Metsera

SURMOUNT TRIAL STUDIES

Summary

14 May 2024

SURMOUNT 4 (Phase 3 double-blind RCT)

670 patients randomized 1:1 to receive tirzepatide max tolerated dose (10 or 15 mg) or placebo SQ QW over 88 weeks. The study design included a 36 week open-label lead-in on Tirzepatide MTD and a 52 week double-blind treatment period on Tirzepatide or placebo. This included a 20 week dose escalation period starting with tirzepatide 2.5 mg QW x 4 weeks and increased weekly until assigned dose was achieved.

Study Start 29-Mar-2021 to 18-May-2023

70 sites in 4 countries (US, Argentina, Brazil, Taiwan)

	Tirzepatide lead-in (N=670) Week 0-36	Randomized Population	
		Tirzepatide MTD (N=335)	Placebo (N=335)
PRIMARY ENDPOINT (Week 36 to Week 88)[a]			
Week 36 mean body weight (kg)	107.2 (week 0-36)	84.6	85.8
Mean Change in body weight (%)	-20.9 (week 0-36)	-5.5	14
ETD (95% CI; P)	N/A	*-19.4 (-21.2 to -17.7; P<.001*	
KEY SECONDARY ENDPOINTS (Week 36 to Week 88)[b]			
Change in body weight from wk 36 to 88, kg	-	-4.7	11.1
ETD (95% CI; P)	-	*-15.8 (-17.3 to -14.3); P<.001*	
Week 36 mean waist circumference (cm)		96.8	98.2
Mean change in waist circumference wk 36 to 88 (cm)	-	-4.3	7.8
ETD (95% CI; P)	-	*-12.1 (-13.5 to -10.6); P<.001*	
Patients maintaining ≥80% of body weight lost during wk 36 lead-in at wk 88 (%)	-	89.5	16.6
		P<.001	
Patients achieving body weight reduction from wk 0-88 (%); *P<.001 Tirzepatide MTD vs Placebo*			
Patients with body weight reduction ≥5% (%)	-	97.3	70.3
Patients with body weight reduction ≥10% (%)	-	92.1	46.2
Patients with body weight reduction ≥15% (%)	-	84.1	25.9
Patients with body weight reduction ≥20% (%)	-	69.5	12.6
Change in body weight from wk 36 to 64 (%)		-5.4	10.0
ETD (95% CI; P)		*-15.4 (-16.8 to -14.1); P<.001*	

SAFETY			
Safety outcomes, n(%)	Tirzepatide Lead-in (n=783) Wk 0-36	Randomized Population Wk 36-88	
		Tirzepatide MTD (N=335)	Placebo (N=335)
Any Adverse Event	-	202 (60.3)	187 (55.8)
Serious Adverse Events	-	10 (3.0)	10 (3.0)
Death[c]	-	1 (0.3)	1 (0.3)
AE leading to treatment discontinuation[d]	-	6 (1.8)	3 (0.9)
Diarrhea	-	2 (0.6)	0
Vomiting	-	1 (0.3)	0
Abdominal Pain	-	1 (0.3)	0
Elevated pancreatic enzymes	-	1 (0.3)	0
Adverse events reported in ≥5% of patients in either treatment group[d]			
Nausea	278 (35.5)	27 (8.1)	9 (2.7)
Diarrhea	165 (21.1)	36 (10.7)	16 (4.8)
Vomiting	128 (16.3)	19 (5.7)	4 (1.2)
Injection site reaction	64 (8.2)	-	-
Hypoglycemia (blood glucose <54 mg/dL)	-	2 (0.6)	0

a. Tested for superiority, controlled for type I error
b. Key secondary endpoints include the time, during the 52-week double-blind period (wk 36-88 in the entire study), to first occurrence of participant returning to >95% baseline body weight if already lost ≥ 5% since week 0.
c. Deaths are also included as serious adverse events and discontinuations due to adverse event
d. Adverse events are listed according to MEDRA version 26.0, preferred terms
e. Includes 6 serious GI events in 3 tirzepatide-treated patients and 1 serious GI event in placeo group

SURMOUNT-3 (Phase 3 double-blind RCT)

579 patients who had ≥5% weight loss by the end of the 12-week lead-in period were randomized 1:1 to receive Tirzepatide Max Tolerated Dose (10mg or 15mg) or placebo SQ QW for 72 weeks. This included a 20 week dose escalation period starting with tirzepatide 2.5 mg QW x 4 weeks and increased weekly until max tolerated dose was achieved.

During the 12-week lead-in, participants followed a low-calorie diet (1200 kcal/day for women, 1500 kcal/day for men), which may have included up to two liquid meal replacements per day. Participants were encouraged to perform at least 150 minutes per week of moderate intensity activity. Participants were also counseled on behavior modification strategies to help implement and adhere to the diet and exercise recommendations.

Study Start 12-Apr-2021 to 03-Sep-2021

65 sites in 4 countries US, Argentina, Brazil, and Puerto Rico

f.

	Tirzepatide MTD (n=287)	Placebo (N=292)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 72) *Tirzepatide vs Placebo P<.001*		
Baseline (week 0, post lead-in) mean body weight (kg)	102.5	101.3
Mean Change in body weight (%)	-18.4	2.5
95% CI	-23.2 to -18.5	
Patients with body weight reduction≥ 5% (%)	87.5	16.5
KEY SECONDARY ENDPOINTS (BASELINE TO WEEK 72) *Tirzepatide vs Placebo P<.001*		
Patients with body weight reduction ≥10% (%)	76.7	8.9
Patients with body weight reduction ≥ 15% (%)	65.4	4.2
Patients with body weight reduction ≥ 20% (%)	44.7	2.2
Baseline (week 0, post lead-in) mean waist circumference (cm)	109.3	109.6
Mean change in waist circumference (cm)	-14.6	0.2
95% CI	-17.2 to -12.5	
Patients maintaining ≥80% of lead-in body weight lost at week 72 (%)	94.0	43.8
SAFETY		
Safety outcomes, n(%)	Tirzepatide MTD (n=287)	Placebo (N=292)
Any Adverse Event	250 (87.1)	224 (76.7)
Serious Adverse Events	17 (5.9)	14 (4.8)
AE leading to treatment discontinuation	30 (10.5)	6 (2.1)
Nausea	24 (8.4)	4 (1.4)
Diarrhea	3 (1.0)	0
Vomiting	6 (2.1)	0
Dyspepsia	3 (1.0)	0
Constipation	2 (0.7)	0
Adverse events reported in ≥ 5% of patients in either treatment group		
Nausea	114 (39.7)	41 (14.0)
Diarrhea	89 (31.0)	27 (9.2)
Constipation	66 (23.0)	20 (6.8)
Vomiting	52 (18.1)	4 (1.4)
Injection site reactions	32 (11.1)	3 (1.0)
Severe Hypoglycemia	0	0

SURMOUNT-2 (Phase 3 double-blind RCT)

938 patients randomized 1:1:1 to receive tirzepatide 10mg, 15mg, or placebo SQ QW for 72 weeks. This included a 20 week dose escalation period starting with tirzepatide 2.5 mg QW x 4 weeks and increased weekly until assigned dose was achieved.

Study Start 29-Mar-2021 to 10-Apr-2023

77 sites in 7 countries (US, Argentina, Brazil, India, Japan, Russia, Taiwan)

	Tirzepatide 10 mg (n=312)	Tirzepatide 15 mg (N=311)	Placebo (n=315)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 72)[a] *Tirzepatide vs Placebo P<.0001*			
Baseline (week 0) mean body weight (kg)	100.9	99.6	101.7
Mean Change in body weight (%)	-12.8	-14.7	-3.2
95% CI	*-11.1 to -8.1*	*-13.0 to -10.1*	
Patients with body weight reduction≥ 5% (%)	79	83	32
KEY SECONDARY ENDPOINTS (BASELINE TO WEEK 72) *Tirzepatide vs Placebo P<.0001*			
Patients with body weight reduction ≥10% (%)	61	65	9
Patients with body weight reduction ≥ 15% (%)	40	48	3
Patients with body weight reduction ≥ 20% (%)	22	31	1
Baseline (week 0) mean waist circumference (cm)	114.2	114.6	116
Mean change in waist circumference (cm)	-10.8	-13.1	-3.3
95% CI	*-9.0 to -5.9*	*-11.2 to -8.3*	
Baseline (week 0) HbA1c	8.00	8.07	7.89
Mean change in A1C (%)	-2.07	-2.08	.51
95% CI	*-1.74 to -1.37*	*-1.76 to -1.37*	
Baseline (week 0) Fasting glucose, mg/dL	158.3	161.2	159.3
Mean change in FPG, mg/dl	-48.9	-48.9	-11.0
95% CI	*-44.1 to -31.8*	*-44.4 to -31.4*	
Duration of Diabetes (years)	8.8	8.0	8.8
Participants with A1C <5.7% (%)	46	49	4
SAFETY			
Safety outcomes, n(%)	Tirzepatide 10 mg (n=312)	Tirzepatide 15 mg (N=311)	Placebo (n=315)
Any Adverse Event	242 (78)	222 (71)	239 (76)
Serious Adverse Events	18 (6)	27 (9)	23 (7)
AE leading to treatment discontinuation[b]	12 (4)	23 (7)	12 (4)
Nausea	1 (<1%)	4 (1%)	0
Diarrhea	0	5 (2%)	0
Vomiting	2 (1%)	0	0
Elevated blood calcitonin	2 (1%)	0	0
Elevated pancreatic enzymes	2 (1%)	0	0
Adverse events reported in ≥ 5% of patients in either treatment group			
Nausea	63 (20)	68 (22)	20 (6)
Diarrhea	62 (20)	67 (22)	28 (9)
Constipation	25 (8)	28 (9)	13 (4)
Vomiting	34 (11)	41 (13)	10 (3)
Hypoglycemia[c]	11 (4)	15 (5)	4 (1)

a. The primary and key secondary endpoints were tested under a type-1 error-control procedure.
b. Adverse events are listed according to MEDRA version 24.1, preferred terms
c. Blood glucose <54mg/dl

SURMOUNT-1 (Phase 3 double-blind RCT)

2539 patients randomized 1:1:1:1 to receive tirzepatide 5mg, 10mg, 15mg, or placebo SQ QW for 72 weeks. This included a 20 week dose escalation period starting with tirzepatide 2.5 mg QW x 4 weeks and increased weekly until assigned dose was achieved.

Study Start December 2019-April 2022

119 sites in 9 countries (US, Argentina, Brazil, China, India, Japan, Mexico, Russia and Taiwan)

	Tirzepatide [a,c] 5mg (n=630)	Tirzepatide 10 mg (n=636)	Tirzpetaide 15 mg (N=630)	Placebo (n=643)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 72)[a] *Tirzepatide vs Placebo P<.0001*				
Baseline (week 0) mean body weight (kg)	102.9	105.8	105.6	104.8
Mean Change in body weight (%)	-15.0	-19.5	-20.9	-3.1
95% CI	-15.9 to -14.2	-20.4 to -18.5	-21.8 to -19.9	
Patients with body weight reduction≥ 5% (%)[b]	85.1	88.9	90.9	34.5
KEY SECONDARY ENDPOINTS (BASELINE TO WEEK 72) *Tirzepatide vs Placebo P<.0001*				
Patients with body weight reduction ≥10% (%)[b]	68.5	78.1	83.5	18.8
Patients with body weight reduction ≥ 15% (%)[b]	48.0	66.6	70.6	8.8
Patients with body weight reduction ≥ 20% (%)[b]	30.0	50.1	56.7	3.1
Baseline (week 0) mean waist circumference (cm)	113.2	114.8	114.4	114.0
Mean change in waist circumference (cm)[c]	-14.0	-17.7	-18.5	-4.0
95% CI	-14.9 to -13.1	-18.7 to -16.8	-19.3 to -17.6	
SAFETY				
Safety outcomes, n(%)	Tirzepatide [a,c] 5mg (n=630)	Tirzepatide 10 mg (n=636)	Tirzpetaide 15 mg (N=630)	Placebo (n=643)
Any Adverse Event	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious Adverse Events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
AE leading to treatment discontinuation[d]	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0
Adverse events reported in ≥ 5% of patients in either treatment group				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Injection-site reaction[e]	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)
Hypoglycemia[f]	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)

a. The change in body weight in the tirzepatide 5 mg arm was not a coprimary endpoint and was analyzed as a key secondary endpoint
b. The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets
c. The specified weight-reduction targets and the change in waist circumference in the tirzepatide 5mg arm were not key secondary endpoints. Data not adjusted for multiplicity, no definite conclusions can be drawn
d. Adverse events are listed according to MEDRA version 24.1, preferred terms
e. None of the events reported as severe or serious
f. Blood glucose <54 mg/dl