Metsera

WEGOVY SUMMARY

Semaglutide

22 May 2024

	Phase 3A Studies[1]					Phase 3B Studies[a]	
	Step 1 68 weeks	**Step 2** 68 weeks	**Step 3** 68 weeks	**Step 4** 68 weeks	**Step Teens[2]** 68 weeks	**Step 5** 104 weeks	**Step 8** 68 weeks
	1961 (2:1)	1210 (1:1:1)	611 (2:1)	803[3] (2:1)	201 (2:1)	304 (1:1)	338 (3:1:3:1[4])
N	Sema N=1306 PBO N=655	Sema N=404 Sema 1mg PBO N=403	Sema N=407 PBO N=204	Sema N=535 PBO N=268	Sema N=134 PBO N=67	Sema N=152 PBO N=152	Sema N=126 Lira 3 N=127
Patient Population	Adults with BMI ≥ 30kmg/m^2 and ≥ one weight-related comorbidity[5] (without diabetes)	Adults with BMI≥ 27 kg/m^2 and T2D (A1C 7%-10%) diagnosed ≥ 180 days before screening	Adults with BMI ≥ 27kg/m^2 and ≥ one weight-related comorbidity[e] (without diabetes)	Adults with BMI ≥ 30kmg/m^2 or ≥ 27 kg/m^2 with ≥one weight-related comorbidity[e]	Adolescents (age 12 to <18 years) with a BMI ≥95th percentile or ≥85th percentile (based on sex and age specific growth charts) with ≥one weight-related comorbidity[e]	Adolescents (age 12 to <18 years) with a BMI≥95th percentile or ≥85th percentile (base on sex and age specific growth charts) with ≥one weight-related comorbidity[e]	Adults with BMI ≥ 30kmg/m^2 and ≥ one weight-related comorbidity[e] (without diabetes)
Background Treatment	Diet and Exercise	Diet and Exercise and 0-3 OADs[6]	Intensive Behavioral Therapy (IBT)	Diet and Exercise	Nutrition and physical activity counseling	Diet and Excerise	Diet and Exercise
Baseline Body Weight (lb)	232.1	220.0	233.2	211.9	237.0	233.7	230.4
Primary Endpoint (end of trial)	*Co-Primary Endpoint:* % change in BW Proportion of patients with ≥5% BW reduction	*Co-Primary Endpoint:* 1.% change in BW 2. Proportion of patients with ≥5% BW reduction	*Co-Primary Endpoint:* 1.% change in BW 2. Proportion of patients with ≥5% BW reduction	% change in BW from week 20-week 68	% change in BMI	*Co-Primary Endpoint:* 1.% change in BW 2. Proportion of patients with ≥5% BW reduction	% change in BW vs lira 3.0
Comparator	Placebo	Placebo, Semaglutide 1mg	Placebo	Placebo	Placebo	Placebo	Liraglutide 3mg, placebo
Mean % change BW **(P<.001 for Sema)**	-14.9 vs -2.4	-9.6 vs -3.4	-16.0 vs -5.7	-7.9 vs +6.9	N/A	-15.2 vs -2.6	-15.8 vs -6.4
% of patients with ≥5% BW reduction **(P<.001 for Sema)**	86.4 vs 31.5	68.8 vs 28.5	86.6 vs 47.6	N/A	N/A	77.1 vs 34.4	N/A
Mean % change in BMI **(P<.001 for Sema)**	N/A	N/A	N/A	N/A	-16.1 vs +0.6	N/A	N/A
GI AEs (%)	74.2 vs 47.9	63.5 vs 34.3	82.8 vs 63.2	41.9 vs 26.1[7]	61.7 vs 41.8	82.2 vs 53.9	84.1 vs 82.7

[1] Each study had a 7 week off-treatment follow-up period
[2] In STEP TEENS, after screening, a 12-week lifestyle intervention run-in period preceded randomization per regulatory guidelines. At randomization, Wegovy® was initiated at 0.25 mg and escalated to 2.4 mg (or maximum tolerated dose) over 16 weeks.
[3] All enrolled patients (N=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (N=803) were randomized to either continue Wegovy® or switchto placebo.
[4] Patients were randomized 3:1:3:1 to Wegovy® (N=126) or matching placebo, or Saxenda® (N=127) or matching placebo (pooled placebo [N=85]).
[5] Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. In STEP TEENS, comorbidities included hypertension, dyslipidemia, obstructive sleep apnea or T2D

[6] Treatment with up to 3 of the following OADs for at least 90 days prior to screening were allowed: MET, SU, SGLT2i, or TZD.
[7] GI AEs during the randomized period (week 20-week 68)

	Phase 3A Studies[1]					Phase 3B Studies[a]	
	Step 1 68 weeks	**Step 2** 68 weeks	**Step 3** 68 weeks	**Step 4** 68 weeks	**Step Teens[2]** 68 weeks	**Step 5** 104 weeks	**Step 8** 68 weeks
	1961 (2:1)	1210 (1:1:1)	611 (2:1)	803[3] (2:1)	201 (2:1)	304 (1:1)	338 (3:1:3:1[4])
Discontinuation due to GI AEs (%)	4.5 vs 0.8	4.2 vs 1.0	3.4 vs 0	0.4 vs 1.5[g]	2.3 vs 1.5	3.9 vs 0.7	0.8 vs 6.3

Step 2

Step 2: Patients randomized 1:1:1 to receive semaglutide 2.4 mg, semaglutide 1 mg or placebo SQ QW for 68 weeks or matching placebo in addition to lifestyle intervention, followed by a 7 week period without any intervention. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose (would need CTR to see results or how many achieved max dose)

Study Start 2018-June-04, completion 2020-May-01 LPLV

149 sites in 12 countries (Argentina, Canada, Germany, Greece, India, Japan, Puerto Rico, Russian Federation, South Africa, Spain, United Arab Emirates, United Kingdom, United States

	Semaglutide 2.4 mg (n=404)	Semaglutide 1 mg (n=403)	Placebo (n=403)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 68)			
Baseline (week 0) mean body weight (kg)	99.9	99.0	100.5
Mean Change in body weight (%)	-9.6	-7.0	-3.4
Sema 2.4mg vs Placebo mg ETD (95% CI); P-value		-6.2 (-7.3 to -5.2); P<.0001	
Sema 2.4mg vs Sema 1mg ETD (95% CI); P-value (confirmatory secondary endpoint)		-2.7 (-3.7 to -1.6); P<.0001	
Patients with body weight reduction≥ 5% (%)	68.8	57.1	28.5
Sema 2.4mg vs Placebo: P-value		P<.0001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)			
Patients with body weight reduction ≥10% — (%)	45.6	28.7	8.2
Sema 2.4mg vs Placebo: P-value		P<.0001	
Patients with body weight reduction ≥ 15% (%)	25.8	13.7	3.2
Sema 2.4mg vs Placebo: P-value		P<.0001	
Baseline (week 0) mean waist circumference (cm)	114.6	113.9	115.5
Mean change in waist circumference (cm)	-9.4	-6.7	-4.5
Sema 2.4mg vs Placebo: P-value		P<.0001	
Baseline (Week 0) mean A1C (%)		8.1	
Mean change in A1C (%)	-1.6	-1.5	-0.4
Sema 2.4mg vs Placebo: P-value		-1.2 (-1.4 to -1.0); P<.0001	

	Semaglutide 2.4 mg (n=404)	Semaglutide 1 mg (n=403)	Placebo (n=403)
Baseline (week 0) mean SBP (mmHg)		127	
Mean change in SBP (mmHg)	-3.9	-2.9	-0.5
Sema 2.4mg vs Placebo: P-value		-3.4 (-5.6 to -1.3); P<.0001	
Baseline (week 0) mean SF-36V2 physical functioning score[a]		49.7	
Mean change in SF-36V2 physical functioning score	2.5	2.4	1.0
Sema 2.4mg vs Placebo: P-value		1.5 (0.4 to 2.6 P<.0001	
Baseline (week 0) mean IWQOL LITE-CT physical function score[b]		69.2	
Mean change in IWQOL LITE-CT physical function score	10.1	8.7	5.3
Sema 2.4mg vs Placebo: P-value		4.8 (1.8 to 7.9); *P*=.0018	
SAFETY[c]			
Safety outcomes, n(%)	Semaglutide 2.4 mg (n=403)	Semaglutide 1 mg (n=402)	Placebo (n=402)
Any Adverse Event	353 (87.6)	329 (81.8)	309 (76.9)
Serious Adverse Events	40 (9.9)	31 (7.7)	37 (9.2)
AE leading to treatment discontinuation	25 (6.2)	20 (5.0)	14 (3.5)
GI disorders leading to discontinuation	17 (4.2)	14 (3.5)	4 (1.0)
Fatal Events[d]	1 (0.2)	1 (0.2)	1 (0.2
Adverse events reported in ≥ 10% of patients in either treatment group			
Nausea	136 (33.7)	129 (32.1)	37 (9.2)
Diarrhea	86 (21.3)	89 (22.1)	48 (11.9)
Vomiting	88 (21.8)	54 (13.4)	11 (2.7)
Constipation	70 (17.4)	51 (12.7)	22 (5.5)
Nasopharyngitis	68 (16.9)	47 (11.7)	59 (14.7)
Upper respiratory tract infection	42 (10.4)	37 (9.2)	38 (9.5)
Hypoglycemia[e]	23 (5.7)	22 (5.5)	12 (3.0

a. SF-36v2 is a 36-item PRO instrument which measures health-related quality of life and general health status across disease areas in 8 health domains. Scores are norm-based (transformed to a scale on which the 2009 US general population has a mean score of 50 and a standard deviation of 10). Scores range from 19.03 to 57.60 for the physical functioning domain and increases in score represents an improvement in health status.

b. IWQOL-Lite-CT is a 20-item PRO instrument which assesses the impact of body weight changes on patients' physical and psychosocial functioning in three composite scores (physical, physical function and psychosocial) and a total score. Scores range from 0 to 100 and higher scores indicate improved patient functioning.

c. Data form the on-treatment observation period (time from first dose to 49 days after last dose), for the safety analysis population (all randomized patients exposed to ≥ 1 dose of trial product) experience ≥1 event

d. Fatal events reported during the in-trial observation period. Deaths: one due to cardiorespiratory arrest (Sema 1 mg), one due to MI (Sema 2.4 mg) and one due to metastatic hepatocellular carcinoma, pulmonary embolism and respiratory failure (placebo).

e. Severe or BG-confirmed (<56 mg/dL) hypoglycemia

Step 1

Step 1: Patients randomized 2:1 to receive semaglutide 2.4 mg SQ QW for 68 weeks or matching placebo in addition to lifestyle intervention, followed by a 7 week period without any intervention. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if

participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose (would need CTR to see results or how many achieved max dose)

Study Start 2018-06-04, completion 2020-03-30 LPLV

129 sites in 16 countries
(Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puer to Rico, Russian Federation, Taiwan, United Kingdom, United States)

	Semaglutide 2.4 mg (n=1306)	Placebo (n=655)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 68)		
Baseline (Week 0) mean body weight (kg)	105.4	105.2
Mean Change in body weight (%)	-14.9	-2.4
ETD (95% CI); P-value	-12.4(-13.4 to -11.5); P<.001	
Patients with body weight reduction≥ 5% (%)	86.4	31.5
P-value	P<.001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)		
Patients with body weight reduction ≥10% — (%)	69.1	12.0
P-value	P<.001	
Patients with body weight reduction ≥ 15% (%)	50.5	4.9
P-value	P<.001	
Baseline (week 0) mean waist circumference (cm)	114.6	114.8
Mean change in waist circumference (cm)	-13.54	-4.13
P-value	-9.4 (-10.4 to -8.6);P<.001	
Baseline (week 0) mean systolic blood pressure (mmHg)	126	127
Mean change in systolic blood pressure (mmHg)	-6.2	-1.1
ETD (95% CI) ; P-value	-5.1 (-6.3 to -3.9); P<.001	
Baseline (week 0) mean SF-36V2 physical functioning score[a]	51.0	50.8
Mean change in SF-36V2 physical functioning score[a]	2.2	0.4
ETD (95% CI) ; P-value	1.8 (1.2 to 2.4); P<.001	
Baseline (week 0) mean IWQOL LITE-CT physical function score[b]	65.4	64.0
Mean change in IWQOL LITE-CT physical function score	14.7	5.3
ETD (95% CI) ; P-value	9.4 (7.5 to 11.4); P<.001	
Safety Outcomes, n (%)[c]		
Any Adverse Event	1171 (89.7)	566 (86.4)
Serious Adverse Events	128 (9.8)	42 (6.4)
AE leading to treatment discontinuation	92 (7.0)	20 (3.1)
GI disorders leading to discontinuation	59 (4.5)	5 (0.8)
Adverse events reported in ≥ 10% of patients		
Nausea	577 (44.2)	114 (17.4)
Diarrhea	412 (31.5)	104 (15.9)
Vomiting	324 (24.8)	43 (6.6)
Constipation	306 (23.4)	62 (9.5)

	Semaglutide 2.4 mg (n=1306)	Placebo (n=655)
Nasopharyngitis	281 (21.5)	133 (20.3)
Headache	192 (15.2)	80 (12.2)
Dyspepsia	135 (10.3)	23 (3.5)
Abdominal Pain	130 (10.0)	36 (5.5)
Upper respiratory tract infection	114 (8.7)	80 (12.2)

a. Scores on the SF-36v2 are norm-based, transformed to a scale on which the 2009 general population of the United States has a mean score of 50 and a standard deviation of 10; higher scores indicate better quality of life.

b. Scoring on the IWQOL-Lite-CT ranges from 0 to 100, with higher scores indicating better patient functioning.

c. based on the safety analysis population, which includes all randomly allocated patients exposed to ≥1 dose of randomized intervention experience ≥1 event

STEP 3 (US ONLY STUDY)

Step 3: Patients randomized 2:1 to receive semaglutide 2.4 mg SQ QW for 68 weeks or matching placebo in addition to intensive behavioral therapy with an off-treatment follow-up period of 7 weeks. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose (would need CTR to see results or how many achieved max dose)

Study Start August 2018, completion April 2020 LPLV

41 sites in the US

	Semaglutide 2.4 mg (n=407)	Placebo (n=204)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 68)		
Baseline (Week 0) mean body weight (kg)	106.9	103.7
Mean Change in body weight (%)	-16.0	-5.7
ETD (95% CI); P-value	-10.3 (-12.0 to -8.6); P<.001	
Patients with body weight reduction≥ 5% (%)	86.6	47.6
P-value	P<.001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)		
Patients with body weight reduction ≥10% — (%)	75.3	27.0
P-value	P<.001	
Patients with body weight reduction ≥ 15% (%)	55.8	13.2
P-value	P<.001	
Baseline (week 0) mean waist circumference (cm)	113.6	111.8
Mean change in waist circumference (cm)	-14.6	-6.3
P-value	P<.001	
Baseline (week 0) mean systolic blood pressure (mmHg)	124	124
Mean change in systolic blood pressure (mmHg)	-5.6	-1.6
ETD (95% CI) ; P-value	-3.9 (-6.4 to -1.5); P=.001	
Baseline (week 0) mean SF-36V2 physical functioning score[a]	51.9	52.1
Mean change in SF-36V2 physical functioning score	2.4	1.6
ETD (95% CI) ; P-value	0.8 (-0.2 to 1.9); P=NS	
Safety outcomes, n(%)[b]		
Patients with ≥1 adverse event	390 (95.8)	6 (2.9)
Patients with ≥1 serious adverse event	37 (9.1)	6 (2.9)
AE leading to treatment discontinuation	24 (5.9)	6 (2.9)
GI disorders leading to discontinuation	14 (3.4)	0
Adverse events reported in ≥ 10% of patients		
Nausea	237 (58.2)	45 (22.1)
Constipation	150 (36.9)	50 (24.5)
Diarrhea	147 (36.1)	45 (22.1)
Vomiting	111 (27.3)	22 (10.8)
Nasopharyngitis	90 (22.1)	49 (24.0)
Upper Respiratory tract infection	85 (20.9)	44 (21.6)
Headache	78 (19.2)	20 (9.8)

	Semaglutide 2.4 mg (n=407)	Placebo (n=204)
Abdominal Pain	54 (13.3)	10 (4.9)
Back Pain	54 (13.3)	10 (4.9)
Dizziness	52 (12.8)	11 (5.4)
Fatigue	52 (12.8)	15 (7.4)
Flatulence	47 (11.5)	13 (6.4)
Viral Gastroenteritis	42 (10.3)	10 (4.9)
Urinary tract infection	42 (10.3)	13 (6.4)
Abdominal distension	41 (10.1)	20 (9.8)
Sinusitis	39 (9.6)	26 (12.7)

a. Scores on the SF-36v2 are norm-based, transformed to a scale on which the 2009 general population of the United States has a mean score of 50 and a standard deviation of 10; higher scores indicate better quality of life.

b. based on the safety analysis population, which includes all randomly allocated patients exposed to ≥1 dose of randomized intervention

Step 4

902 patients (all received Semaglutide titrated to 2.4 mg for the first 20 weeks, including 16 week escalation). Then 803 patients Patients randomized 2:1 to continue semaglutide 2.4 mg SQ QW or matching placebo for 48 weeks. Throughout the 68 weeks, all patients underwent lifestyle intervention, followed by a 7 week period without any intervention. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose

FPFV 2018-Jun-04 LPFV 2020-Feb-22

73 sites in 10 countries (Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine, United States

	Semaglutide 2.4 mg (n=535)	Placebo (n=268)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 68)		
Mean body weight at randomization (Week 20) (kg)	96.5 (107.2 at week 0)	95.4 (107.2 at week 0)
Mean Change in body weight (%)	-7.9	6.9
ETD (95% CI); P-value	-14.8 (-16.0 to -13.5); P<.001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)		
Mean waist circumference at randomization (week 20) (cm)	105.5 (115.3 at week 0)	104.7 (115.3 at week 0)
Mean change in waist circumference (cm)	-6.4	3.3
ETD (95% CI);P-value	-9.7(-10.9 to -8.5);P<.001	
Mean systolic blood pressure at randomization (week 20) (mmHg)	121 (127 at week 0)	121 (127 at week 0)
Mean change in systolic blood pressure (mmHg)	0.5	4.4
ETD (95% CI) ; P-value	-3.9 (-5.8 to -2.0); P<.001	
Mean SF-36V2 physical functioning score[a,b] at randomization (week 20)	53.8	54.1
Mean change in SF-36V2 physical functioning score	1.0	-1.5
ETD (95% CI) ; P-value	2.5 (1.6 to 3.3); P<.001	
Safety outcomes during Week 20-68, n(%)[c]		
Patients with ≥1 adverse event	435 (81.3)	201 (75.0)
Patients with ≥1 serious adverse event	41 (7.7)	15 (5.6)
AE leading to treatment discontinuation	13 (2.4)	6 (2.2
Adverse events reported in ≥ 5% of patients		
Diarrhea	77 (14.4)	19 (7.1)
Nausea	75 (14.0)	13 (4.9)
Constipation	62 (11.6)	17 (6.3)
Nasopharyngitis	58 (10.8)	39 (14.6)
Vomiting	55 (10.3)	8 (3.0)
Headache	41 (7.7)	10 (3.7)
Influenza	39 (7.3)	19 (7.1)

	Semaglutide 2.4 mg (n=535)	Placebo (n=268)
Abdominal Pain	35 (6.5)	8 (3.0)
Back Pain	28 (5.2)	18 (6.7)
Arthralgia	25 (4.7)	14 (5.2)
Safety outcomes during Week 0-20 (%)[c]	Semaglutide 2.4 mg (n=902)	
Patients with ≥1 adverse event	760 (84.3)	
Patients with ≥1 serious adverse event	21 (2.3)	
AE leading to treatment discontinuation	48 (5.3)	
Adverse events reported in ≥ 5% of patients		
Nausea	422 (46.8)	
Diarrhea	212 (23.5)	
Constipation	200 (22.2)	
Vomiting	140 (15.5)	
Dyspepsia	103 (11.4)	
Decreased Appetite	102 (11.3)	
Headache	96 (10.6)	
Nasopharyngitis	92 (10.2)	
Eructation	71 (7.9)	
Abdominal Pain	68 (7.5)	
Fatigue	67 (7.4)	
GERD	58 (6.4)	
Abdominal distension	50 (5.5)	
Flatulence	50 (5.5)	
Abdominal Pain Upper	49 (5.4)	

a. Scores on the SF-36v2 are norm-based, transformed to a scale on which the 2009 general population of the United States has a mean score of 50 and a standard deviation of 10; higher scores indicate better quality of life.

b. There were 534 patietns in the Sema 2.4mg treatment arm that were analyzed for this endpoint

c. based on the safety analysis population, which includes all randomly allocated patients exposed to ≥1 dose of randomized intervention experience ≥1 event

Step Teens

After mandatory 12 week lifestyle intervention run-in period, adolescent patients (12 to <18 years) randomized 2:1 to receive semaglutide mg SQ QW or matching placebo in addition to lifestyle intervention for 68 weeks followed by an off-treatment 7 week period. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose. Of the 120 patients who completed semaglutide treatment at week 68, 87% compelted the trial at 2.4mg

FPFV 2019-OCT-07, LPFV 2022-03-25

37 sites in 8 countries (Austria, Belgium, Croatia, Ireland, Mexico, Russian Federation, United Kingdom, United States

	Semaglutide 2.4 mg (n=134)	Placebo (n=67)
Baseline (Week 0) body weight, kg	107.5	
PRIMARY ENDPOINT (BASELINE TO WEEK 68)		
Baseline (Week 0) BMI	37	
% Change in BMI from Week 0 to 68	-16.1	0.6
ETD (95% CI); P-value	-16.7 (-20.3 to -13.2), P<.001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)		
Patients with body weight reduction≥ 5%[a] (%)	73	18
P-value	P<.001	
Safety outcomes, n(%)[b]		
Any AE	105 (79)	55 (82)
Serious AE	15 (11)	6 (9)
AE leading to treatment discontinuation	6(5)	3(4)
GI Disorders	3(2)	1 (1)
Fatal AEs[c]	0	0
Select GI AEs		
Nausea	56 (42)	12 (18)
Vomiting	48 (36)	7 (10)
Diarrhea	29 (22)	13 (19)
Abdominal Pain	20 (15)	4 (6)

a. Observed data from in-trial period (uninterrupted time from randomization to last contact with trial site). This included 131 and 62 patients randomized to semaglutide and placebo, respectively

b. Observed proportions assessed during the ont-treatment period (time from first to last trial product administration plus 49 days after the last dose, with the exclusion of any temporary interruptions), unless otherwise noted

c. Observed data from the in-trial period (uninterrupted time from randomization to last contact with trial site, regardless of rescue intervention or adherence to trial product).

STEP 5

Step 5: Patients randomized 1:1 to receive semaglutide 2.4 mg SQ QW for 104 weeks or matching placebo as adjunct to a reduced-calorie diet and increased physical activity with an off-treatment follow-up period of 7 weeks. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 88 weeks on max dose

Study Start 5 October 2018, completion 29 Jan 2021 LPLV

41 sites in the Canada, Hungary, Italy, Spain, USA

	Semaglutide 2.4 mg (n=152)	Placebo (n=152)
COPRIMARY ENDPOINTS (BASELINE TO WEEK 68)		
Baseline (Week 0) mean body weight (kg)	105.6	106.5
Mean Change in body weight (%)	-15.2	-2.6
ETD (95% CI); P-value	-12.6 (-15.3 to -9.8); *P*<.0001	
Patients with body weight reduction≥ 5%[a] (%)	77.1	34.4
P-value	*P*<.0001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)		
Patients with body weight reduction ≥10% [a] — (%)	61.8	13.3
P-value	*P*<.0001	
Patients with body weight reduction ≥ 15% [a] (%)	52.1	7.0
P-value	*P*<.0001	
Baseline (week 0) mean waist circumference (cm)	115.8	115.7
Mean change in waist circumference (cm)	-14.4	-5.2
P-value	-9.2 (-12.2 to -6.2)*P*<.0001	
Baseline (week 0) mean systolic blood pressure (mmHg)	126	125
Mean change in systolic blood pressure (mmHg)	-5.7	-1.6
ETD (95% CI) ; P-value	-4.2 (-7.3 to -1.0) *P*=.0102	
Safety outcomes, n(%)[b]		
Patients with ≥1 adverse event	146(96.1)	136 (89.5)
Patients with ≥1 serious adverse event	12 (7.9)	18 (11.8)
AE leading to treatment discontinuation	9 (5.9)	7 (4.6)
GI disorders leading to discontinuation	6 (3.9)	1 (0.7)
Adverse events reported in ≥ 10% of patients		
Nausea	81 (53.3)	33 (21.7)
Diarrhea	53 (34.9)	36 (23.7)
Constipation	47 (30.9)	17 (11.2)
Vomiting	46 (30.3)	7 (4.6)
Nasopharyngitis	24 (15.8)	23 (15.1)
Abdominal Pain upper	22 (14.5)	10 (6.5)
Abdominal Pain	20 (13.2)	4 (2.6)
Dyspepsia	20 (13.2)	7 (4.6)

	Semaglutide 2.4 mg (n=152)	Placebo (n=152)
Flatulence	20 (13.2)	4 (2.6)
Gastroenteritis	20 (13.2)	4 (2.6)
Influenza	20 (13.2)	16 (10.5)
Upper Respiratory Tract Infection	20 (13.2)	23 (15.1)
Decreased Appetite	17 (11.2)	6 (3.9)
Eructation	17 (11.2)	1 (0.7)
Headache	16 (10.5)	16 (10.5)
Back Pain	15 (9.9)	19 (12.5)
Adverse Events within Safety Focus Areas		
GI disorders	125 (82.2)	82 (53.9)
Gallbladder-related disorders	4 (2.6)	2 (1.3)
Hepatic disorders	3 (2.0)	3 (2.0)
Acute pancreatitis	0	0
Cardiovascular disorders[c]	17 (11.2)	32 (21.1)
Allergic reactions	23 (15.1)	8 (5.3)
Injection site reactions	10 (6.6)	15 (9.9)
Malignant neoplasms	2 (1.3)	4 (2.6)
Psychiatric disorders	26 (17.1)	25 (16.4)
Acute renal failure	0	0
Hypoglycemia	4 (2.6)	0
Rare Events[d]	0	1 (0.7)
Overdose	0	1 (0.7)

a. Observed data from the in-trial period (uninterrupted time from randomization to last contact with trial site). This included 144 and 128 patients randomized to sema 2.4 and placebo, respectively.

b. Observed proportions assessed during the on-treatment period (time from first to last trial product administration plus 7 weeks of follow-up and excluding any period of temporary treatment interruption defined as >7 consecutive missed doses), unless otherwise noted.

c. Events occurred during the in-trial period (uninterrupted time from randomization to last contact with trial site, regardless of rescue intervention or adherence to trial product

d. One serious adverse event of Arnold-Chiari malformation was identified in a patient in the placebo arm. The event was serious, judged to be unlikely related to trial product and not recovered (chronic condition)

Step 8

Step 8: Patients randomized 3:1:3:1 to receive semaglutide 2.4 mg or matching placebo or liraglutide 3.0 mg or matching placebo SQ QW for 68 weeks both as adjunct to reduced-calorie diet and increased physical activity followed by a 7 week period without any intervention. Semaglutide was administered in a prefilled injector, initiated at 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to achieve target maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects at 2.4mg dose) 52 weeks on max dose. Assignment to Wegovy vs Saxenda treatment arms were open-label; however each of the active treatment groups were double-blinded against placebo

Study Start 2019-Sep-11, LPLV 2021-Mar-27 19 US sites

	Semaglutide 2.4 mg (n=126)	Liraglutide 3 mg (n=127)	Pooled Placebo (n=85)
PRIMARY ENDPOINT (BASELINE TO WEEK 68)			
Baseline (week 0) mean body weight (kg)	102.5	103.7	108.8
Mean Change in body weight (%)	-15.8	-6.4	-1.9
Sema 2.4mg vs Lira 3.0 mg ETD (95% CI); P-value[a]		--9.4 (-12.0 to -6.8) P<.001	
CONFIRMATORY SECONDARY ENDPOINTS (BASELINE TO WEEK 68)[b]			
Patients with body weight reduction ≥10% — (%)	70.9	25.6	15.4
Sema 2.4mg vs Lira 3.0 mg OR (95% CI); P-value		6.3 (3.5 to 11.2);P<.0001	
Patients with body weight reduction ≥ 15% (%)	55.6	12.0	6.4
Sema 2.4mg vs Lira 3.0 mg OR (95% CI); P-value		7.9 (4.1 to 15.4);P<.0001	
Patients with body weight reduction ≥ 20% (%)	38.5	6.0	2.6
Sema 2.4mg vs Lira 3.0 mg (95% CI); P-value		8.2 (3.5 to 19.1);P<.0001	
SAFETY (n,%)			
Any Adverse Event	120 (95.2)	122 (96.1)	81 (95.3
Serious Adverse Events	10 (7.9	14 (11.0)	6 (7.1)
Fatal Adverse Events	0	0	0
AEs leading to permanent treatment discontinuation	4 (3.2)	16 (12.6)	3 (3.5)
GI AEs leading to permanent treatment discontinuation	1 (0.8)	8 (6.3)	1 (1.2)
Gastrointestinal Disorders[c]	106 (84.1)	105 (82.7)	47 (55.3)
Nausea	77 (61.1)	75 (59.1)	19 (22.4)
Constipation	49 (38.9)	40 (31.5)	20 (23.5)
Diarrhea	35 (27.8)	23 (18.1)	22 (25.9)
Vomiting	32 (25.4)	26 (20.5)	5 (5.9)
Safety Areas of Interest[c]			
Cardiovascular disorders[d]	16 (12.7)	18 (14.2)	9 (10.6)
Injection site reactions	0	14 (11.0)	5 (5.9)
Malignant neoplasms[d]	3 (2.4)	3 (2.4)	1 (1.2)
Hepatic disorders	2 (1.6)	1 (0.8)	3 (3.5)
Gallbladder-related disorders	1 (0.8)	4 (3.1)	1 (1.2)
Cholelithiasis	1 (0.8)	2 (1.6)	1 (1.2)

Hypoglycemia	0	1 (0.8)	0
Acute Pancreatitis	0	1 (0.8)	0
Acute kidney failure	1 (0.8)	0	1 (1.2)

a. Primary endpoint controlled for multiplicity

b. Confirmatory secondary endpoints controlled for multiplicity

c. Data are for the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention)

d. Identfied via MedDRA v 23.1 searches