide, and tirzepatide in the SCALE Obesity and Prediabetes, STEP-1, and SURMOUNT-1 studies.[7,11,13]

	Liraglutide 3mg n=2481	Semaglutide 2.4mg n=1306	Tirzepatide 5mg n=630	Tirzepatide 10mg n=636	Tirzepatide 15mg n=630
Abdominal pain	2%	5%	2%	2%	2%
Constipation	11%	14%	11%	11%	6%
Diarrhea	12%	16%	11%	14%	16%
Dyspepsia	6%	7%	5%	6%	7%
Nausea	26%	27%	15%	24%	22%
Vomiting	12%	18%	7%	9%	11%

Conclusion

While additional data on the safety of tirzepatide for the treatment of overweight or obesity are warranted and forthcoming, results from the SURMOUNT-1 study suggest that it may provide superior weight-loss effects without additional safety concerns when indirectly compared to semaglutide. If tirzepatide receives approval for this indication, clinicians should consider the cost of therapy and other patient-specific factors alongside safety and efficacy data to determine if tirzepatide should replace semaglutide as the preferred weight-loss medication.

References

1.) Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Co.; May 2022.

2.) Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143-155.

3.) Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503-515.

4.) Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583-598.

5.) Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet. 2021;398(10313):1811-1824.

6.) Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: The SURPASS-5 Randomized Clinical Trial. JAMA. 2022;327(6):534-545.

7.) Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216.

8.) Lilly receives U.S. FDA Fast Track designation for tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities. Eli Lilly and Company. https://investor.lilly.com/news-releases/news-release-details/lilly-receives-us-fda-fast-track-designation-tirzepatide. Published October 6, 2022.

9.) Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 randomized clinical trial. JAMA. 2022;327(2):138-150.

10.) Perreault L (Pi-Sunyer FX, Givens J [ed]). Obesity in adults: drug therapy. UpToDate. Updated October 6, 2022.

11.) Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989-1002.

12.) McDermid E. A quick guide to the SURPASS and SURMOUNT trials. Medicine Matters - Diabetes. Springer Healthcare Limited. https://diabetes.medicinematters.com/tirzepatide/type-2-diabetes/a-quick-guide-to-the-surpass-and-surmount-trials/18478154. Updated August 2022.

13.) Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.

14.) Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE Diabetes randomized clinical trial. JAMA. 2015;314(7):687-699.

15.) Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: The SCALE Insulin randomized controlled trial. Diabetes Care. 2020;43(5):1085-1093.

16.) Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: The SCALE IBT randomized controlled trial. Obesity (Silver Spring). 2020;28(3):529-536.

17.) 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. Lancet. 2021;397(10278):971-984.

18.) Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA. 2021;325(14):1403-1413.

19.) Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083-2091.