



*Società  
Medico Chirurgica  
di Ferrara*

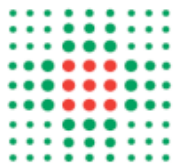
**Obesità:  
inquadramento clinico  
e innovazioni terapeutiche**

*21 Ottobre 2023*

# Semaglutide ed obesità

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**SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA**  
Azienda Ospedaliero - Universitaria di Ferrara



**Università  
degli Studi  
di Ferrara**

# Obesità: quale trattamento?

Dieta

Attività fisica



## TERAPIA MEDICA

Orlistat  
Naltrexone/Bupropione  
Liraglutide 3.0 mg



**Agonista GLP-1R**

Chirurgia Bariatrica

## GLP-1 = ormone incretinico

GLP-1 is synthesized and secreted by:

Neurons in hindbrain



L-cells of the gut



GLP-1R is expressed in:



Brain



Lungs



Heart (AV node)



Pancreas



Kidney



GI tract



Muscle

GLP-1R is not expressed in the liver

## Obesità

↓ Body weight  
↓ Appetite  
↑ Satiety

↓ Glucose production  
↓ Gastric emptying  
↓ Glucagon secretion  
↓ Apoptosis  
↑ Natriuresis  
↑ Diuresis  
↑ Insulin secretion & bio-synthesis

## Diabete

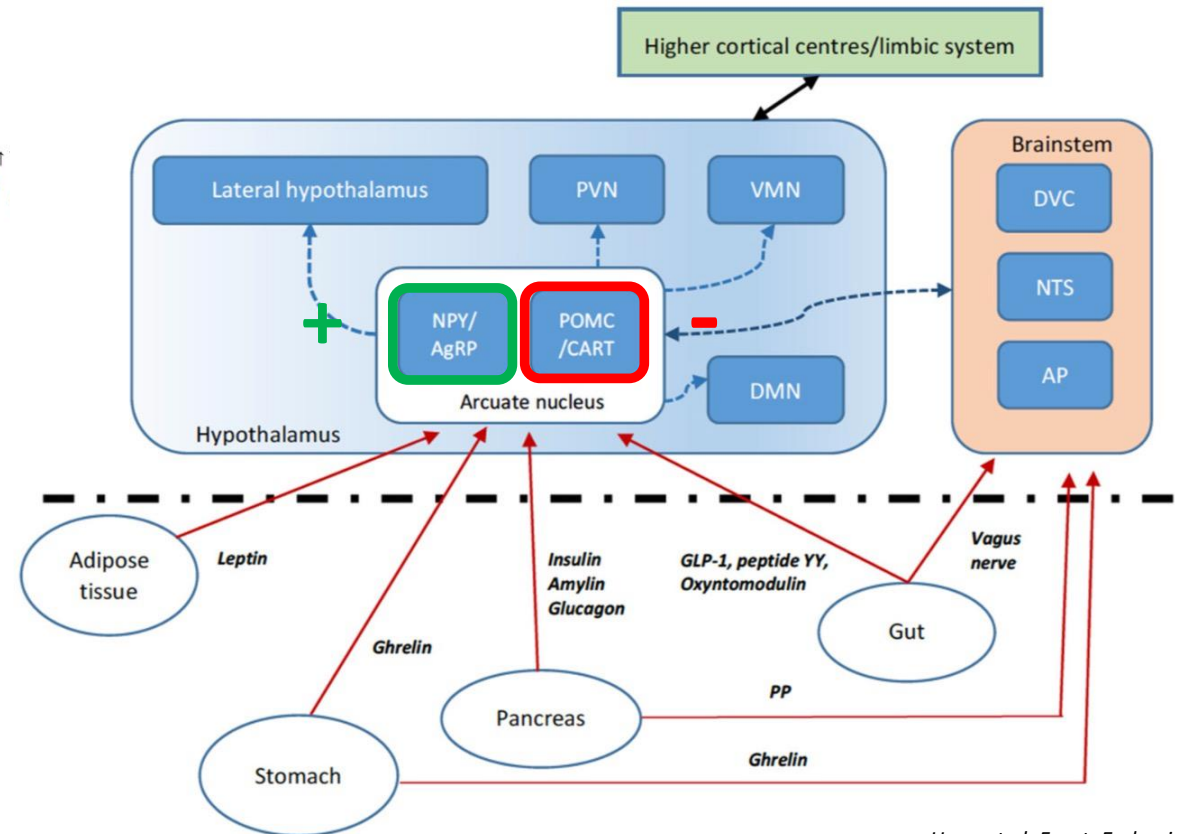
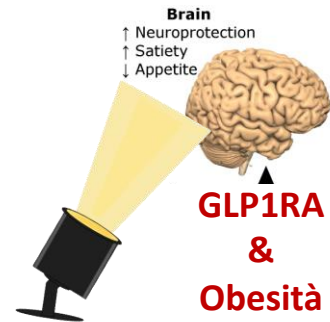
# Agonisti GLP-1R: effetti centrali

## Riduce:

- Apporto energetico
- Senso di fame
- Craving

## Aumenta:

- Senso di sazietà



# Liraglutide 3 mg

Unico agonista GLP-1R approvato e commercializzato in Italia per il trattamento dell'obesità o del sovrappeso in pazienti con BMI  $\geq 30$  kg/m<sup>2</sup> oppure in soggetti con BMI  $\geq 27$  kg/m<sup>2</sup> con altri fattori di rischio o altre patologie correlate all'obesità

**Phase 3a**

**SCALE Obesity and Prediabetes (1839)<sup>1</sup>**

Weight management and delayed onset of diabetes	<table border="0" style="width: 100%;"> <tr> <td style="background-color: #003366; color: white; padding: 2px;">Liraglutide 3.0 mg n=2487</td> </tr> <tr> <td style="background-color: #cccccc; padding: 2px;">Placebo n=1244</td> </tr> </table>	Liraglutide 3.0 mg n=2487	Placebo n=1244
Liraglutide 3.0 mg n=2487			
Placebo n=1244			

**SCALE Diabetes (1922)<sup>2</sup>**

Weight management in type 2 diabetes	<table border="0" style="width: 100%;"> <tr> <td style="background-color: #003366; color: white; padding: 2px;">Liraglutide 3.0 mg n=423</td> </tr> <tr> <td style="background-color: #0070c0; color: white; padding: 2px;">Liraglutide 1.8 mg n=211</td> </tr> <tr> <td style="background-color: #cccccc; padding: 2px;">Placebo n=212</td> </tr> </table>	Liraglutide 3.0 mg n=423	Liraglutide 1.8 mg n=211	Placebo n=212
Liraglutide 3.0 mg n=423				
Liraglutide 1.8 mg n=211				
Placebo n=212				

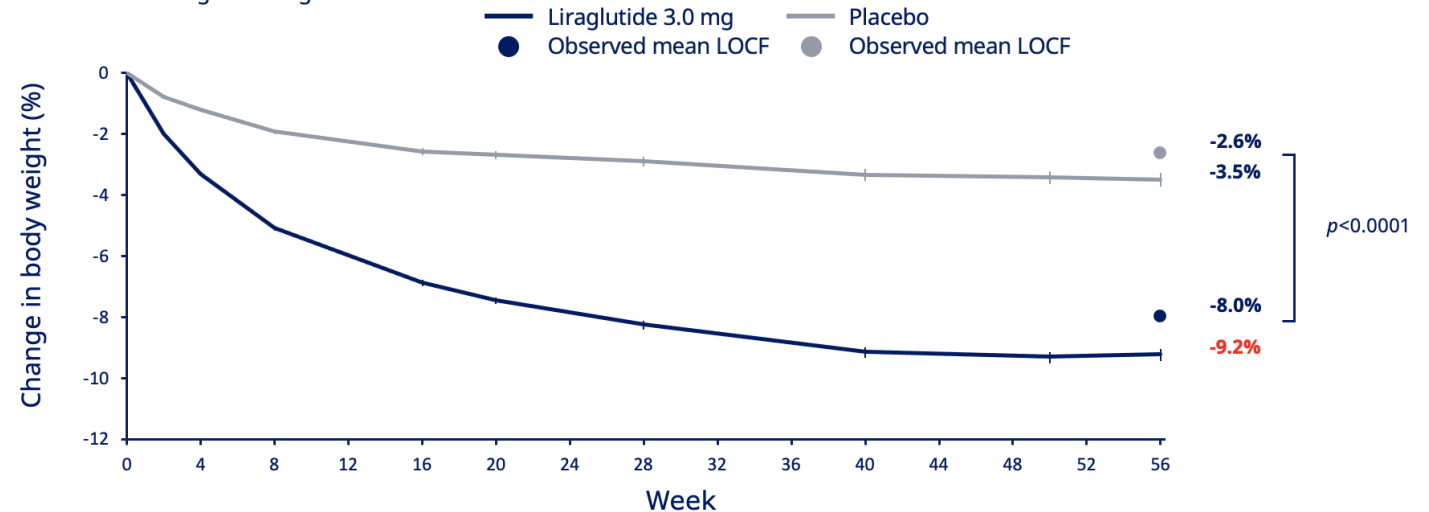
**SCALE Maintenance (1923)<sup>3</sup>**

Prevention of weight regain	<table border="0" style="width: 100%;"> <tr> <td style="background-color: #003366; color: white; padding: 2px;">Liraglutide 3.0 mg n=212</td> </tr> <tr> <td style="background-color: #cccccc; padding: 2px;">Placebo n=210</td> </tr> </table>	Liraglutide 3.0 mg n=212	Placebo n=210
Liraglutide 3.0 mg n=212			
Placebo n=210			

**SCALE Sleep Apnoea (3970)<sup>4</sup>**

Effect of liraglutide in subjects with obesity and moderate to severe OSA	<table border="0" style="width: 100%;"> <tr> <td style="background-color: #003366; color: white; padding: 2px;">Liraglutide 3.0 mg n=180</td> </tr> <tr> <td style="background-color: #cccccc; padding: 2px;">Placebo n=179</td> </tr> </table>	Liraglutide 3.0 mg n=180	Placebo n=179
Liraglutide 3.0 mg n=180			
Placebo n=179			

Mean baseline weight: 106 kg



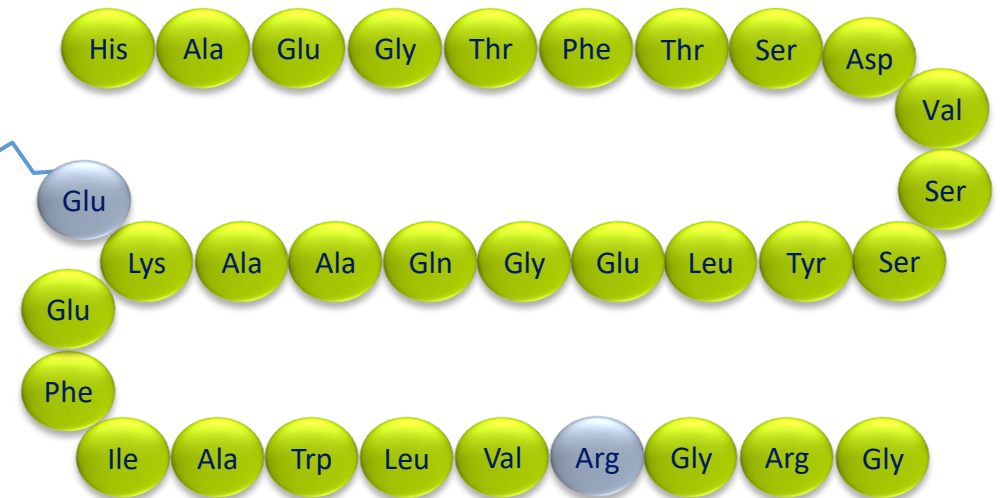
FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.  
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Pi-Sunyer et al. Diabetologia 2014;57(Suppl. 1): Abstract 73-OR

**Somministrazione sottocutanea e giornaliera**

# Liraglutide 3 mg

C-16 fatty acid  
(palmitoyl)

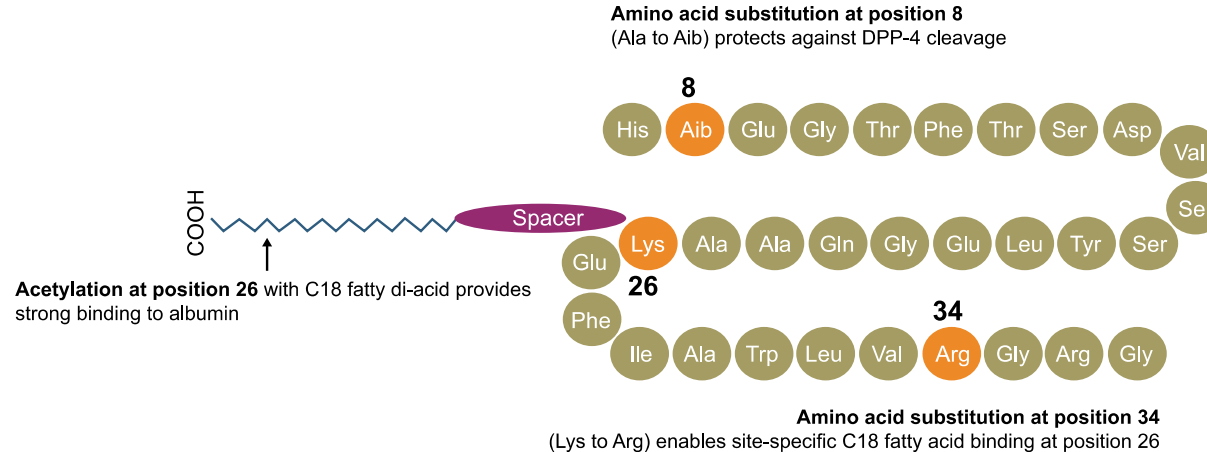


Somministrazione sottocutanea e giornaliera

## POSOLOGIA

- Prima settimana: 0.6 mg/die sottocute
- Seconda settimana: 1.2 mg/die sottocute
- Terza settimana: 1.8 mg/die sottocute
- Quarta settimana: 2.4 mg/die sottocute
- Quinta settimana: **3.0 mg/die sottocute**

# Semaglutide 2.4mg



Approvazione FDA ed EMA (2021) per il trattamento dell'obesità o del sovrappeso in pazienti con BMI  $\geq 30$  kg/m<sup>2</sup> oppure in soggetti con BMI  $\geq 27$  kg/m<sup>2</sup> con altri fattori di rischio o altre patologie correlate all'obesità

**NON ANCORA COMMERCIALIZZATO IN ITALIA PER IL TRATTAMENTO DELL'OBESITA'**

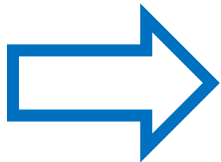
Somministrazione sottocutanea e settimanale

# Semaglutide 2.4mg

Garvey et al. JCEM 2022

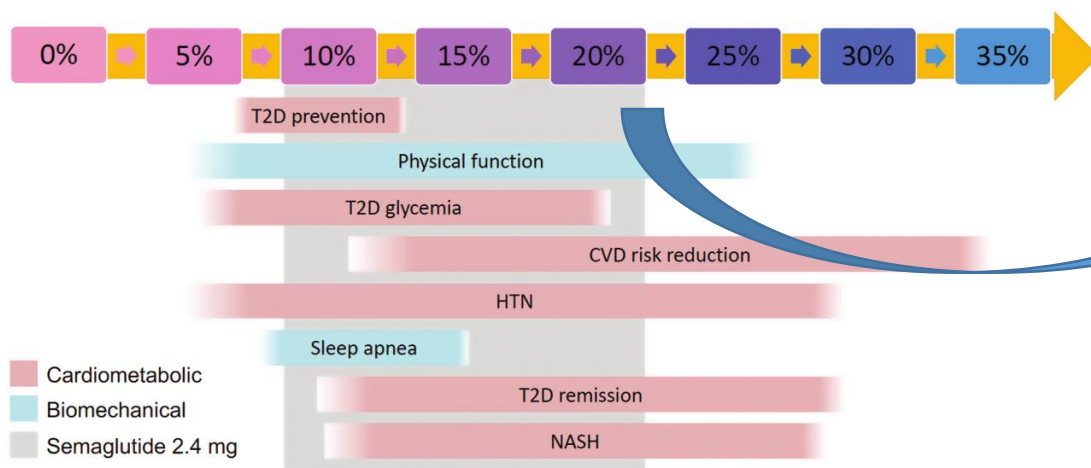
**Table 1.** Efficacy of obesity medications in randomized clinical trials

Drug	% Weight loss		% with ≥ 10%		% with ≥ 15%		% with ≥ 20%	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Orlistat (ref 25)								
XENDOS 1 year	10.6	6.2	41	20.8				
XENDOS 4 year	5.8	3.0	26.2	15.6				
Phentermine/topiramate ER <sup>a</sup> (26-28)								
EQUIP	10.9	1.6	47.2	7.4	32.3	3.4		
CONQUER	9.8	1.2	37.0	7.0				
SEQUEL 2 yr	9.3	1.8	50.3	11.5	24.2	6.6	9.2	2.2
Naltrexone ER/bupropion ER (29-31)								
COR-I	6.1	1.3	25.0	7.0	12	2		
COR-II	6.4	1.2	28.3	5.7	13.5	2.4		
COR-BMOD	9.3	5.1	41.5	20.2	29.1	10.9		
Liraglutide 3 mg (32-34)								
SCALE Maintenance	6.7	0.1	26.1	6.3	11.0	3.1		
SCALE Ob & PreDM 1 year	9.2	3.5	33.1	10.6	14.4	3.5		
SCALE Ob & PreDM 3 year	7.1	2.7	24.8	9.9	11.0	3.1		
Semaglutide 2.4 mg (22-24,35,36)								
STEP 1	14.8	2.4	69.1	12.0	50.5	4.9	32.0	1.7
STEP 3	16.0	5.7	75.3	27.0	55.8	13.2	35.7	3.7
STEP 4	17.4	5.0	79.0	20.4	63.7	9.2	39.6	4.8
STEP 5 2 year	15.2	2.6	61.6	13.3	52.1	7.0	36.1	2.8
STEP 8	15.8	1.9	70.9	15.4	55.6	6.4	38.5	2.6



# Semaglutide 2.4mg: farmaco di seconda generazione

- ↑ Efficacia rispetto ai farmaci precedenti approvati per il trattamento dell'obesità (Perdita > 10% del peso iniziale)
- ↑ Benefici associati al % di calo ponderale
- % di calo ponderale come marker di efficacia del trattamento



Si riduce la forbice tra obiettivi raggiunti con la terapia medica e con la chirurgia bariatrica

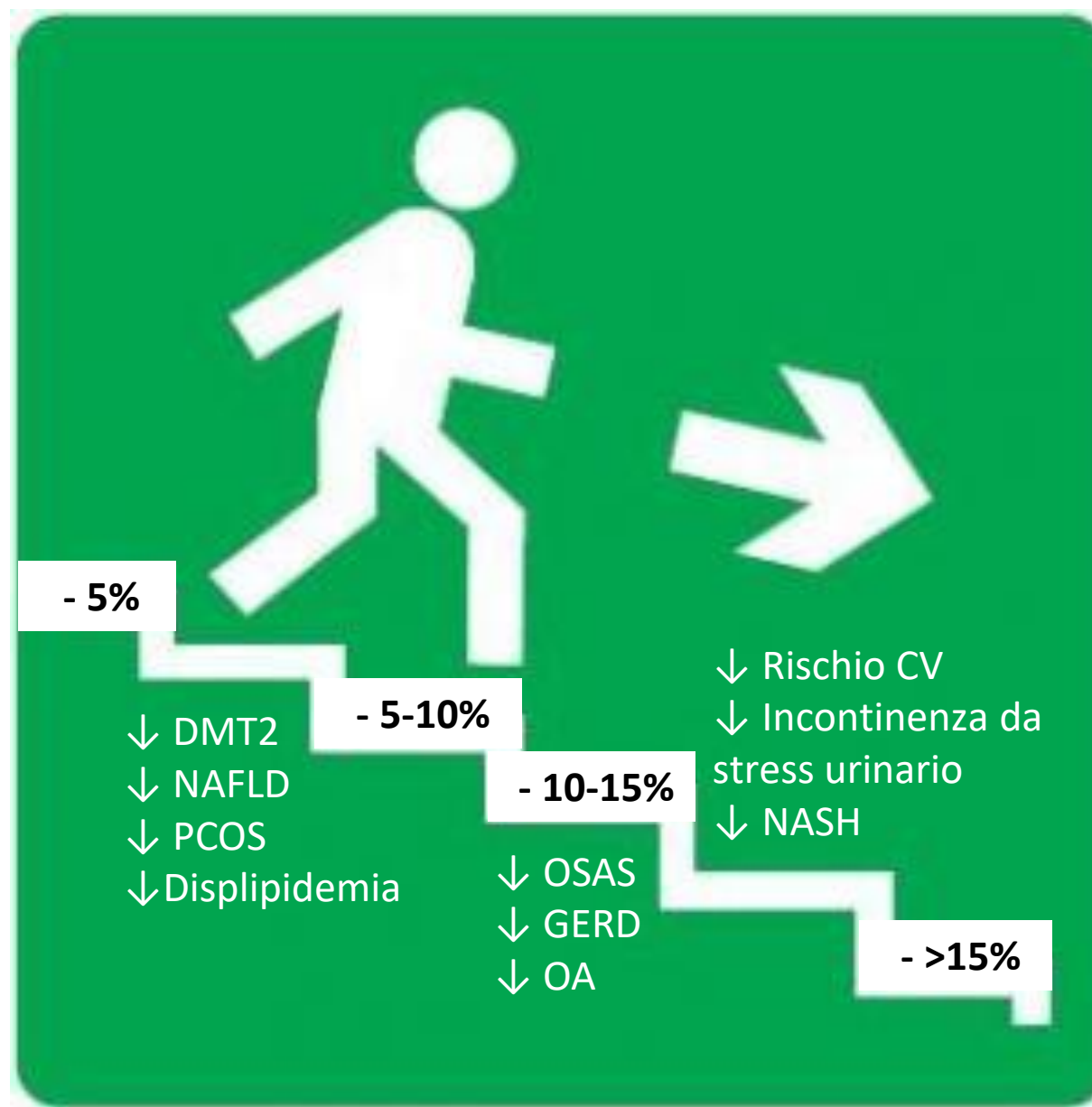
*Ruolo di Semaglutide nel ridurre gli eventi CV e la mortalità CV equivalente alla chirurgia bariatrica?*

Loading...





↓ Ipertensione  
↓ Iperglicemia



↓ DMT2  
↓ NAFLD  
↓ PCOS  
↓ Dislipidemia

↓ OSAS  
↓ GERD  
↓ OA

↓ Rischio CV  
↓ Incontinenza da stress urinario  
↓ NASH

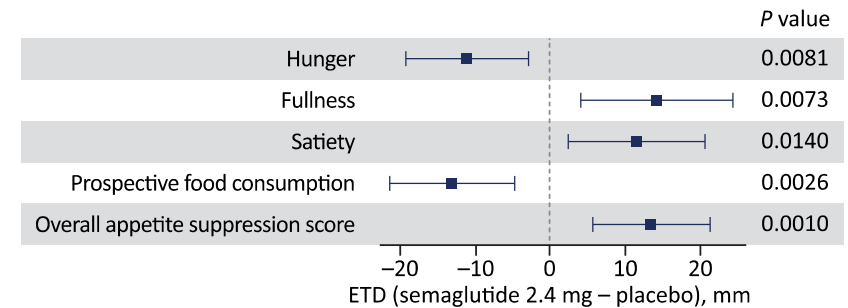
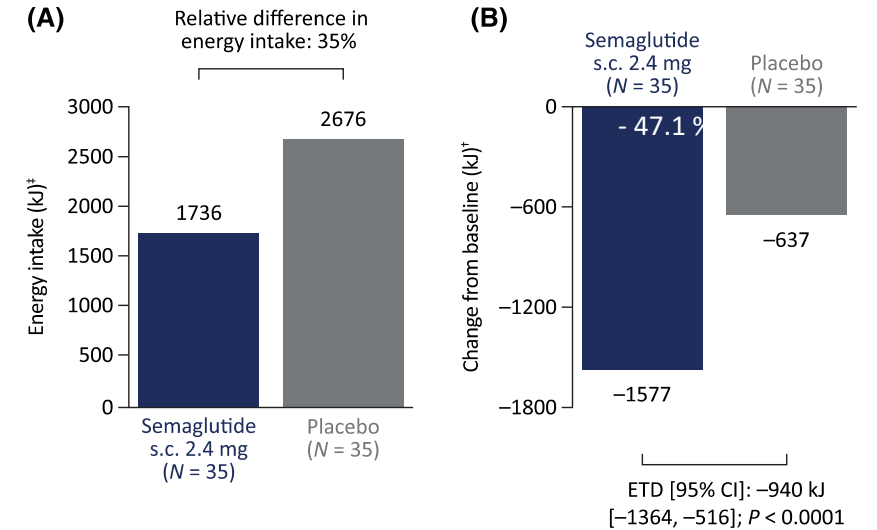
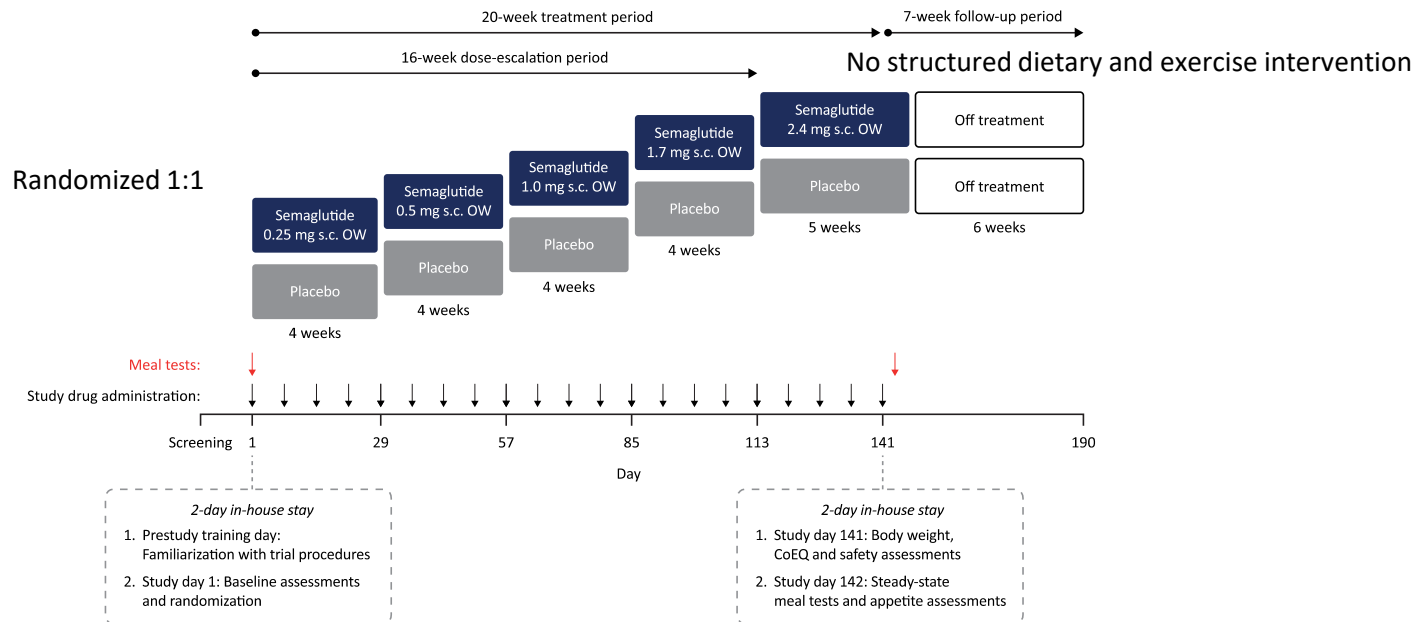
↓ Mortalità CV

# Semaglutide 2.4mg



Friedrichsen *et al.* Diabetes Obes Metab 2021

- Studio di FASE 1 su 72 pazienti adulti con BMI  $\geq 30$  kg/m<sup>2</sup>
- Studio monocentrico, randomizzato in doppio cieco caso-controllo
- Obiettivo I: effetto sullo svuotamento gastrico?
- Obiettivo II: effetto sull'appetito e l'introito energetico?

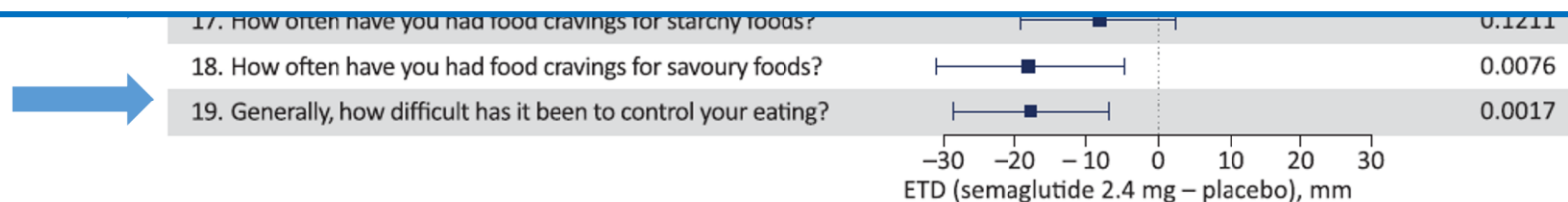


## Control of eating and food craving at w20 (Control of Eating Questionnaire CoEQ)



Negli adulti con BMI > 30 kg/m<sup>2</sup> semaglutide 2.4 mg/settimana:

- riduce l'appetito post-prandiale, il "food craving", l'introito energetico e il peso corporeo
- migliora il controllo della fame
- aumenta il senso di sazietà vs. placebo



# STEP Trials

Cinque studi di fase 3 randomizzati

in doppio cieco, caso-controllo

per testare efficacia, sicurezza e tollerabilità di semaglutide 2.4 mg sc settimanale

## Primary endpoint

- ✓ %  $\Delta$  peso baseline-EOT
- ✓  $\geq -5\%$  del peso all'EOT

## Secondary endpoint

- ✓  $\geq -10\%$  e  $\geq -15\%$  del peso all'EOT
- ✓  $\Delta$  cfr vita, PA, clinical outcomes

## Semaglutide Treatment Effect in People with obesity (STEP)



Phase 3 trial program  
Semaglutide 2.4 mg for  
the treatment of obesity

Primary endpoint  
for all STEP trials  
is **weight loss**

### Trial design

STEP 1 **Weight management**  
68-week treatment

STEP 2 **Weight management in T2D**  
68-week treatment

STEP 3 **Weight management with IBT**  
68-week treatment

STEP 4 **Sustained weight management**  
68-week treatment

STEP 5 **Long-term weight management**  
104-week treatment

16-week dose  
escalation

7 weeks off treatment  
follow-up for safety  
assessments

Change to: IBT, intensive behavioral therapy; T2D, type 2 diabetes.

### Eligibility criteria

Unsuccessful  
diet history  
Age  $\geq 18$  years

BMI  
 $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup>  
+ weight-related  
complications

No  $>5$  kg  
weight change,  
<90 days before  
screening

STEP 2  $\geq 27$  kg/m<sup>2</sup> + T2D

### Treatment



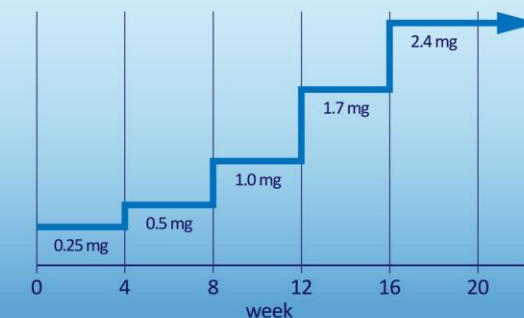
Semaglutide

VS



Placebo

### Dose escalation



### STEP 1, 2, 4, and 5: Lifestyle intervention



150 min/week  
physical activity



-500 kcal/day diet

### STEP 3: Intensive behavioral therapy



Dietitian  
counseling

Increased  
physical activity



Initial 8-week  
low-calorie diet

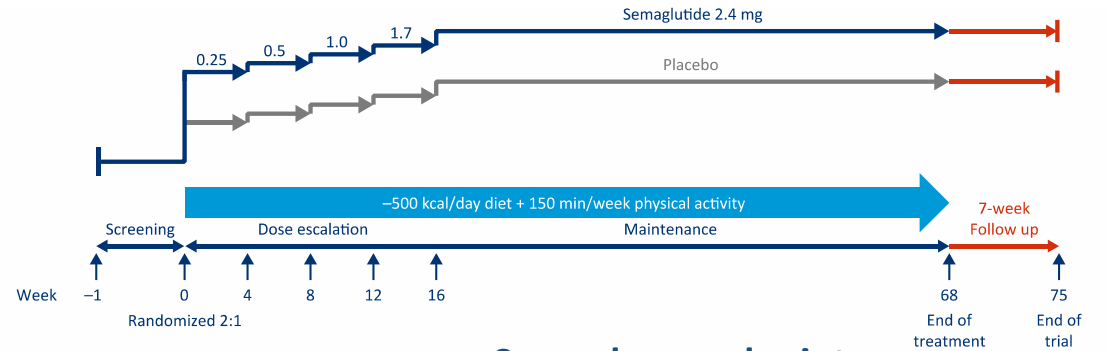
60-week  
hypocaloric diet

# STEP 1



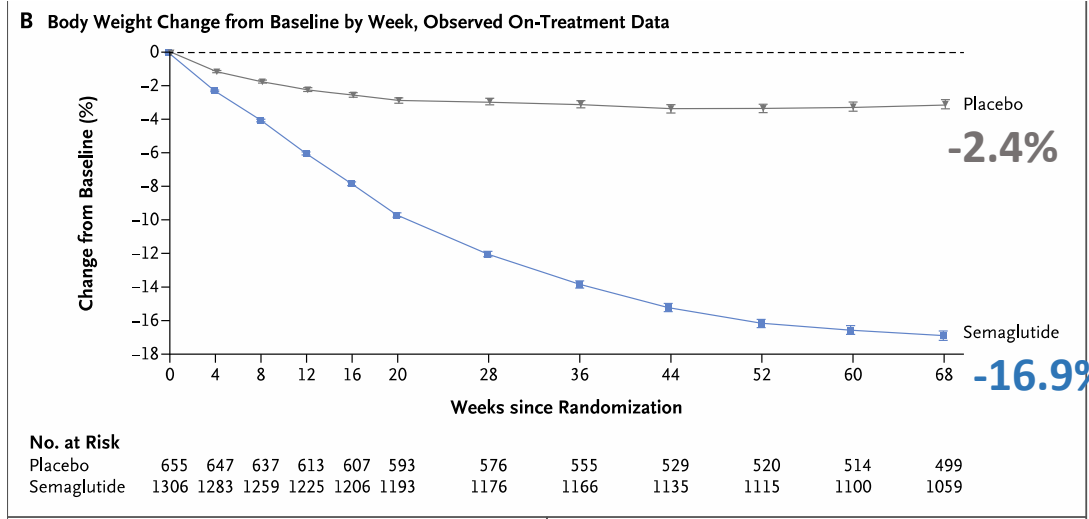
## Superiorità di semaglutide 2.4 mg/settimana vs. placebo

1961 adults with obesity or overweight, without T2D

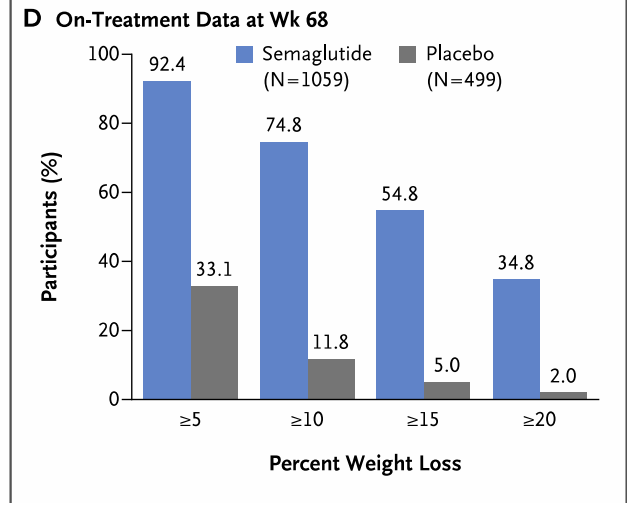


% change in body weight from baseline to week 68

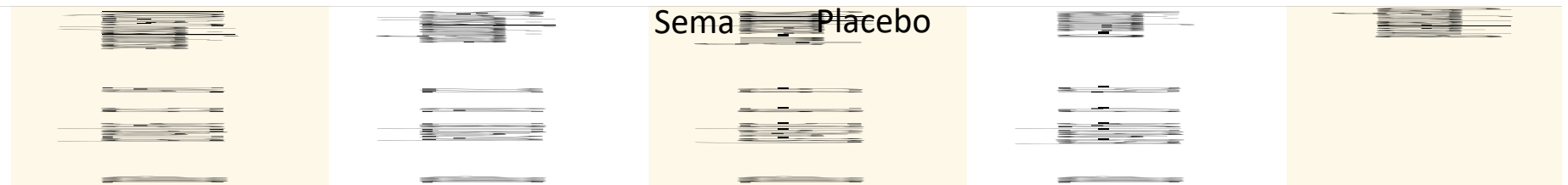
≥ -5% from baseline to week 68



### Secondary endpoint



Secondary end points



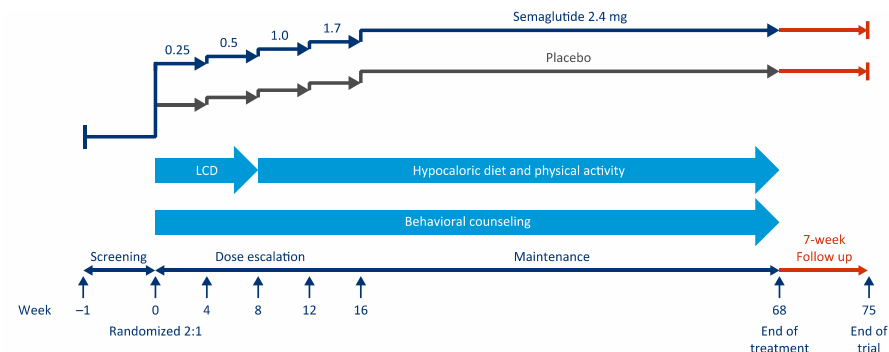
Wilding et al. N Engl J Med 2021

# STEP 3



## Massimizzare l'effetto di semaglutide 2.4 mg/settimana vs. placebo

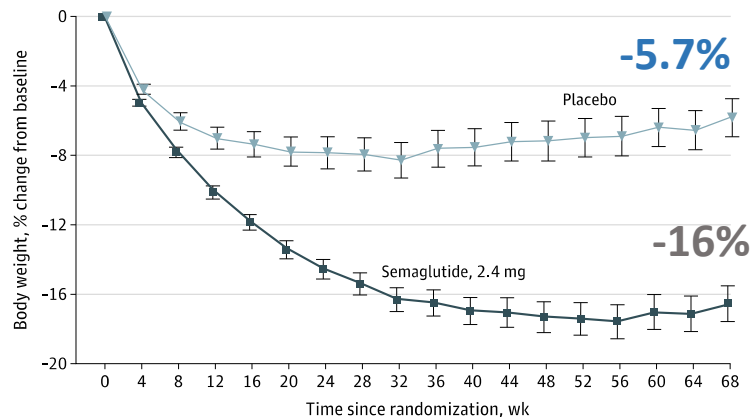
611 adults with obesity or overweight, without T2D



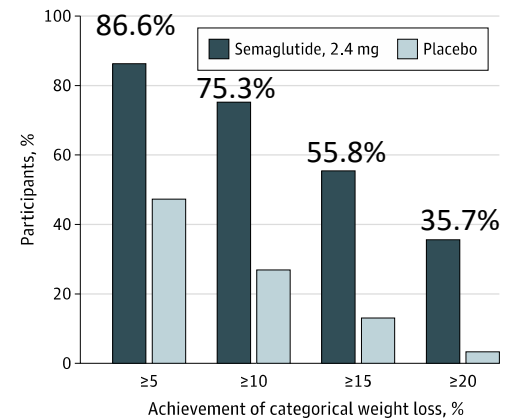
% change in body weight from baseline to week 68

≥ -5% from baseline to week 68

**A** Change from baseline by week in body weight



**B** Weight loss at week 68



### Secondary endpoints

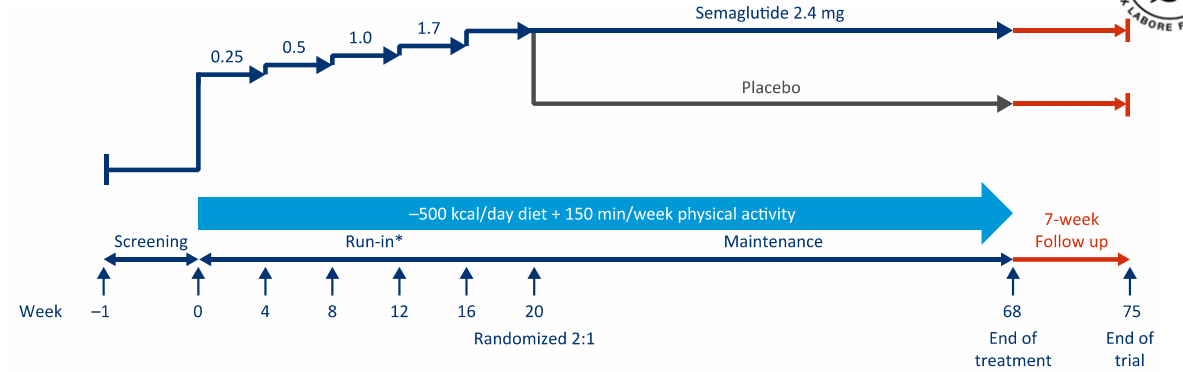
Confirmatory secondary end points	Sema	Placebo		
Waist circumference, cm	-14.6	-6.3	-8.3 (-10.1 to -6.6)	<.001
Systolic blood pressure, mm Hg	-5.6	-1.6	-3.9 (-6.4 to -1.5)	.001
SF-36 physical functioning score <sup>d</sup>	2.4	1.6	0.8 (-0.2 to 1.9)	.12
Body weight reduction ≥10%, proportion of participants at week 68, %	75.3	27.0	7.4 (4.9 to 11.0)	<.001
Body weight reduction ≥15%, proportion of participants at week 68, %	55.8	13.2	7.9 (4.9 to 12.6)	<.001

# STEP 4



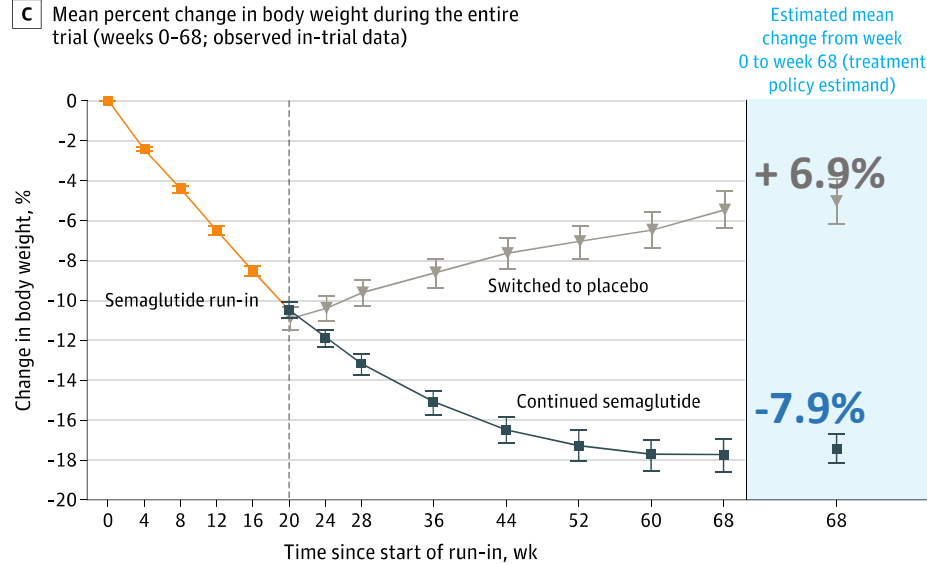
## Superiorità di semaglutide 2.4 mg/settimana vs. placebo

902 participants with obesity or overweight, without T2D

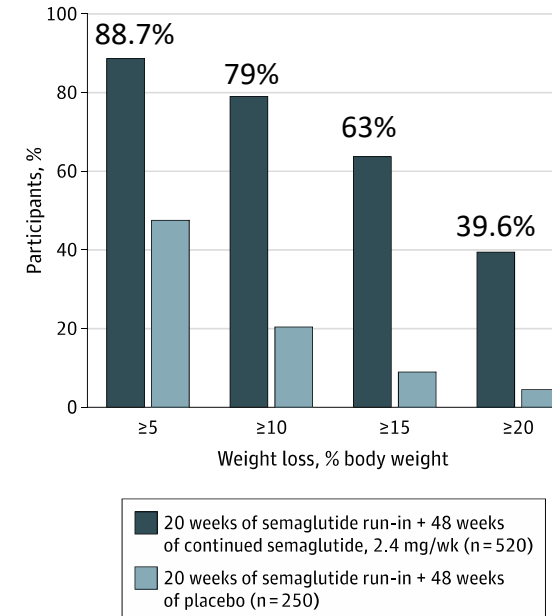


**% change in body weight from randomization to week 68**

**C** Mean percent change in body weight during the entire trial (weeks 0-68; observed in-trial data)



**D** Proportion of participants achieving thresholds of weight loss during the entire trial (weeks 0-68; observed in-trial data)

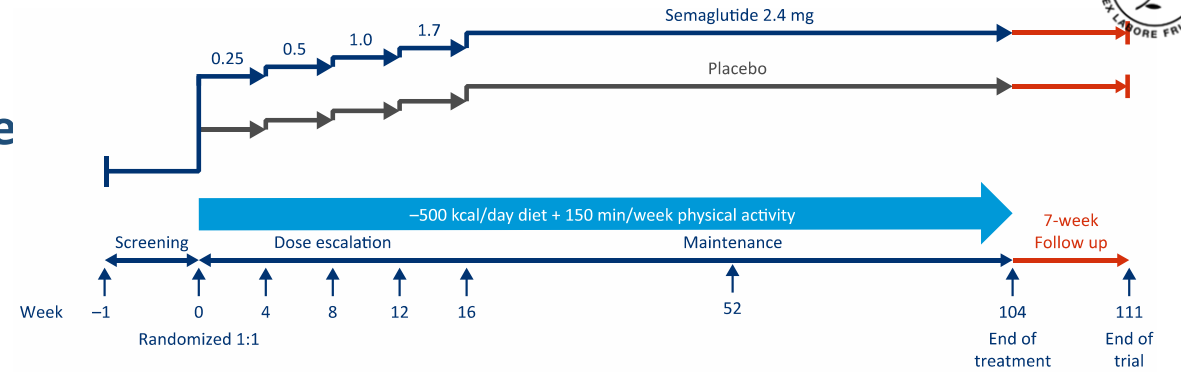


# STEP 5



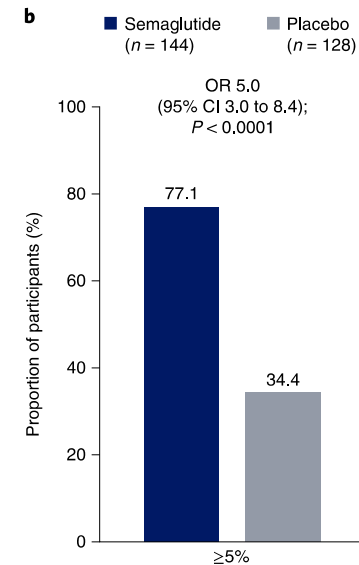
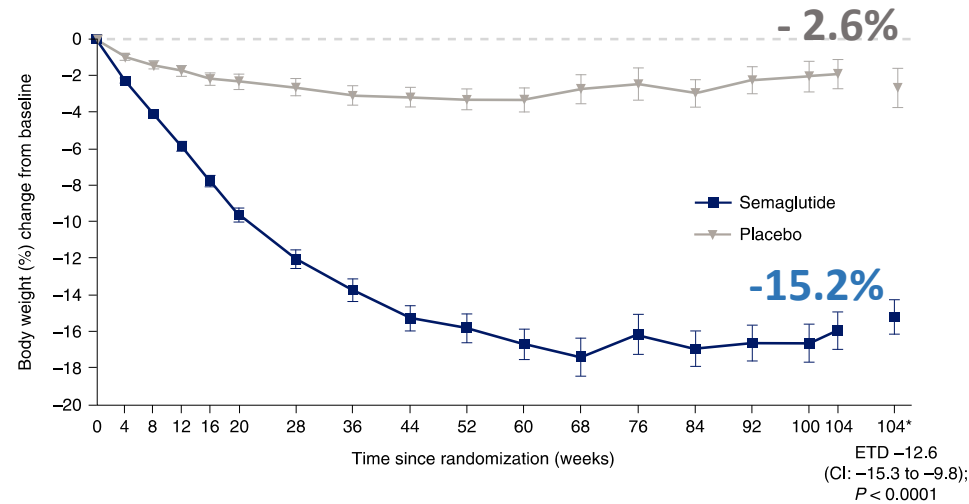
Superiorità nel lungo termine di semaglutide 2.4 mg/settimana vs. placebo

304 participants with obesity or overweight, without T2D



% change in body weight from baseline to week 104

≥ -5% from baseline to week 104



There was no additional weight loss between weeks 52–104



# STEP Trials: Profilo di sicurezza

**Table 3.** Summary of AEs from the STEP 1 to 5 trials [2,44–48].

	STEP 1 Weight management		STEP 2 <sup>a</sup> Weight management in T2D			STEP 3 Weight management with IBT (US only)		STEP 4 Sustained weight management			STEP 5 Long-term weight management	
	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Semaglutide 1.0 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg		Placebo (randomized period)	Semaglutide 2.4 mg	Placebo
								Run-in (semaglutide 2.4 mg)	(randomized period)			
AEs, %	89.7	86.4	87.6	81.8	76.9	95.8	96.1	84.3	81.3	75	96.1	89.5
GI AEs, %	74.2	47.9	63.5	57.5	34.3	82.8	63.2	71.4	41.9	26.1	82.2	53.9
Nausea	4.2	17.4	33.7	32.1	9.2	58.2	22.1	46.8	14.0	4.9	53.3	21.7
Diarrhea	31.5	15.9	21.3	22.1	11.9	36.1	22.1	23.5	14.4	7.1	34.9	23.7
Constipation	23.4	9.5	17.4	12.7	5.5	36.9	24.5	22.2	11.6	6.3	30.9	11.2
Vomiting	24.8	6.6	21.8	13.4	2.7	27.3	10.8	15.5	10.3	3.0	30.3	4.6
Median duration of GI AEs, days												
Nausea	8	6	8	10	6	5	5	NR	NR	NR	4	2
Diarrhea	3	3	5	4	4	3	3	NR	NR	NR	5	3
Constipation	35	25	55	51	21	27	16	NR	NR	NR	58	39
Vomiting	2	1	1	2	1	2	2	NR	NR	NR	2	2
SAEs, %	9.8	6.4	9.9	7.7	9.2	9.1	2.9	2.3	7.7	5.6	7.9	11.8
AEs leading to trial product discontinuation, %	7.0	3.1	6.2	5.0	3.5	5.9	2.9	5.3	2.4	2.2	5.9	4.6
GI AEs leading to trial product discontinuation, %	4.5	0.8	4.2	3.5	1.0	3.4	0	NR	NR	NR	3.9	0.7

<sup>a</sup>STEP 2 was the only trial that enrolled patients with T2D.

AEs, adverse events; GI, gastrointestinal; IBT, intensive behavioral therapy; NR, not reported; SAEs, serious adverse events; T2D, type 2 diabetes.

No symptomatic hypoglycemia

**Few participants discontinued treatment due to such AEs**

# STEP Trials: Profilo di sicurezza

## PANCREATITE

- Esclusione di pz con storia di pancreatite cronica o pancreatite acuta negli ultimi 3 mesi
- STEP 1-5: 0-0.2% casi di pancreatite senza differenza tra Gruppo di trattamento e di controllo
- STEP 3: 1 pz con aumento di lipasi e 1 pz con aumento di amilasi

## COLECISTOPATIE

- La presenza di litiasi biliare non costitutiva criterio di esclusione!
- STEP 1,3,5: AE biliari > nel Gruppo di trattamento rispetto al Gruppo placebo

## CA MIDOLLARE

- Esclusione di pz con anamnesi personale o familiare di MTC o MEN2
- STEP 1-5: Nessun caso di carcinoma midollare
- Nessuna differenza dei livelli di calcitonina tra il Gruppo di trattamento e di controllo

ORIGINAL ARTICLE

Clinical Trials and Investigations



# Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics

How might these results change the direction of research or the focus of clinical practice?

- The SELECT study will provide evidence as to whether treatment with semaglutide in this population with overweight or obesity but without diabetes can lower cardiovascular events. Given the broad range of relevant risk factors in this population, we will be able to explore the cardiovascular effects of semaglutide in these various relevant subgroups of people.

# Grazie!

