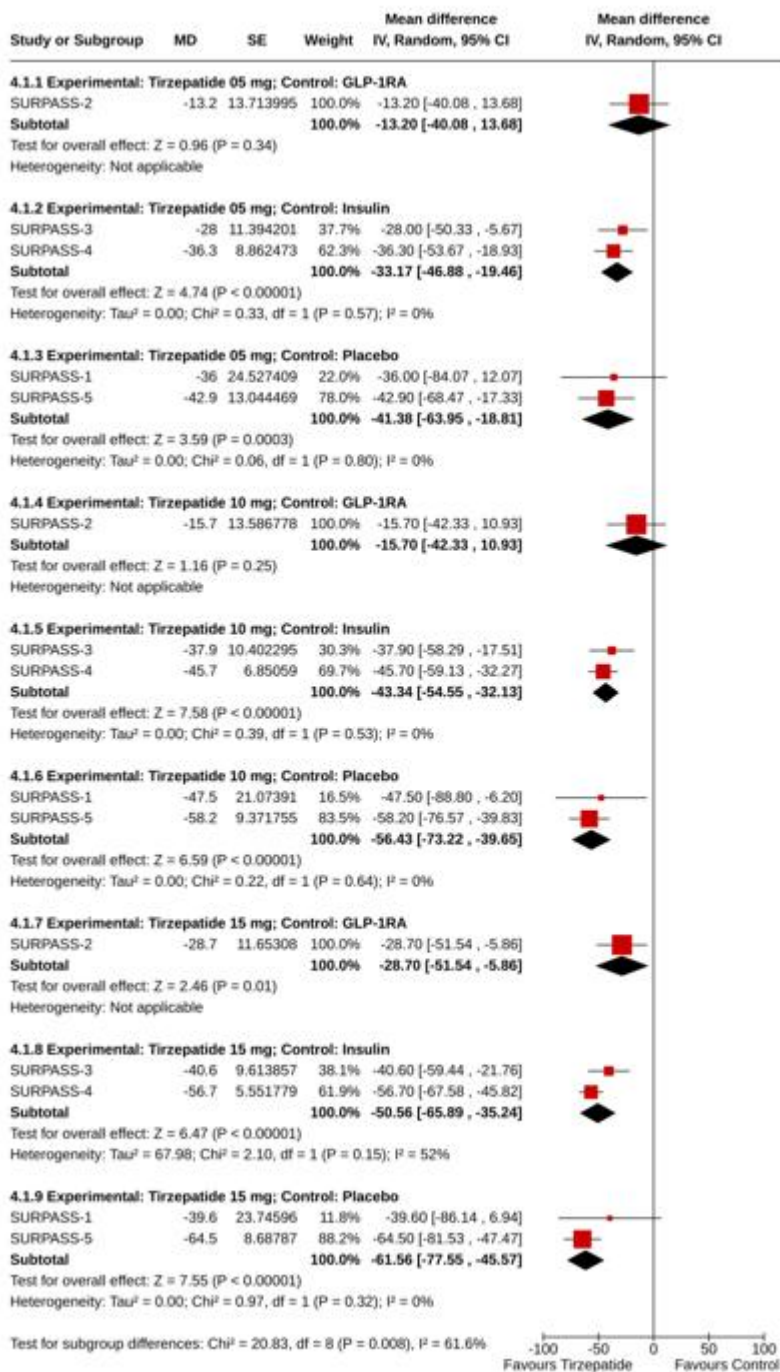
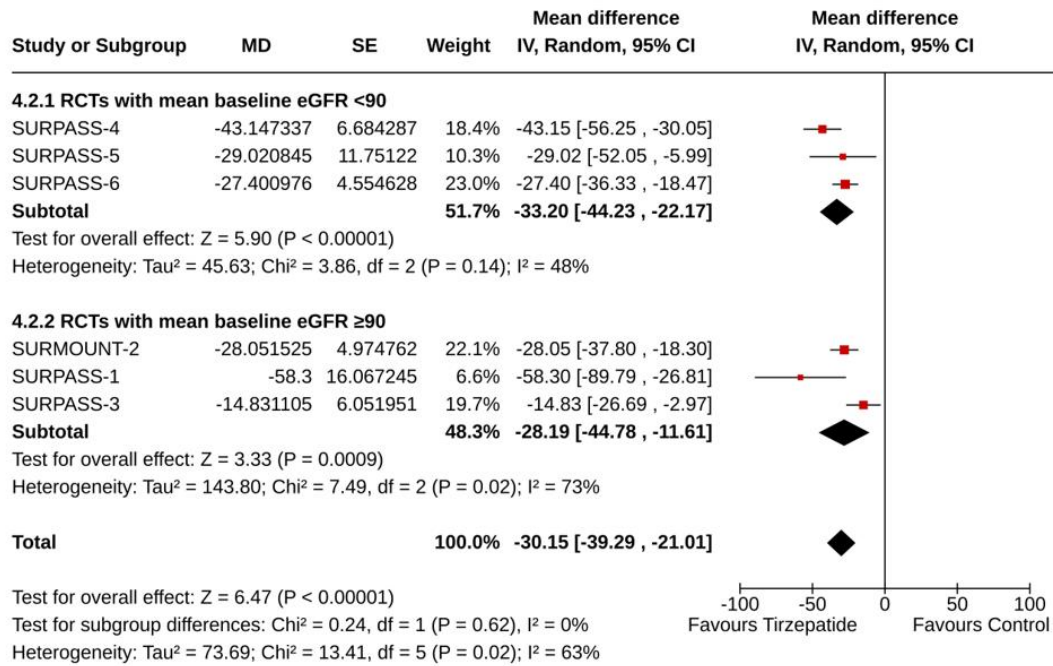


**Supplementary Figure 1 Forest plot highlighting the percent change from baseline in urine albumin-to-creatinine ratio in Tirzepatide vs. Placebo groups in subjects with diabetes and without diabetes.**



Supplementary Figure 2 Forest plot highlighting the percent change from baseline in urine albumin-to-creatinine ratio in Tirzepatide vs. Control groups in subjects with baseline urine albumin-to-creatinine ratio  $\geq 30$  mg/g.



**Supplementary Figure 3 Forest plot highlighting the percent change from baseline in urine albumin-to-creatinine ratio in Tirzepatide vs. Control groups in randomized controlled trials with estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>) < 90 and ≥ 90.**

**Supplementary Table 1 The baseline characteristics of the included randomized controlled trials**

Registration no., Phase, Place of the Trial	Trial ID (name), Authors (publication year)	Major characteristics of the study subjects	Study arms	N	Age (y), mean (SD)	eGFR, mean (SD), or median (IQR)	UACR, mean (SD)	Duration
NCT03131687, Phase 2, Multicenter in Poland, Puerto Rico, Slovakia, and USA	Frias 2018, Frias <i>et al.</i> (2018)[24]	Adults with T2D on diet and exercise ( $\pm$ metformin), HbA1c 7–10.5%, BMI 23–50 kg/m <sup>2</sup>	Tirzepatide 1 mg	52	57.4 (8.9)	95.6 (16.8)	NA	26 weeks
			Tirzepatide 5 mg	55	57.9 (8.2)	92.2 (17.2)	NA	
			Tirzepatide 10 mg	51	56.5 (9.9)	93.7 (18.6)	NA	
			Tirzepatide 15 mg	53	56.0 (7.6)	91.8 (17.9)	NA	
			Placebo	51	56.6 (8.9)	95.3 (15.3)	NA	

			Dulaglutide 15 mg	54	58.7 (7.8)	90.7 (17.6)	NA	
NCT04184622, Phase 3, Multicenter in multiple countries	<b>SURMOUNT-1,</b> Jastreboff <i>et al.</i> (2022)[25]	Adults with BMI ≥30, or ≥27 kg/m <sup>2</sup> and at least one weight-related complication, excluding diabetes	Tirzepatide 5 mg	630	45.6 (12.7)	97.6 (17.87)	7.6 (0.3)	72 weeks
			Tirzepatide 10 mg	636	44.7 (12.4)	98.3 (18.26)	7.9 (0.3)	
			Tirzepatide 15 mg	630	44.9 (12.3)	98.2 (17.67)	8.0 (0.3)	
			<b>Placebo</b>	642	44.4 (12.5)	98.1 (18.28)	7.6 (0.3)	
NCT04657003, Phase 3, Multicenter in multiple countries	<b>SURMOUNT-2,</b> Garvey <i>et al.</i> (2023)[26]	Adults with T2D, BMI ≥ 27 kg/m <sup>2</sup> , HbA1c 7-10%	Tirzepatide 10 mg	312	54.3 (10.7)	95.9 (17.8)	17.4 (1.5)	72 weeks
			Tirzepatide 15 mg	311	53.6 (10.6)	96.2 (17.5)	17.3 (1.5)	
			Placebo	315	54.7 (10.5)	93.5 (19.1)	16.4 (1.4)	

NCT04657016, Phase 3, Multicenter in USA, Argentina and Brazil	<b>SURMOUNT-3</b> , Wadden <i>et al.</i> (2023)[27]	Adults with BMI ≥30, or ≥27 kg/m <sup>2</sup> and at least one weight-related complication, excluding diabetes	Tirzepatide MTD (10 or 15 mg)*	287	45.4 (12.6)	95.6 (17.1)	5.8 (0.33)	72 weeks
			Placebo	292	45.7 (11.8)	97.1 (16.7)	6.0 (0.35)	
NCT05024032, Phase 3, Multicenter in China	<b>SURMOUNT-CN</b> , Zhao <i>et al.</i> (2024)[28]	Adults with BMI ≥28, or ≥24 kg/m <sup>2</sup> and at least one weight-related comorbidity, excluding diabetes	Tirzepatide 10 mg	70	34.7 (7.2)	114.7 (12.3)	8.8 (1.1)	52 weeks
			Tirzepatide 15 mg	71	35.8 (9.3)	111.1 (13.4)	8.6 (1.1)	
			<b>Placebo</b>	69	37.8 (10.2)	112.3 (13.1)	7.8 (1.0)	
NCT05412004, Phase 3, Multicenter in multiple	<b>SURMOUNT-OSA</b> , Malhotra <i>et al.</i> (2024)[29]	Adults with moderate-to-severe obstructive sleep apnea and obesity	Trial 1 <sup>†</sup>					52 weeks
			Tirzepatide MTD*	114	47.3 (11.0)	NA	NA	
			<b>Placebo</b>	120	48.4	NA	NA	

countries		(BMI $\geq$ 30 kg/m <sup>2</sup> ), excluding diabetes			(11.9)			
			Trial 2 <sup>†</sup>					
			Tirzepatide MTD*	120	50.8 (10.7)	NA	NA	
			<b>Placebo</b>	115	52.7 (11.3)	NA	NA	
NCT03954834, Phase 3, Multicenter in India, Japan, Mexico, and USA	SURPASS-1, Rosenstock <i>et al.</i> (2021)[30]	Adults with T2D inadequately controlled with diet and exercise alone and who were naive to injectable diabetes therapy, HbA1c 7-9.5%, BMI $\geq$ 23 kg/m <sup>2</sup>	Tirzepatide 5 mg	121	54.1 (11.9)	94.7 (20.6)	10.7	40 weeks
			Tirzepatide 10 mg	121	55.8 (10.4)	92.1 (18.2)	10.3	
			Tirzepatide 15 mg	121	52.9 (12.3)	96.2 (19.7)	10.8	
			Placebo	115	53.6 (12.8)	93.4 (20.2)	10.1	

NCT03987919, Phase 3, Multicenter in multiple countries	SURPASS-2, Frías <i>et al.</i> (2021)[31]	Adults with T2D inadequately controlled with metformin, HbA1c 7-10.5%, BMI ≥ 25 kg/m <sup>2</sup>	Tirzepatide 5 mg	470	56.3 (10.0)	96.6 (17.51)	14.1	40 weeks
			Tirzepatide 10 mg	469	57.2 (10.5)	95.5 (16.62)	13.4	
			Tirzepatide 15 mg	470	55.9 (10.4)	96.3 (16.92)	13.6	
			Semaglutide	469	56.9 (10.8)	95.6 (17.25)	12.2	
NCT03882970, Phase 3, Multicenter in multiple countries	SURPASS-3, Ludvik <i>et al.</i> (2021)[32]	Adults with T2D treated with any combination of metformin, SU, or SGLT2i, HbA1c 7-10.5%, BMI ≥ 25 kg/m <sup>2</sup>	Tirzepatide 5 mg	358	57.2 (10.1)	95.1 (17.2)	15.1	52 weeks
			Tirzepatide 10 mg	360	57.4 (9.7)	93.7 (16.9)	12.1	
			Tirzepatide 15 mg	359	57.5 (10.2)	93.1 (17.3)	13.9	
			Insulin degludec	360	57.5 (10.1)	94.6 (16.8)	14.5	



NCT03730662, Phase 3, Multicenter in multiple countries	SURPASS-4, Del Prato <i>et al.</i> (2021)[33] Heerspink <i>et al.</i> (2022)[14]	Adults with T2D inadequately controlled with metformin ± an SGLT2i, HbA1c 7-10.5%, BMI ≥ 25 kg/m <sup>2</sup>	Tirzepatide 5 mg	329	62.9 (8.6)	80.3 (22.66)	16.0	52 weeks
			Tirzepatide 10 mg	328	63.7 (8.7)	81.4 (20.44)	23.9	
			Tirzepatide 15 mg	338	63.7 (8.6)	81.6 (21.22)	19.0	
			Insulin glargine	1000	63.8 (8.5)	81.5 (20.78)	17.6	
NCT04039503, Phase 3, Multicenter in multiple countries	SURPASS-5, Dahl <i>et al.</i> (2022)[34]	Adults with T2D receiving stable doses of once daily insulin glargine ± metformin, HbA1c 7-10.5%, BMI ≥ 23 kg/m <sup>2</sup>	Tirzepatide 5 mg	116	62 (10)	86.1 (18.1)	19.8	40 weeks
			Tirzepatide 10 mg	119	60 (10)	87.1 (18.2)	19.6	
			Tirzepatide 15 mg	120	61 (10)	84.1 (17.2)	16.0	
			Placebo	120	60 (10)	84.7 (17.8)	14.4	

NCT04537923, Phase 3b, Multicenter in multiple countries	SURPASS-6, Rosenstock <i>et al.</i> (2023)[35]	Adults with T2D inadequately controlled with basal insulin ± up to two OADs, HbA1c 7.5–11%, BMI 23–45 kg/m <sup>2</sup>	Tirzepatide 5 mg	243	58.0 (10.2)	89.0 (20.7)	28.9 (2.97)	52 weeks
			Tirzepatide 10 mg	238	59.6 (9.4)	89.5 (18.0)	24.4 (2.54)	
			Tirzepatide 15 mg	236	58.2 (9.6)	89.3 (19.9)	23.7 (2.46)	
			Insulin lispro	708	59.0 (9.7)	88.8 (18.8)	27.2 (1.65)	
NCT04093752, Phase 3, Multicenter in China, South Korea, Australia and India	SURPASS-AP-Combo, Gao <i>et al.</i> (2023)[36]	Adults with T2D inadequately controlled with metformin ± SU, HbA1c 7.5–11%, BMI ≥23 kg/m <sup>2</sup>	Tirzepatide 5 mg	230	53.1 (11.2)	NA	27.0	40 weeks
			Tirzepatide 10 mg	228	53.5 (11.1)	NA	24.0	
			Tirzepatide 15 mg	229	54.3 (11.6)	NA	23.6	
			Insulin	220	55.6	NA	20.5	

			glargine		(11.4)			
NCT03861052, Phase 3, Multicenter in Japan	SURPASS J-mono, Inagaki <i>et al.</i> (2022)[37]	Age ≥20 years with T2D on diet and exercise or discontinued OAD monotherapy, HbA1c 7-10%, BMI ≥23 kg/m <sup>2</sup>	Tirzepatide 5 mg	159	56.8 (10.1)	78 (68-86)	NA	52 weeks
			Tirzepatide 10 mg	158	56.2 (10.3)	80 (72-86)	NA	
			Tirzepatide 15 mg	160	56.0 (10.7)	80 (71-86)	NA	
			Dulaglutide 075 mg	159	57.5 (10.2)	79 (71-86)	NA	
NCT04166773, Phase 2, Multicenter in multiple countries	SYNERGY-NASH, Loomba <i>et al.</i> (2024)[38]	Adults with biopsy-confirmed MASH and stage F2 or F3 fibrosis, with or without T2D, BMI 27-50 kg/m <sup>2</sup>	Tirzepatide 5 mg	47	55.0 (11.6)	NA	NA	52 weeks
			Tirzepatide 10 mg	47	54.3 (12.1)		NA	
			Tirzepatide 15 mg	48	54.9 (10.0)	NA	NA	
			Placebo	48	53.5	NA	NA	

					(11.6)			
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BMI, Body mass index; eGFR (ml/min/1.73m<sup>2</sup>), Estimated glomerular filtration rate (using chronic kidney disease epidemiology collaboration, CKD-EPI formula); HbA1c, Glycated hemoglobin; IQR, Interquartile range; MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; MTD, Maximum tolerated dose; NA, Not available; NAFLD, Nonalcoholic fatty liver disease; OHA, Oral anti-diabetic drugs; SD, Standard deviation; SGLT2i, Sodium-glucose cotransporter-2 inhibitors; SU, Sulphonylureas; T2D, Type 2 diabetes; UACR (mg/g), Urine albumin-to-creatinine ratio

\*Tirzepatide MTD was analyzed as Tirzepatide 15 mg.

†Outcome results of Tirzepatide MTD and placebo groups in Trials 1 and 2 were pooled into single groups of Tirzepatide MTD and placebo.

**Supplementary Table 2 The proportions of study subjects with eGFR < 60 and UACR ≥30 in the overall study population**

Study ID [Reference no.]	eGFR < 60, n (%)	UACR ≥30, n (%)
Frias 2018[19]	NA	NA
SURMOUNT-1[20]	NA	NA

SURMOUNT-2[21]	NA	NA
SURMOUNT-3[22]	NA	NA
SURMOUNT-CN[23]	NA	NA
SURMOUNT-OSA[24]	NA	NA
SURPASS-1[25]	NA	104 (21.8%)
SURPASS-2[26]	64 (3.4%)	461 ((24.5%)
SURPASS-3[27]	56 (4%)	402 (27.8%)
SURPASS-4[28]	342 (17%)	707 (35.3%)
SURPASS-5[29]	16 (13.3%)	172 (36.2)
SURPASS-6[30]	130 (9.1%)	NA
SURPASS-AP-Combo[31]	12 (1.3)	NA
SURPASS J-mono[32]	NA	NA
SYNERGY-NASH[33]	NA	NA

eGFR (ml/min/1.73m<sup>2</sup>), Estimated glomerular filtration rate (using chronic kidney disease epidemiology collaboration, CKD-EPI formula); UACR (mg/g), Urine albumin-to-creatinine ratio

**Supplementary Table 3 The basic characteristics of the excluded randomized controlled trials**

<b>Trial reg. no.</b>	<b>Authors (publication year)</b>	<b>Reason of exclusion</b>
NCT03882970	Battelino <i>et al.</i> (2022)[39]	Substudy of the SURPASS-3 trial
NCT03882970	Cariou <i>et al.</i> (2023)[40]	Substudy of the SURPASS-3 trial
NCT03882970	Gastaldelli <i>et al.</i> (2022)[41]	Substudy of the SURPASS-3 trial
NCT03131687	Hartman <i>et al.</i> (2018)[42]	Post hoc analysis of included study by Frias <i>et al.</i> (2018)
NCT03131687	Pirro <i>et al.</i> (2022)[43]	Post hoc analysis of included study by Frias <i>et al.</i> (2018)
NCT03131687	Thomas <i>et al.</i> (2021)[44]	Post hoc analysis of included study by Frias <i>et al.</i> (2018)
NCT03131687	Wilson <i>et al.</i> (2020)[45]	Post hoc analysis of included study by Frias <i>et al.</i> (2018)
NCT03131687	Wilson <i>et al.</i> (2022)[46]	Post hoc analysis of included study by Frias <i>et al.</i> (2018)
NCT04235959	Feng <i>et al.</i> (2023)[47]	Not reported the outcome(s) of interest
NCT03311724	Frias <i>et al.</i> (2020)[48]	Not reported the outcome(s) of interest
NCT03322631	Furihata <i>et al.</i> (2021)[49]	Not reported the outcome(s) of interest
NCT03951753	Heise <i>et al.</i> (2022)[50]	Not reported the outcome(s) of interest
NCT03861039	SURPASS J-combo trial	Not reported the outcome(s) of interest

	Kadowaki <i>et al.</i> (2022)[51]	
NCT04143802	Urva <i>et al.</i> (2022)[52]	Not reported the outcome(s) of interest
NCT04660643	SURMOUNT-4 trial Aronne <i>et al.</i> (2024)[53]	An open-label tirzepatide lead-in period followed by a double-blind, placebo-controlled period

**Supplementary Table 4 Summary of findings table**

Outcomes	Anticipated absolute effects* (95%CI)	No. of participants(studies)	Certainty of the evidence (GRADE)
	Risk with Tirzepatide		
UACR - Tirzepatide 5 mg <i>vs</i> Placebo	MD <b>20.68 Lower</b> (45.43 Lower to 4.08 higher)	1,745 (3 RCTs)	⊕⊕○○Low <sup>a</sup>
UACR - Tirzepatide 10 mg <i>vs</i> Placebo	MD <b>26.95 Lower</b> (40.13 Lower to 13.76 Lower)	2,520 (5 RCTs)	⊕⊕○○Low <sup>a</sup>
UACR - Tirzepatide 15 mg <i>vs</i> Placebo	MD <b>18.03 Lower</b> (28.58 Lower to 7.47 Lower)	3,094 (6 RCTs)	⊕⊕⊕○Moderate <sup>b</sup>
UACR - Tirzepatide 5 mg <i>vs</i> Insulin	MD <b>25.74 Lower</b> (33.79 Lower to 17.7 Lower)	3,448 (4 RCTs)	⊕○○○Very low <sup>b,c</sup>

UACR – Tirzepatide 10 mg <i>vs</i> Insulin	MD <b>30.36 Lower</b> (42.13 Lower to 18.59 Lower)	3,442 (4 RCTs)	⊕○○○Very low <sup>a,c</sup>
UACR – Tirzepatide 15 mg <i>vs</i> Insulin	MD <b>29.65 Lower</b> (37.62 Lower to 21.68 Lower)	3,450 (4 RCTs)	⊕○○○Very low <sup>b,c</sup>
eGFR – Tirzepatide 5 mg <i>vs</i> Insulin	MD <b>0.36 higher</b> (1.41 Lower to 2.14 higher)	2,998 (3 RCTs)	⊕○○○Very low <sup>a,c</sup>
eGFR – Tirzepatide 10 mg <i>vs</i> Insulin	MD <b>1.17 higher</b> (0.22 Lower to 2.56 higher)	2,994 (3 RCTs)	⊕○○○Very low <sup>b,c</sup>
eGFR – Tirzepatide 15 mg <i>vs</i> Insulin	MD <b>1.42 higher</b> (0.04 Lower to 2.88 higher)	3,001 (3 RCTs)	⊕○○○Very low <sup>b,c</sup>

**\*The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95%CI).**CI:** confidence interval; **eGFR:** estimated glomerular filtration rate; **MD:** mean difference; **UACR:** urine albumin-to-creatinine ratio

**GRADE Working Group grades of evidence****High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.**Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect



estimate is limited: The true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

- a. High heterogeneity among the studies present.
- b. Moderate heterogeneity among the studies present.
- c. All the included studies have a high overall risk of bias.

**Supplementary Table 5 Leave-one-out sensitivity analysis for percent CFB in UACR and CFB in eGFR**

Comparison group	Study omitted	For percent CFB in UACR			For CFB in eGFR		
		MD [95%CI]	P	I <sup>2</sup> (%)	MD [95%CI]	P	I <sup>2</sup> (%)
Tirzepatide 5 mg vs. Placebo	SURMOUNT-1	-28.29 [-60.25, 3.66]	0.08	82	Data not available		
	SURPASS-1	-7.93 [-15.43, -0.44]	0.04	0			
	SURPASS-5	-24.97 [-60.04, 10.09]	0.16	95			
Tirzepatide 10 mg vs. Placebo	SURMOUNT-1	-32.09 [-39.34, -24.83]	< 0.00001	3			
	SURMOUNT-2	-26.68 [-44.14, -9.22]	0.003	84			
	SURMOUNT-CN	-27.78 [-43.60, -11.97]	0.0006	86			
	SURPASS-1	-22.92 [-35.79, -10.06]	0.0005	76			

	SURPASS-5	-25.52 [-40.77, -10.26]	0.001	84				
Tirzepatide 15 mg vs. Placebo	SURMOUNT-1	-25.52 [-40.77, -10.26]	0.0002	61				
	SURMOUNT-2	-15.62 [-26.78, -4.46]	0.006	66				
	SURMOUNT-3	-21.19 [-33.05, -9.33]	0.0005	73				
	SURMOUNT-CN	-18.32 [-30.42, -6.22]	0.003	78				
	SURPASS-1	-15.79 [-26.91, -4.67]	0.005	73				
	SURPASS-5	-16.17 [-27.57, -4.78]	0.005	74				
Tirzepatide 5 mg vs. Insulin	SURPASS-3		< 0.00001		0.58	[-1.97,	0.66	89
		-29.00 [-34.94, -23.07]		0	3.12]			
	SURPASS-4		< 0.0001		-0.53	[-1.63,	0.35	0
		-26.01 [-37.82, -14.20]		69	0.58]			
	SURPASS-6		< 0.00001		0.93	[-1.01,	0.35	78
		-23.12 [-32.29, -13.95]		52	2.87]			
	SURPASS-AP-Combo	-24.10 [-34.69, -13.51]	< 0.00001	66	Data not available			
Tirzepatide 10 mg vs.	SURPASS-3		< 0.00001		1.18	[-0.97,	0.28	84
		-36.24 [-43.26, -29.23]		40	3.33]			

Insulin	SURPASS-4	-28.46 [-46.21, -10.71]	0.002	87	0.45 [-0.65, 1.56]	0.42	0
	SURPASS-6	-30.15 [-46.39, -13.90]	0.0003	87	1.81 [0.70, 2.91]	0.001	37
	SURPASS-AP-Combo	-25.97 [-39.24, -12.69]	0.0001	79	Data not available		
Tirzepatide 15 mg vs. Insulin	SURPASS-3	-33.20 [-39.41, -26.99]	< 0.00001	17	1.86 [0.21, 3.51]	0.03	73
	SURPASS-4	-26.98 [-36.81, -17.15]	< 0.00001	56	0.67 [-0.42, 1.76]	0.23	0
	SURPASS-6	-30.78 [-40.88, -20.68]	< 0.00001	67	1.60 [-0.54, 3.75]	0.14	82
	SURPASS-AP-Combo	-27.42 [-37.76, -17.09]	< 0.00001	67	Data not available		

CFB, Change from baseline; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; MD: Mean difference; UACR: Urine albumin-to-creatinine ratio.