NEWER GENERATION ANTI-OBESITY MEDICATIONS AND THEIR IMPACT ON METABOLIC HEALTH

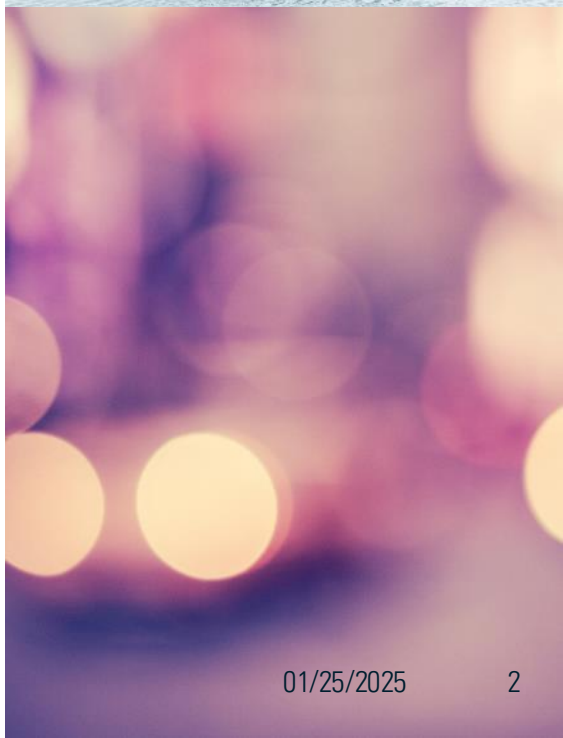
Dr. Turki Al-Ahbabi
Consultant Bariatric Medicine
HMC, Qatar

AGENDA

Newer Generation Medications

Weight loss outcomes

Impact on metabolic Health



DISCLOSURE STATEMENT

Speaker:

Dr. Turki Al-Ahbabi

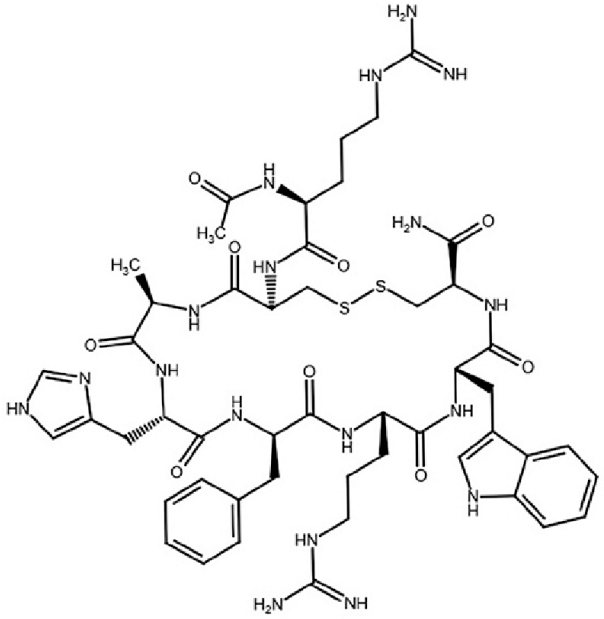
- Has no relevant financial/non-financial relationships to disclose.
- Will not be discussing unlabeled/unapproved use of drugs or products.

NEW GENERATION ANTI-OBESITY MEDICATIONS

- Setmelanotide
- Semaglutide 2.4mg
- Tirzepatide

SETMELANOTIDE

- Melanocortin-4 (MC4) Receptor Agonist
- Developed for treatment of rare genetic obesity disorders of POMC, PCSK-1 and Leptin Receptor Deficiency
- 8-amino acid cyclic peptide analogue of α-MSH



Markham A. Setmelanotide: First Approval. Drugs. 2021 Feb;81(3):397-403. doi: 10.1007/s40265-021-01470-9. PMID: 33638809.

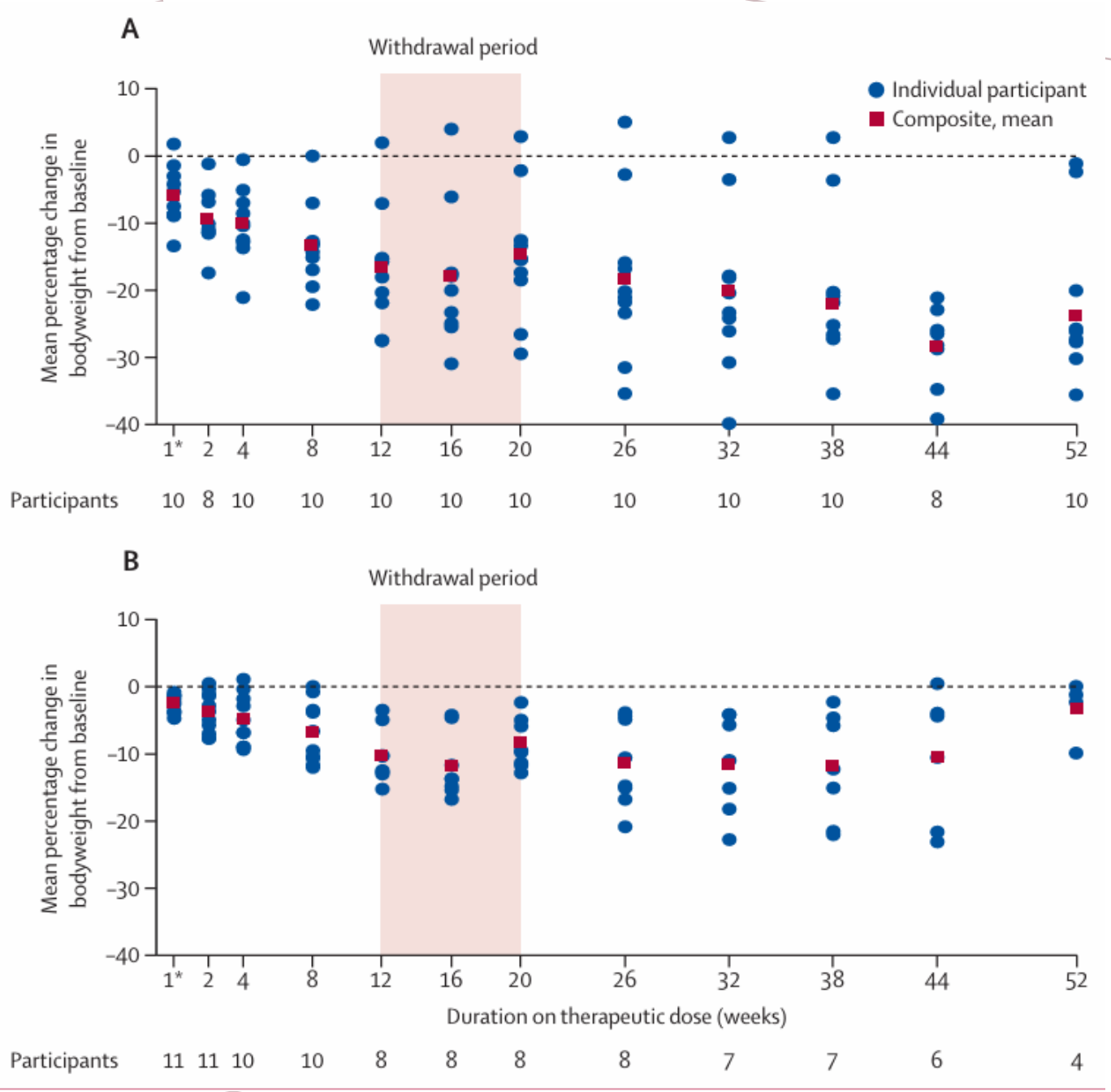
Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials

Karine Clément [1], Erica van den Akker [2], Jesús Argente [3], Allison Bahm [4], Wendy K Chung [5], Hillori Connors [6], Kathleen De Waele [7], I Sadaf Farooqi [8], Julie Gonneau-Lejeune [9], Gregory Gordon [6], Katja Kohlsdorf [10], Christine Poitou [1], Lia Puder [11], James Swain [12], Murray Stewart [6], Guojun Yuan [6], Martin Wabitsch [13], Peter Kühnen [14]; Setmelanotide POMC and LEPR Phase 3 Trial Investigators

- **Single Arm, Multicentre, Open-label**
- **10 Hospitals (US, Belgium, Canada, France, Germany, Netherlands and UK)**
- **12 weeks of Setmelanotide (POMC and LEPR)**

	Participants with POMC deficiency obesity (n=10†)	Participants with LEPR deficiency obesity (n=11)
Age, years	18·4 (6·2; 11·0–30·0)	23·7 (8·4; 13·0–37·0)
Sex		
Male	5 (50%)	3 (27%)
Female	5 (50%)	8 (73%)
Genotype		
Compound heterozygous	2 (20%)	6 (55%)
Homozygous	8 (80%)	5 (45%)
Ethnicity		
Hispanic or Latino	1 (10%)	0
Not Hispanic or Latino	8 (80%)	11 (100%)
Unknown	1 (10%)	0
Race		
White	7 (70%)	10 (91%)
Other	3 (30%)	1 (9%)
Bodyweight, kg	118·7 (37·5; 55·9–186·7)	133·3 (26·0; 89·4–170·4)
BMI, kg/m²	40·4 (9·0; 26·6–53·3)	48·2 (10·4; 35·8–64·6)

Clément K, et all. Efficacy and safety of Setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or P OMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol. 2020 Dec;8(12):960-970. Doi: 10.1016/S2213-8587(20)30364-8. Epub 2020 Oct 30. PMID: 33137293.



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OUTCOME

	Participants with POMC deficiency obesity			Participants with LEPR deficiency obesity		
	Baseline (n=10)	Approximately 1 year at therapeutic dose (n=10)	Percentage change from baseline (n=10)	Baseline (n=11)	Approximately 1 year at therapeutic dose (n=9)	Percentage change from baseline (n=9)
Bodyweight*, kg	115·0 (37·8)†	83·1 (21·4)†	−25·6% (9·9); 90% CI −28·8 to −22·0; p<0·0001	131·7 (32·6)‡	115·0 (29·6)‡	−12·5% (8·9); 90% CI −16·1 to −8·8; p<0·0001
Waist circumference*, cm	118·9 (17·6)†	100·5 (12·4)†	−14·9% (7·6); 90% CI −18·4 to −11·4; p<0·0001	127·3 (22·5)‡	114·4 (20·0)§	−7·2% (5·0); 90% CI −9·9 to −4·0; p=0·0002
Body composition*, kg						
Non-bone lean mass	57·8 (19·3)†	46·6 (10·3)¶	−10·7% (8·2); 90% CI −14·4 to −4·7; p=0·0028	58·5 (9·5)§	52·2 (8·5)§	−7·4% (5·1); 90% CI −9·2 to −4·6; p=0·0004
Total fat mass	55·3 (21·1)†	30·3 (11·3)¶	−38·6% (15·4); 90% CI −50·2 to −31·9; p<0·0001	69·3 (24·6)§	53·6 (25·1)§	−15·0% (14·6); 90% CI −24·8 to −6·3; p=0·0086

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Cardiovascular parameters						
Heart rate, beats per min	81·0 (12·1)	75·4 (7·2)	−5·8% (11·4); 90% CI −12·5 to 0·8; p=0·14	79·5 (12·6)	77·9 (16·5)	−1·3% (15·5); 90% CI −10·9 to 8·3; p=0·80
Diastolic blood pressure, mm Hg	73·1 (10·8)	71·5 (9·2)	−1·8% (6·3); 90% CI −5·4 to 1·8; p=0·38	67·7 (5·8)	66·5 (8·6)	−1·6% (13·0); 90% CI −9·7 to 6·5; p=0·73
Systolic blood pressure, mm Hg	111·6 (7·8)	109·8 (6·1)	−1·4% (5·1); 90% CI −4·3 to 1·6; p=0·42	121·7 (8·8)	115·1 (14·6)	−3·8% (9·9); 90% CI −9·9 to 2·4; p=0·29
Glucose metabolism						
Fasting glucose, mg/dL	135·8 (107·7)	107·0 (85·5)	−17·2% (18·8); 90% CI −28·1 to −6·3; p=0·018	106·1 (49·2)	108·9 (55·4)	−0·7% (7·0); 90% CI −5·0 to 3·7; p=0·78
HbA_{1c}, %	6·1% (1·8)	5·8% (1·9)	−4·0% (10·5); 90% CI −10·1 to 2·1; p=0·26	5·7% (0·8)‡	5·5% (0·7)‖	−4·9% (7·8); 90% CI −12·3 to 2·6; p=0·24
HbA_{1c}, mmol/mol	43·5 (20·5)‡	39·1 (23·6)‡	..	54·8 (40·9)**	53·8 (38·8)**	..
Insulin during oral glucose load††, nmol/L	136·0 (104·6)¶	78·8 (104·1)‡	..	134·9 (104·3)†	129·5 (40·9)‡‡	..
Lipids, mg/dL						
HDL cholesterol	40·4 (17·7)	52·9 (14·1)	45·0% (43·8); 90% CI 19·6 to 70·3; p=0·010	41·9 (14·4)	49·2 (16·2)	19·6% (24·0); 90% CI 4·8 to 34·5; p=0·040
LDL cholesterol	88·7 (25·9)	80·6 (28·2)	−7·6% (23·1); 90% CI −21·1 to 5·8; p=0·32	105·8 (24·8)	93·3 (22·1)	−10·0% (12·1); 90% CI −17·5 to −2·5; p=0·038
Triglycerides	178·4 (158·3)	78·9 (24·8)	−36·6% (30·4); 90% CI −54·2 to −19·0; p=0·0041	112·3 (46·0)	96·5 (30·2)	−7·0% (26·6); 90% CI −23·4 to 9·5; p=0·46
Alanine aminotransferase, IU/L	35·6 (22·3)	17·2 (6·5)	..	22·2 (8·8)	16·8 (7·6)**	..
Aspartate aminotransferase, IU/L	33·1 (16·1)	22·2 (5·4)	..	23·4 (5·4)	19·5 (4·04)**	..
Bilirubin, µmol/L	7·6 (2·6)	8·2 (3·9)	..	6·8 (3·7)	8·0 (7·4)	..
Creatinine, µmol/L	49·7 (12·5)	55·2 (16·2)	..	58·1 (14·8)	56·6 (17·5)	..

	Participants with POMC deficiency obesity (n=10)	Participants with LEPR deficiency obesity (n=11)
Treatment-related adverse events	10 (100%)	11 (100%)
Injection site reaction	10 (100%)	11 (100%)
Skin and subcutaneous disorders related to hyperpigmentation	10 (100%)	5 (45%)
Skin hyperpigmentation	10 (100%)	4 (36%)
Pigmentation disorder	0	4 (36%)
Skin discolouration	0	2 (18%)
Nausea	5 (50%)	4 (36%)
Vomiting	3 (30%)	..
Serious adverse events	4* (40%)	3† (27%)
Serious treatment-related adverse events	0	0
Treatment-emergent adverse events leading to discontinuation	0	1 (9%)
Treatment-emergent adverse events leading to death	0	1 (9%)‡

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- First approved in 2021
- Chronic weight management in patients older than 6 years
- Obesity caused by POMC, PCSK-1 and LEPR
- Evaluated in phase III trial for the treatment of other genetic disorders such as Bardiet-Biedel Syndrome, Alstrom Syndrome and other MC4 pathway disorders

SEMAGLUTIDE

- 94% homology to human GLP-1
- It has a $t_{½}$ of 1 week approximately
- Approved for the treatment of obesity at dose of 2.4mg weekly in 2021

STEP 1 TRIAL

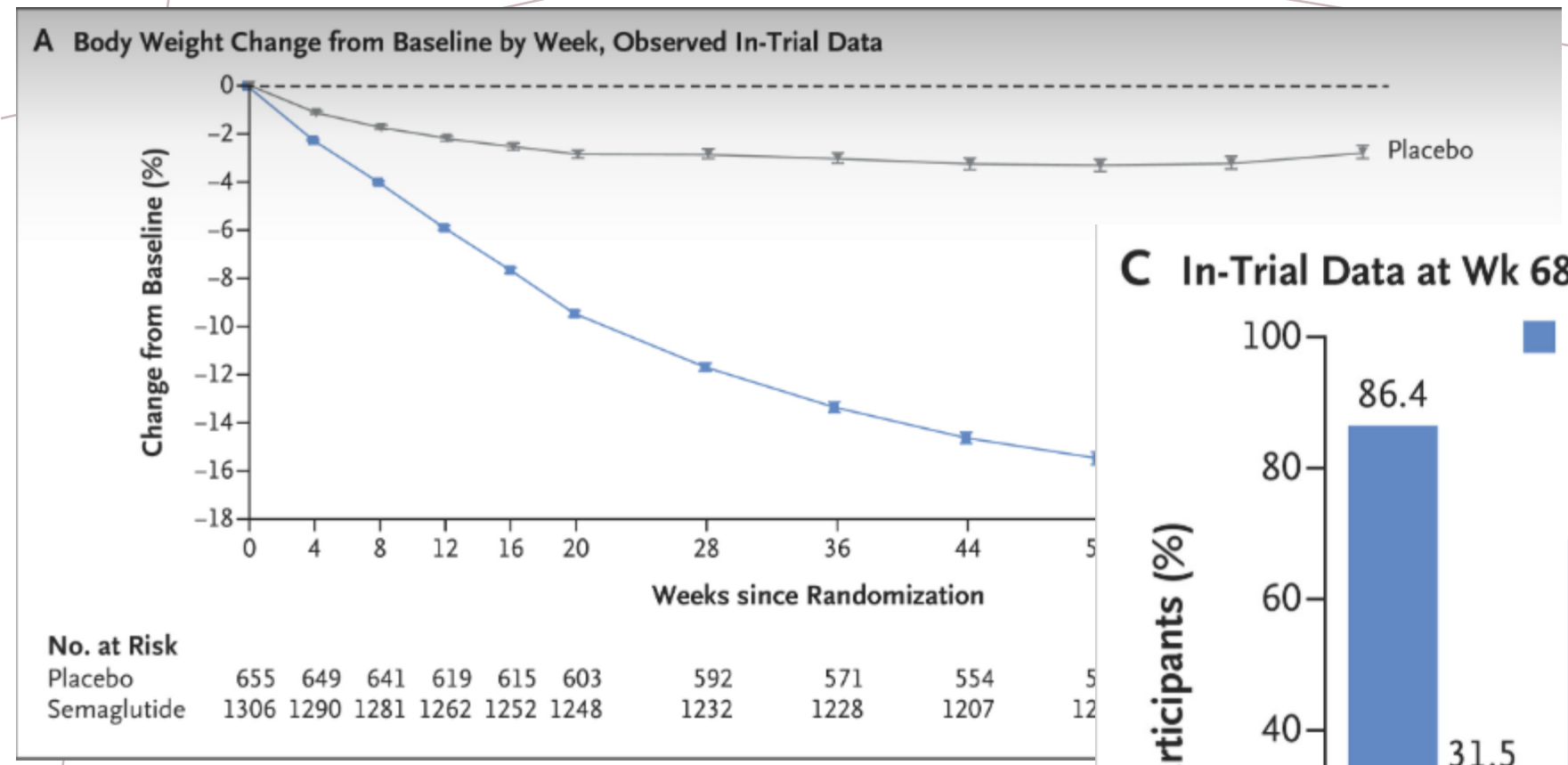
- Randomized, Double blind, Placebo-controlled (129 sites in 16 countries)

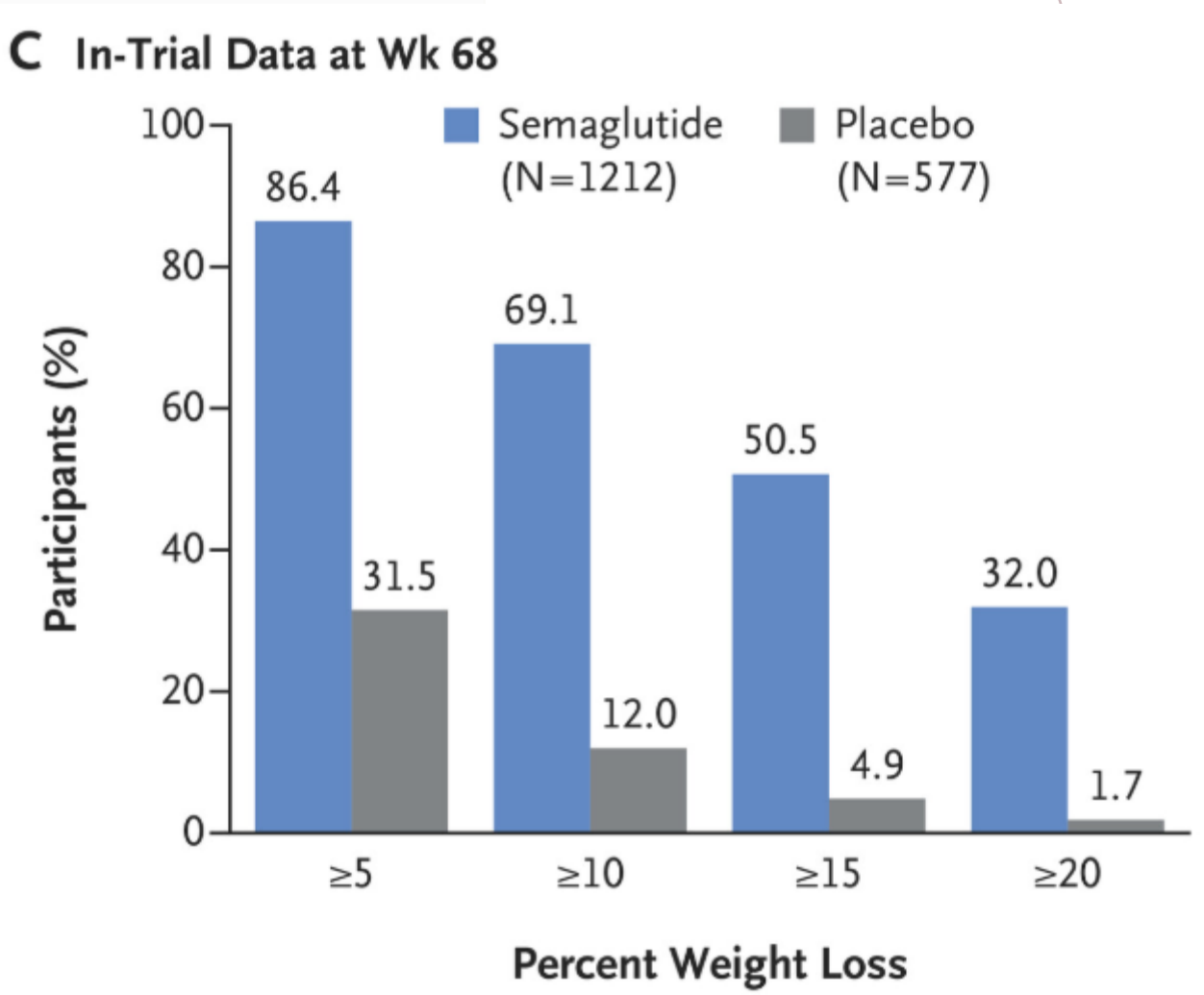
- Participants > 18 yrs, BMI: ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 comorbidity
- Primary end-point %-weight loss and 5%-responders

Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.

Characteristic	Semaglutide (N=1306)	Placebo (N=655)
Age — yr	46±13	47±12
Female sex — no. (%)	955 (73.1)	498 (76.0)
Race or ethnic group — no. (%)†		
White	973 (74.5)	499 (76.2)
Asian	181 (13.9)	80 (12.2)
Black or African American	72 (5.5)	39 (6.0)
Other	80 (6.1)	37 (5.6)
Hispanic or Latino ethnic group — no. (%)†	150 (11.5)	86 (13.1)
Body weight — kg	105.4±22.1	105.2±21.5
Body-mass index‡		
Mean	37.8±6.7	38.0±6.5

Characteristic	Semaglutide (N=1306)	Placebo (N=655)
Waist circumference — cm	114.6±14.8	114.8±14.4
Glycated hemoglobin — %	5.7±0.3	5.7±0.3
Prediabetes — no. (%)§	593 (45.4)	263 (40.2)
Blood pressure — mm Hg		
Systolic	126±14	127±14
Diastolic	80±10	80±10
Pulse — beats/min	72±10	72±10
Lipid levels — geometric mean mg/dl (coefficient of variation)¶		
Total cholesterol	189.6 (20.5)	192.1 (19.4)
HDL cholesterol	49.4 (25.6)	49.5 (25.0)
LDL cholesterol	110.3 (31.6)	112.5 (29.8)
VLDL cholesterol	24.5 (45.8)	24.9 (46.5)
Free fatty acids	12.3 (57.9)	12.7 (53.8)
Triglycerides	126.2 (47.4)	127.9 (49.0)





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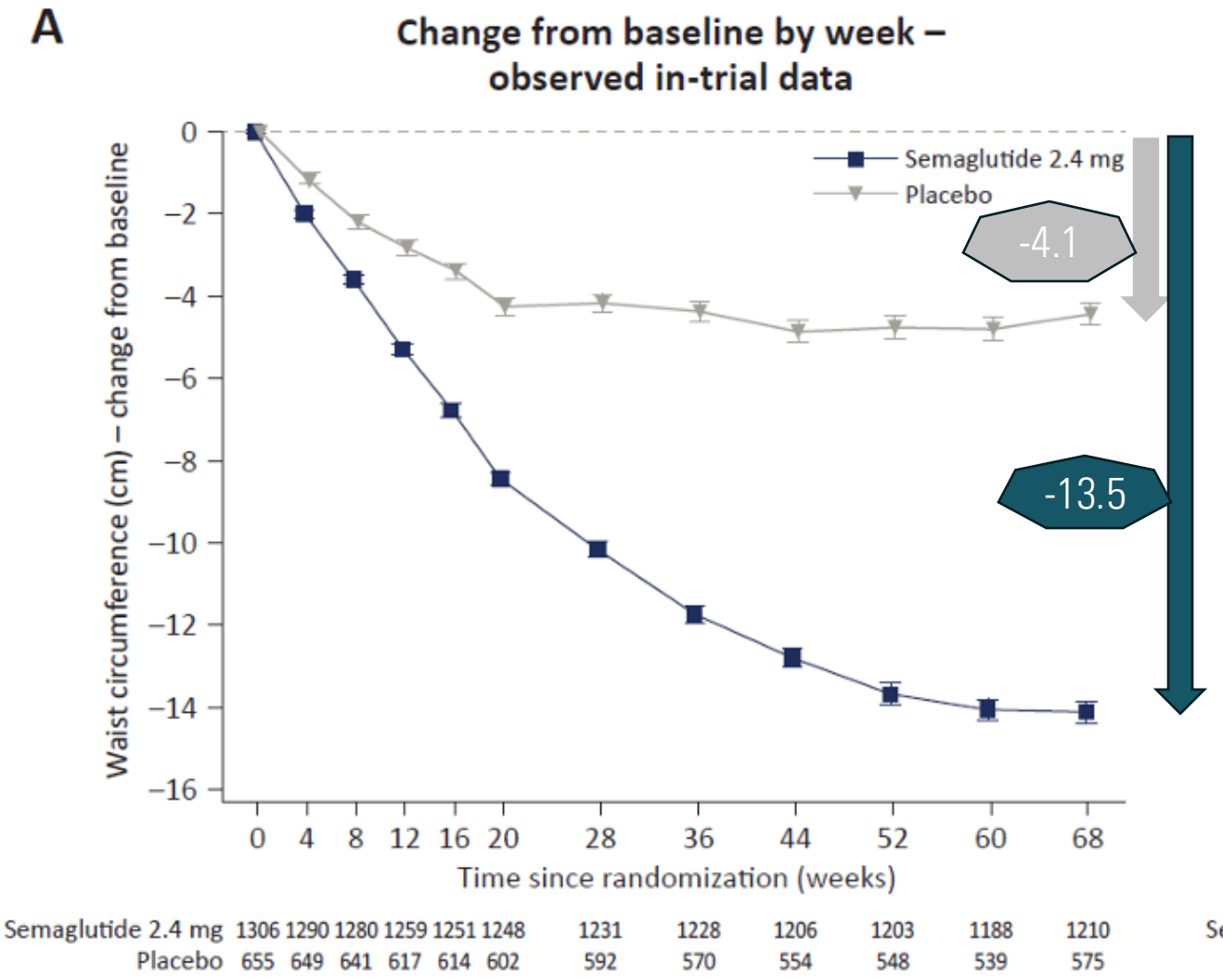

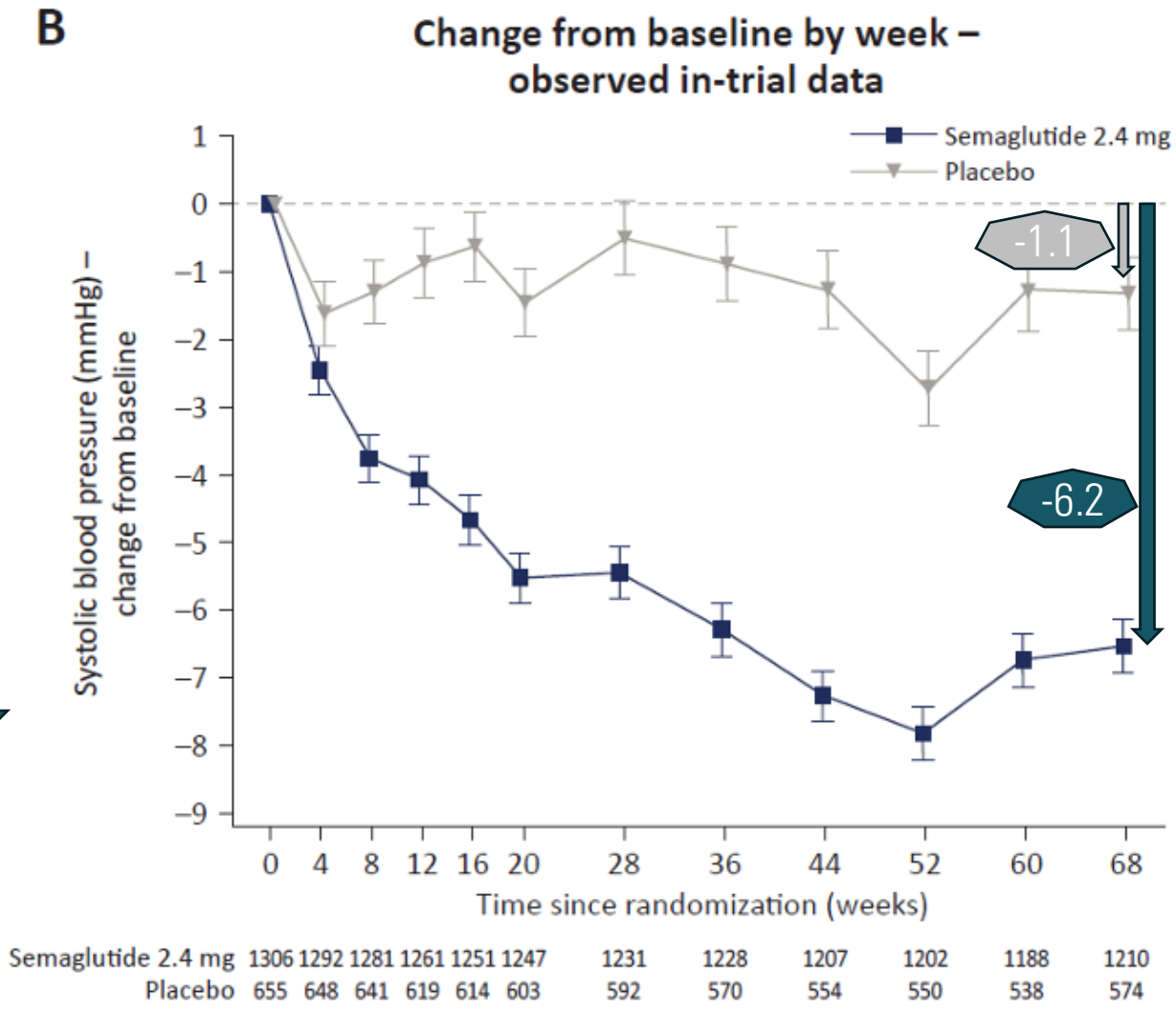

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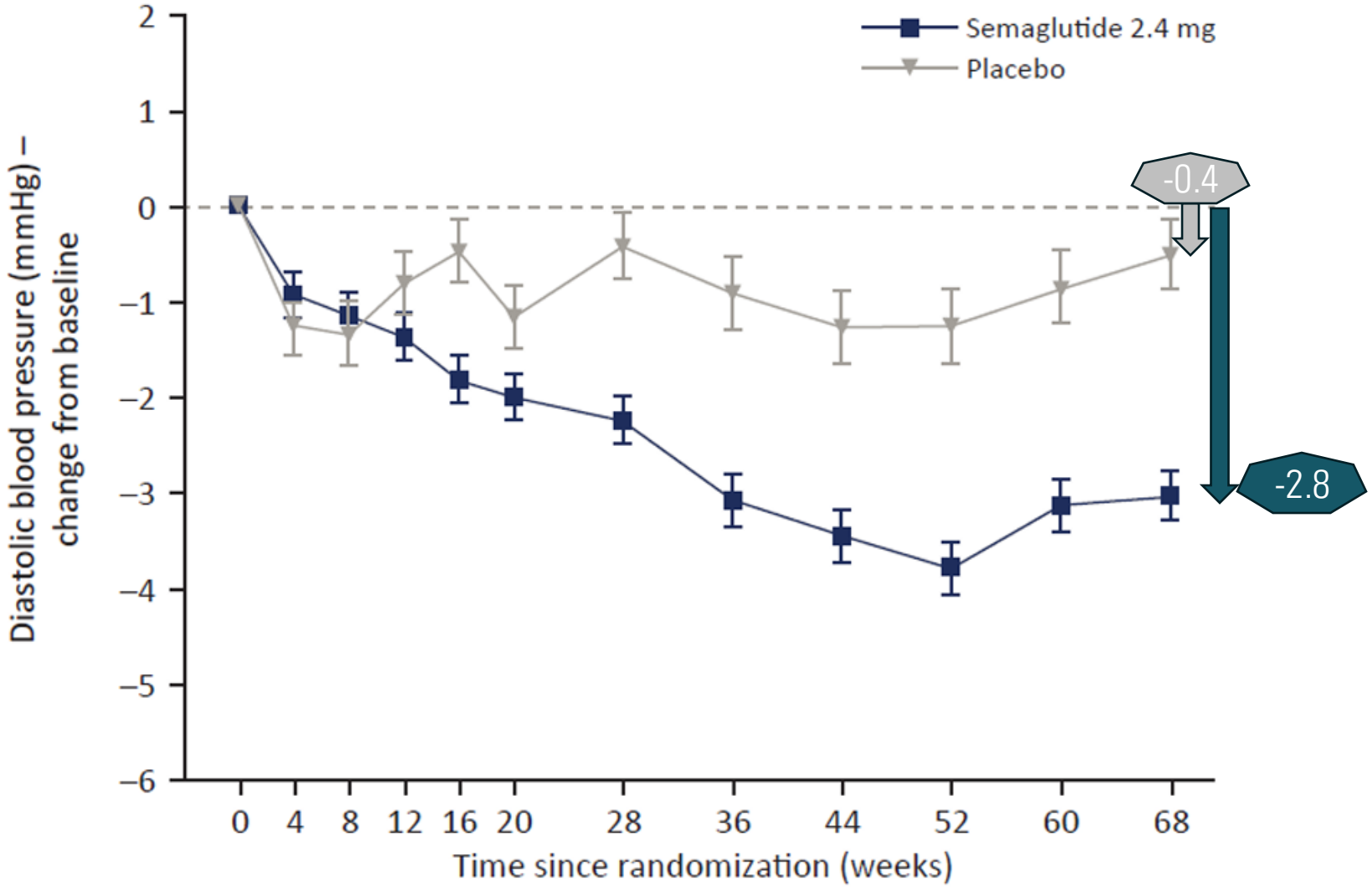
Change from baseline by week – observed in-trial data



Semaglutide 2.4 mg	1306	1292	1280	1261	1251	1247	1231	1228	1207	1202	1188	1210
Placebo	655	648	641	619	614	603	592	570	554	550	538	574

End Point	Semaglutide (N=1306)	Placebo (N=655)	Difference between Semaglutide and Placebo (95% CI)†	Odds Ratio
Glycated hemoglobin — percentage points	–0.45	–0.15	–0.29 (–0.32 to –0.26)	
Fasting plasma glucose — mg/dl	–8.35	–0.48	–7.87 (–9.04 to –6.70)	
Diastolic blood pressure — mm Hg	–2.83	–0.42	–2.41 (–3.25 to –1.57)	
Lipid levels, ratio of wk 68 value to baseline¶				
Total cholesterol	0.97	1.00	0.97 (0.95 to 0.98)	
HDL cholesterol	1.05	1.01	1.04 (1.02 to 1.05)	
LDL cholesterol	0.97	1.01	0.96 (0.94 to 0.98)	
VLDL cholesterol	0.78	0.93	0.84 (0.81 to 0.87)	
Free fatty acids	0.83	0.93	0.89 (0.83 to 0.94)	
Triglycerides	0.78	0.93	0.84 (0.81 to 0.87)	
C-reactive protein, ratio of wk-68 value to baseline¶	0.47	0.85	0.56 (0.51 to 0.61)	

Adverse Event	Semaglutide (N=1306)			
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)
Adverse events reported in ≥10% of participants§				
Nausea	577 (44.2)	1068	62.6	114 (17.4)
Diarrhea	412 (31.5)	766	44.9	104 (15.9)
Vomiting	324 (24.8)	636	37.3	43 (6.6)
Constipation	306 (23.4)	390	22.9	62 (9.5)
Nasopharyngitis	281 (21.5)	480	28.1	133 (20.3)
Headache	198 (15.2)	387	22.7	80 (12.2)
Dyspepsia	135 (10.3)	179	10.5	23 (3.5)
Abdominal pain	130 (10.0)	175	10.3	36 (5.5)
Upper respiratory tract infection	114 (8.7)	158	9.3	80 (12.2)

CONCLUSIONS AND KEY TAKEAWAYS

STEP 1

- Among adults with overweight or obesity (without diabetes), semaglutide 2.4 mg plus lifestyle intervention was associated with substantial, sustained, clinically relevant mean weight loss of 14.9%, with 86% of participants attaining at least 5% weight loss
- Approximately 70% and 50% of participants achieved a weight loss of at least 10%, and like respectively. Furthermore, one third of participants treated with semaglutide lost at least 20% of baseline weight
- Weight loss with Semaglutide was accompanied by greater improvements than placebo with respect to cardiometabolic risk factors and physical functioning
- The safety profile of Semaglutide 2.4 mg like other GLP-1RAs:
    - Gastrointestinal disorders (nausea being the most common) were the most frequently reported adverse events, and were mostly transient and mild-to-moderate in severity

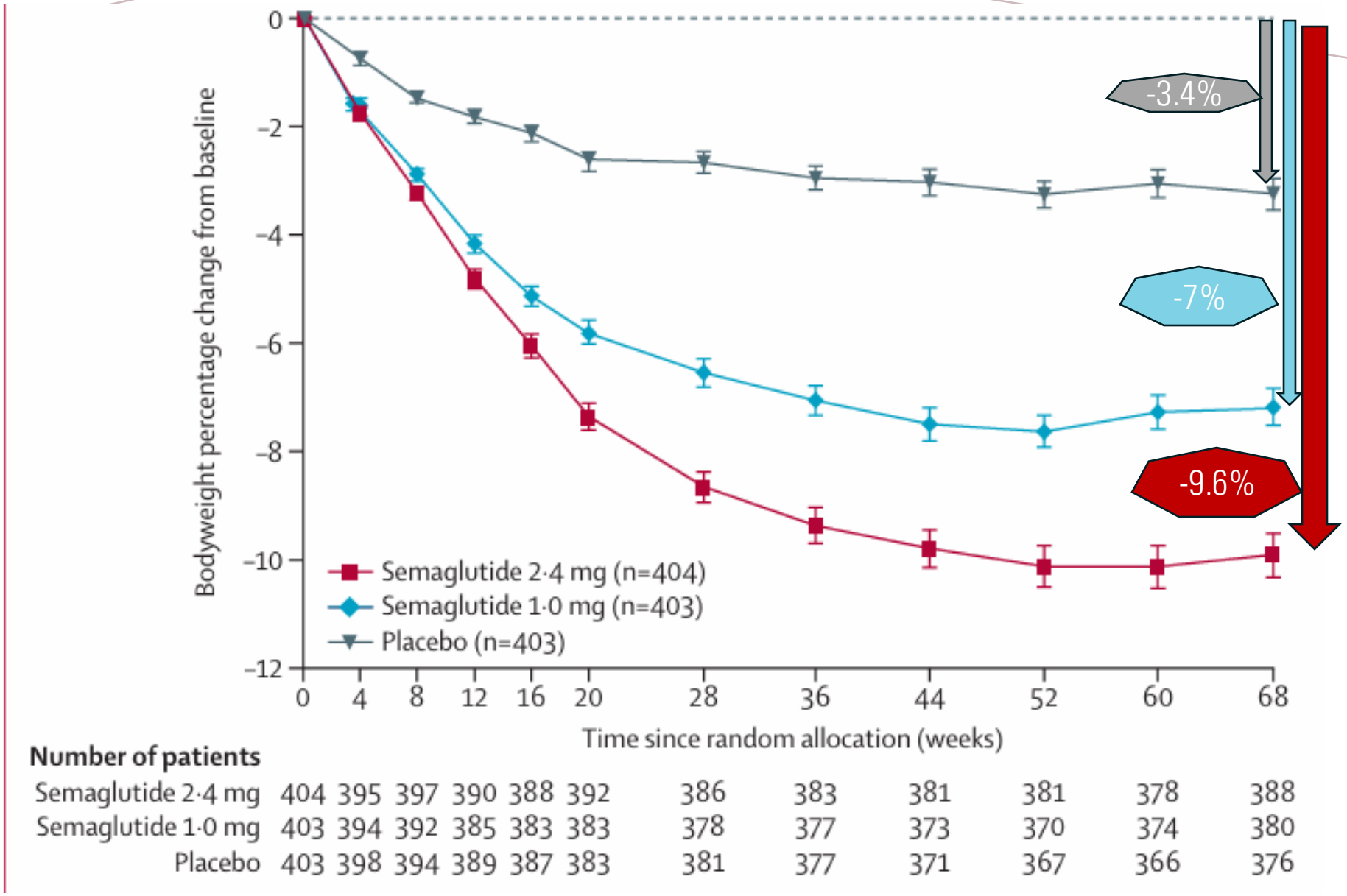
STEP-2 TRIAL

TRIAL DESIGN

- Randomised, double-blind, double-dummy, placebo-controlled, multicentre superiority study
- 149 outpatient clinics, 12 countries
- 1210 enrolled in the study
- Participants > 18 yrs, BMI ≥27 kg/m^2, HbA1c of 7–10%, diagnosed with type 2 diabetes at least 180 days before screening

	Semaglutide 2·4 mg (n=404)	Semaglutide 1·0 mg (n=403)	Placebo (n=403)	Total (n=1210)
Glucose-lowering drug class				
Biguanides	370 (91·6%)	379 (94·0%)	362 (89·8%)	1111 (91·8%)
Sulfonylureas	110 (27·2%)	99 (24·6%)	99 (24·6%)	308 (25·5%)
SGLT2 inhibitors	99 (24·5%)	96 (23·8%)	105 (26·1%)	300 (24·8%)
Thiazolidinediones	19 (4·7%)	16 (4·0%)	19 (4·7%)	54 (4·5%)
DPP-4 inhibitors†	2 (0·5%)	3 (0·7%)	1 (0·2%)	6 (0·5%)
α-Glucosidase inhibitors	1 (0·2%)	1 (0·2%)	0	2 (0·2%)
GLP-1 receptor agonists†	0	1 (0·2%)	0	1 (<0·1%)
Fast-acting insulins and insulin analogues for injection†	0	0	1 (0·2%)	1 (<0·1%)
Other blood glucose-lowering drugs	1 (0·2%)	0	0	1 (<0·1%)
Number of oral glucose-lowering drugs				
Diet and physical activity only	18 (4·5%)	17 (4·2%)	21 (5·2%)	56 (4·6%)
One	221 (54·7%)	229 (56·8%)	216 (53·6%)	666 (55·0%)
Two	133 (32·9%)	127 (31·5%)	138 (34·2%)	398 (32·9%)
Three	32 (7·9%)	29 (7·2%)	27 (6·7%)	88 (7·3%)
Four†	0	1 (0·2%)	1 (0·2%)	2 (0·2%)
Blood pressure, mm Hg				
Systolic	130 (13)	130 (14)	130 (13)	130 (14)
Diastolic	80 (9)	80 (9)	80 (9)	80 (9)
Lipids geometric mean (CV), mmol/L				
Total cholesterol	4·4 (23·0); n=402	4·5 (25·0); n=399	4·4 (23·3); n=402	4·4 (23·8); n=1203
LDL cholesterol	2·3 (37·3); n=402	2·3 (46·7); n=399	2·3 (37·8); n=402	2·3 (40·7); n=1203

Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. 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 Mar 13;397(10278):971-984. doi: 10.1016/S0140-6736(21)00213-0. Epub 2021 Mar 2. PMID: 33667417.



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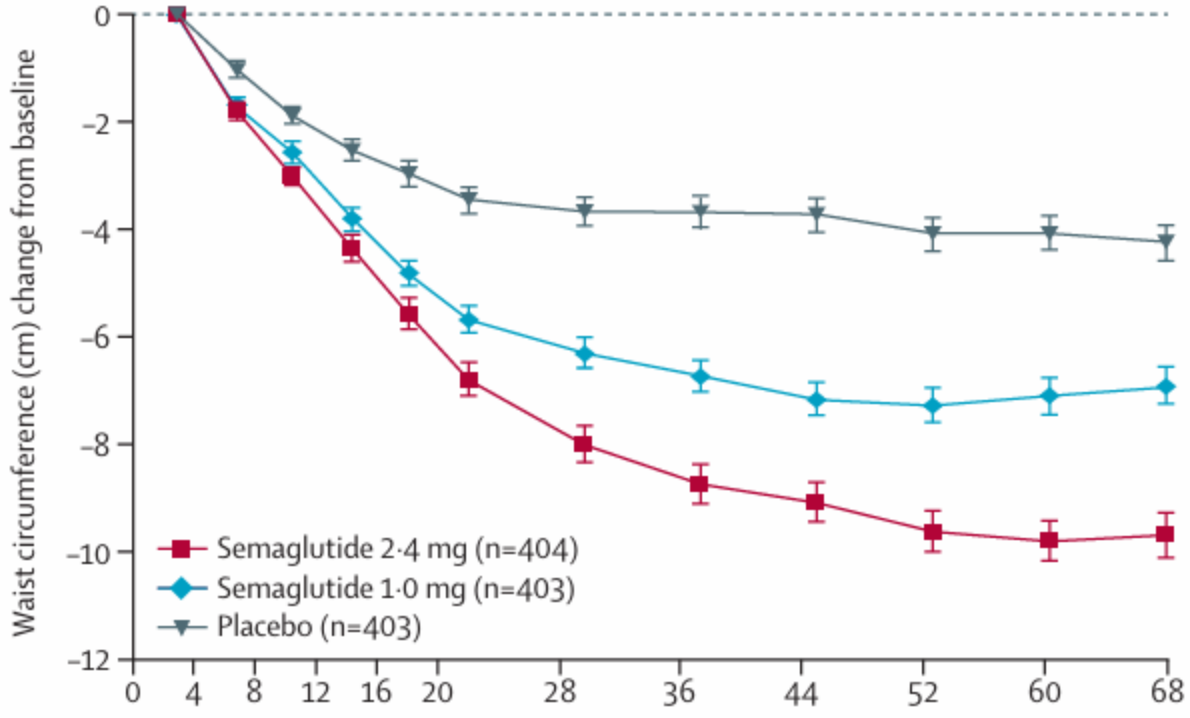
WAIST CIRCUMFERENCE



Number of patients

Semaglutide 2·4 mg	404	395	397	390	389	392	386	383	381	381	378	387
Semaglutide 1·0 mg	403	393	392	385	383	383	378	377	373	370	374	380
Placebo	403	398	393	389	387	383	381	377	371	367	365	375

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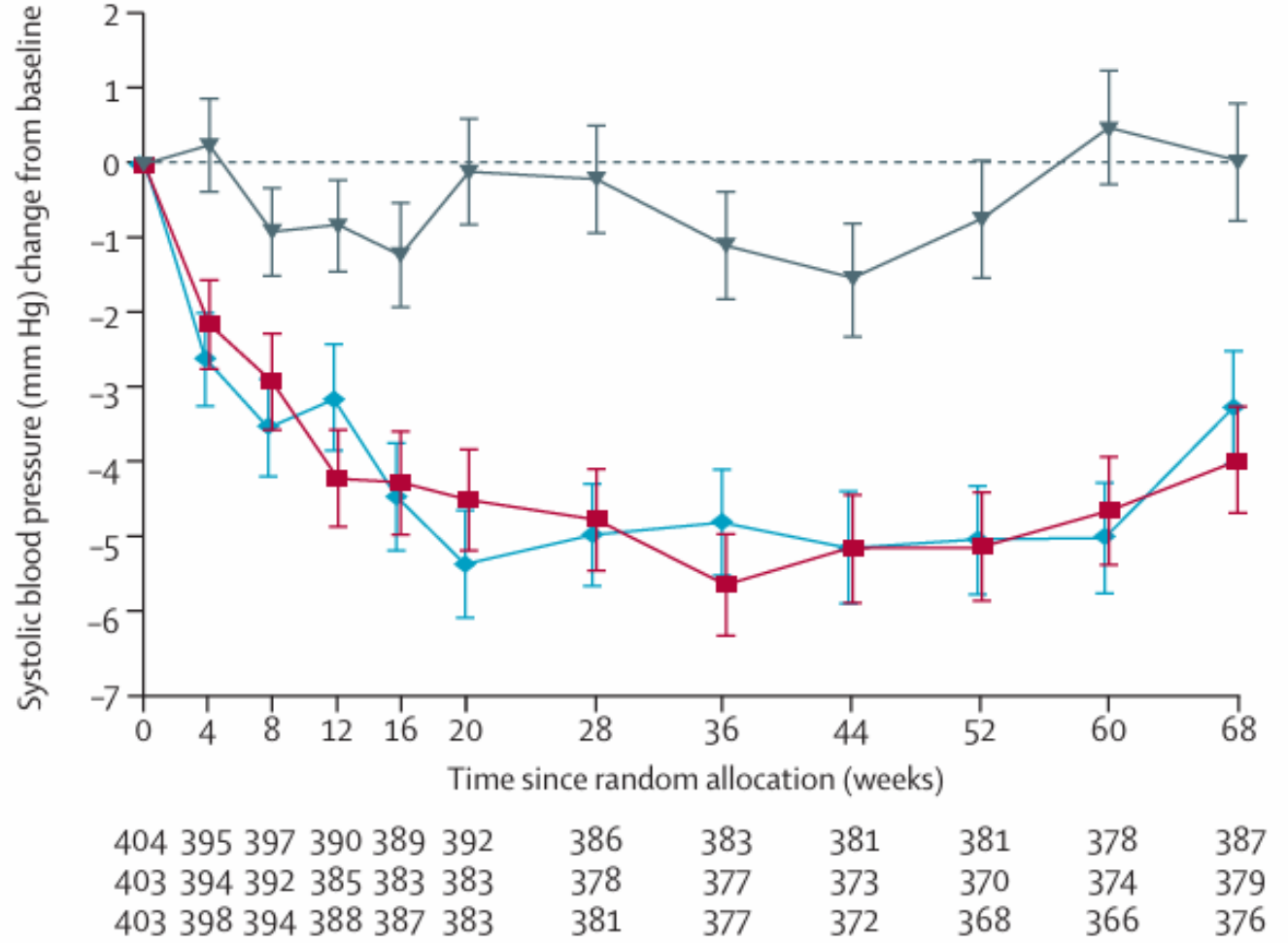
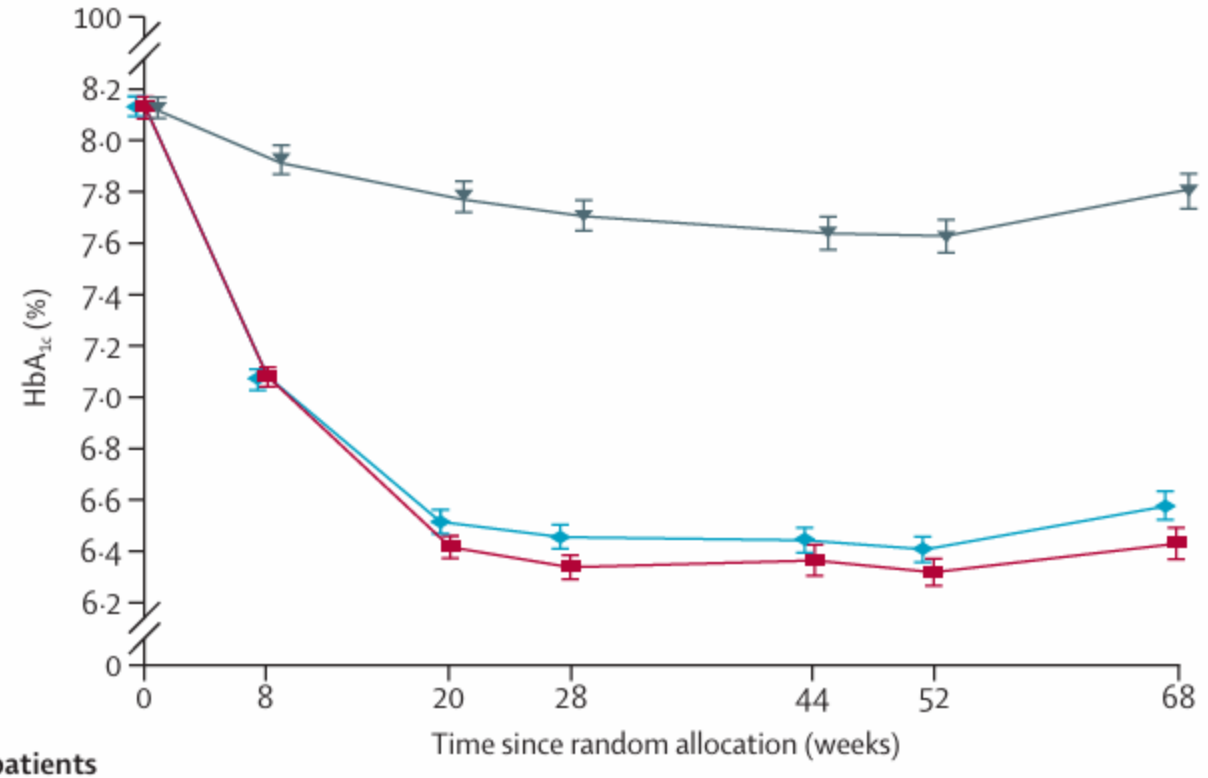
SYSTOLIC BP



Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. 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 Mar 13;397(10278):971-984. doi: 10.1016/S0140-6736(21)00213-0. Epub 2021 Mar 2. PMID: 33667417.

HBA1C

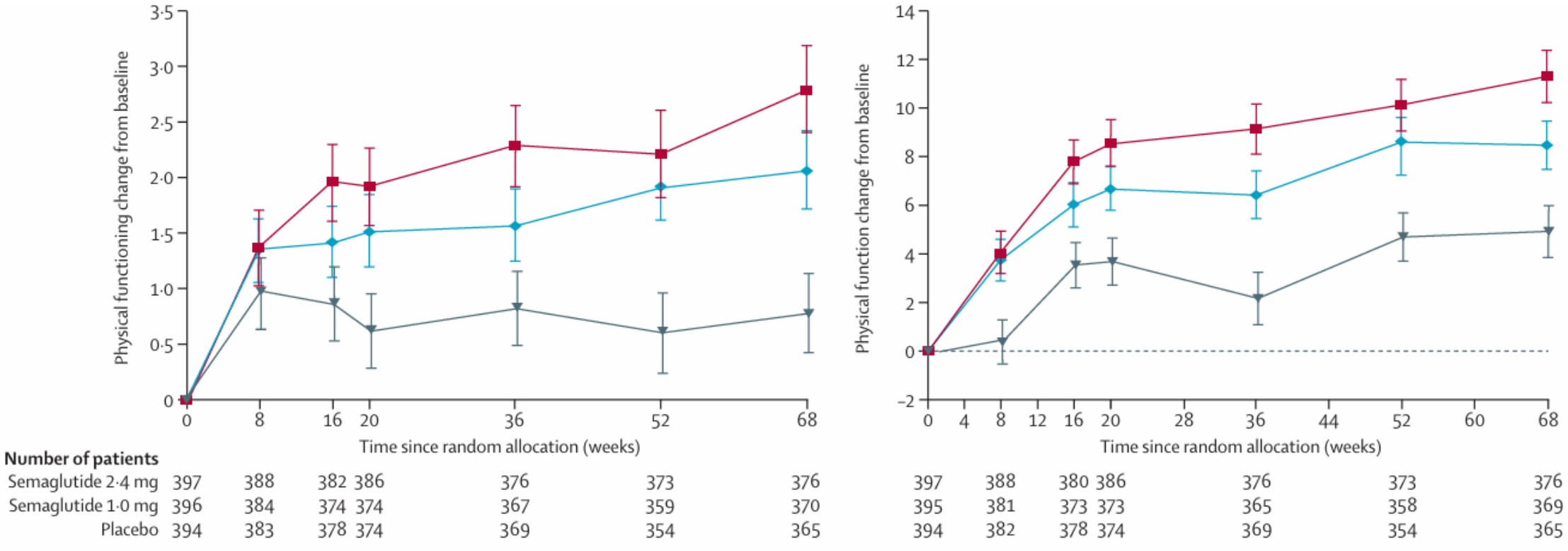


Number of patients

Semaglutide 2·4 mg	404	390	388	385	379	380	381
Semaglutide 1·0 mg	403	386	382	377	369	370	376
Placebo	403	391	381	379	371	366	374

Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. 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 Mar 13;397(10278):971-984. doi: 10.1016/S0140-6736(21)00213-0. Epub 2021 Mar 2. PMID: 33667417.

PHYSICAL FUNCTIONING



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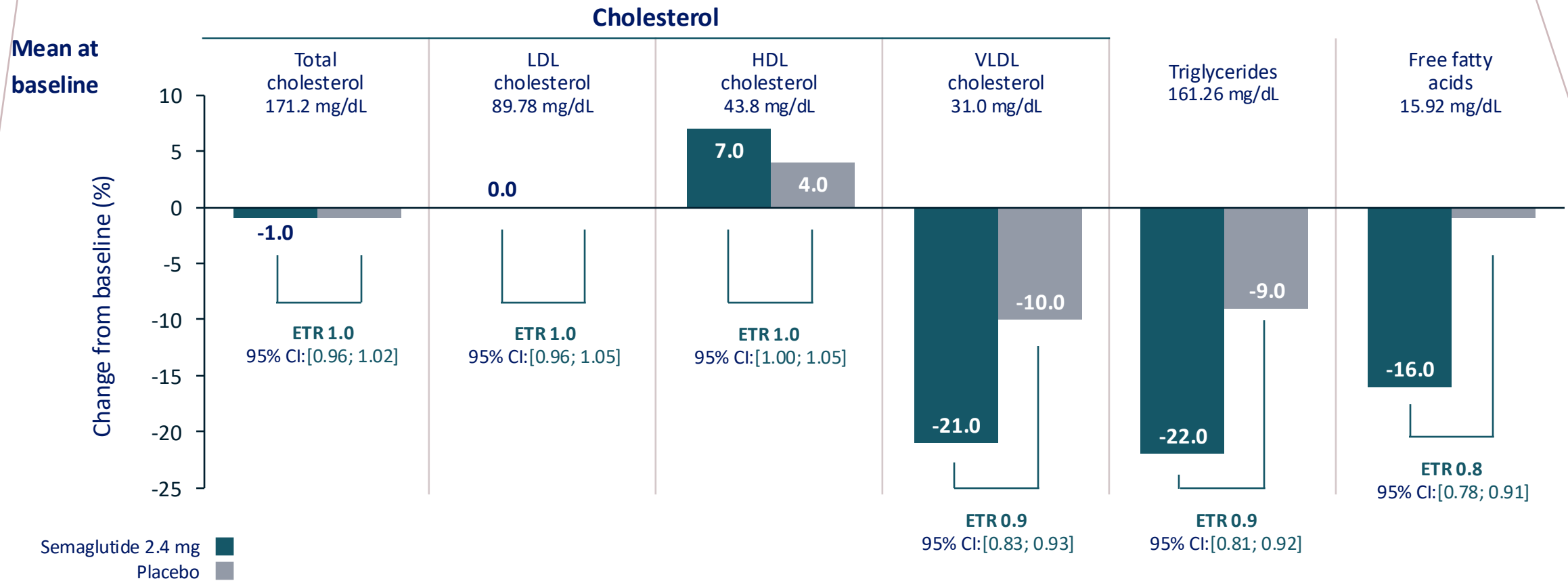
CHANGE IN FASTING LIPIDS

STEP 2: SEMAGLUTIDE 2.4 VS PLACEBO



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	Semaglutide 2·4 mg (n=403)			Semaglutide 1·0 mg (n=402)			Placebo (n=402)		
	Patients	Events	Events per 100 patient- years	Patients	Events	Events per 100 patient- years	Patients	Events	Events per 100 patient- years
Any adverse events	353 (87·6%)	2197	412·2	329 (81·8%)	1859	350·9	309 (76·9%)	1388	262·7
Serious adverse events	40 (9·9%)	71	13·3	31 (7·7%)	53	10·0	37 (9·2%)	53	10·0
Adverse events leading to trial product discontinuation	25 (6·2%)	34	6·4	20 (5·0%)	23	4·3	14 (3·5%)	18	3·4
Gastrointestinal disorders leading to trial product discontinuation	17 (4·2%)	24	4·5	14 (3·5%)	16	3·0	4 (1·0%)	6	1·1
Fatal events*†	1 (0·2%)	1	0·2	1 (0·2%)	1	0·2	1 (0·2%)	3	0·5
Adverse events reported in at least 10% of patients‡									
Nausea	136 (33·7%)	249	46·7	129 (32·1%)	198	37·4	37 (9·2%)	45	8·5
Vomiting	88 (21·8%)	188	35·3	54 (13·4%)	93	17·6	11 (2·7%)	12	2·3
Diarrhoea	86 (21·3%)	141	26·5	89 (22·1%)	158	29·8	48 (11·9%)	66	12·5
Constipation	70 (17·4%)	82	15·4	51 (12·7%)	70	13·2	22 (5·5%)	26	4·9
Nasopharyngitis	68 (16·9%)	115	21·6	47 (11·7%)	69	13·0	59 (14·7%)	92	17·4
Upper respiratory tract infection	42 (10·4%)	48	9·0	37 (9·2%)	54	10·2	38 (9·5%)	50	9·5
Safety areas of interest§									
Gastrointestinal disorders	256 (63·5%)	924	173·3	231 (57·5%)	724	136·7	138 (34·3%)	262	49·6
Gallbladder-related disorders	1 (0·2%)	2	0·4	4 (1·0%)	4	0·8	3 (0·7%)	4	0·8
Hepatobiliary	1 (0·2%)	2	0·4	3 (0·7%)	3	0·6	3 (0·7%)	4	0·8
Cholelithiasis	1 (0·2%)	1	0·2	3 (0·7%)	3	0·6	3 (0·7%)	3	0·6
Hepatic disorders	10 (2·5%)	12	2·3	10 (2·5%)	11	2·1	14 (3·5%)	21	4·0
Acute pancreatitis*¶	1 (0·2%)	2	0·3	0	0	0	1 (0·2%)	1	0·2
Cardiovascular events*¶	6 (1·5%)	6	1·0	6 (1·5%)	7	1·2	5 (1·2%)	7	1·2
Allergic reactions	26 (6·5%)	29	5·4	22 (5·5%)	24	4·5	18 (4·5%)	21	4·0
Injection site reactions	12 (3·0%)	18	3·4	6 (1·5%)	7	1·3	10 (2·5%)	18	3·4
Malignant neoplasms*	5 (1·2%)	6	1·0	7 (1·7%)	8	1·4	8 (2·0%)	9	1·6
Psychiatric disorders	24 (6·0%)	29	5·4	23 (5·7%)	28	5·3	15 (3·7%)	16	3·0
Acute renal failure	4 (1·0%)	5	0·9	2 (0·5%)	2	0·4	2 (0·5%)	2	0·4
Hypoglycaemia‖	23 (5·7%)	51	9·6	22 (5·5%)	29	5·5	12 (3·0%)	18	3·4

CONCLUSIONS AND KEY TAKEAWAYS

STEP 2

- In adults with overweight or obesity and type 2 diabetes, semaglutide 2.4 mg as adjunct to lifestyle intervention was significantly more effective at reducing body weight than either semaglutide 1.0 mg or placebo
- 5% of baseline weight was lost by 69% of participants on semaglutide 2.4 mg versus 57% on semaglutide 1.0 mg and 28% on placebo
- More than two-thirds (67.5%) of participants treated with semaglutide 2.4 mg achieved a target HbA_{1c} of 6.5% or less
- Greater improvements in cardiometabolic risk factors and physical functioning were seen in participants treated with semaglutide 2.4 mg compared with placebo
- The safety profile of semaglutide 2.4 mg was similar to other GLP-1RAs:
  - Gastrointestinal disorders were the most frequently reported adverse events, which were mostly transient and mild-to-moderate in severity

STEP 3 TRIAL

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

Thomas A Wadden [1], Timothy S Bailey [2], Liana K Billings [3], Melanie Davies [4 5], Juan P Frias [6], Anna Koroleva [7], Ildiko Lingvay [8], Patrick M O'Neil [9], Domenica M Rubino [10], Dorthe Skovgaard [7], Signe O R Wallenstein [7], W Timothy Garvey [11]; STEP 3 Investigators

Affiliations + expand

PMID: 33625476 PMCID: PMC7905697 DOI: 10.1001/jama.2021.1831

Conclusions and relevance: Among adults with overweight or obesity, once-weekly subcutaneous semaglutide compared with placebo, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss during 68 weeks. Further research is needed to assess the durability of these findings.

Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey WT; STEP 3 Investigators. 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 Apr 13;325(14):1403-1413. doi: 10.1001/jama.2021.1831. PMID: 33625476; PMCID: PMC7905697.

STEP 4 TRIAL

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial

Domenica Rubino [1], Niclas Abrahamsson [2], Melanie Davies [3 4], Dan Hesse [5], Frank L Greenway [6], Camilla Jensen [5], Ildiko Lingvay [7], Ofri Mosenzon [8], Julio Rosenstock [9], Miguel A Rubio [10], Gottfried Rudofsky [11], Sayeh Tadayon [5], Thomas A Wadden [12], Dror Dicker [13]; STEP 4 Investigators

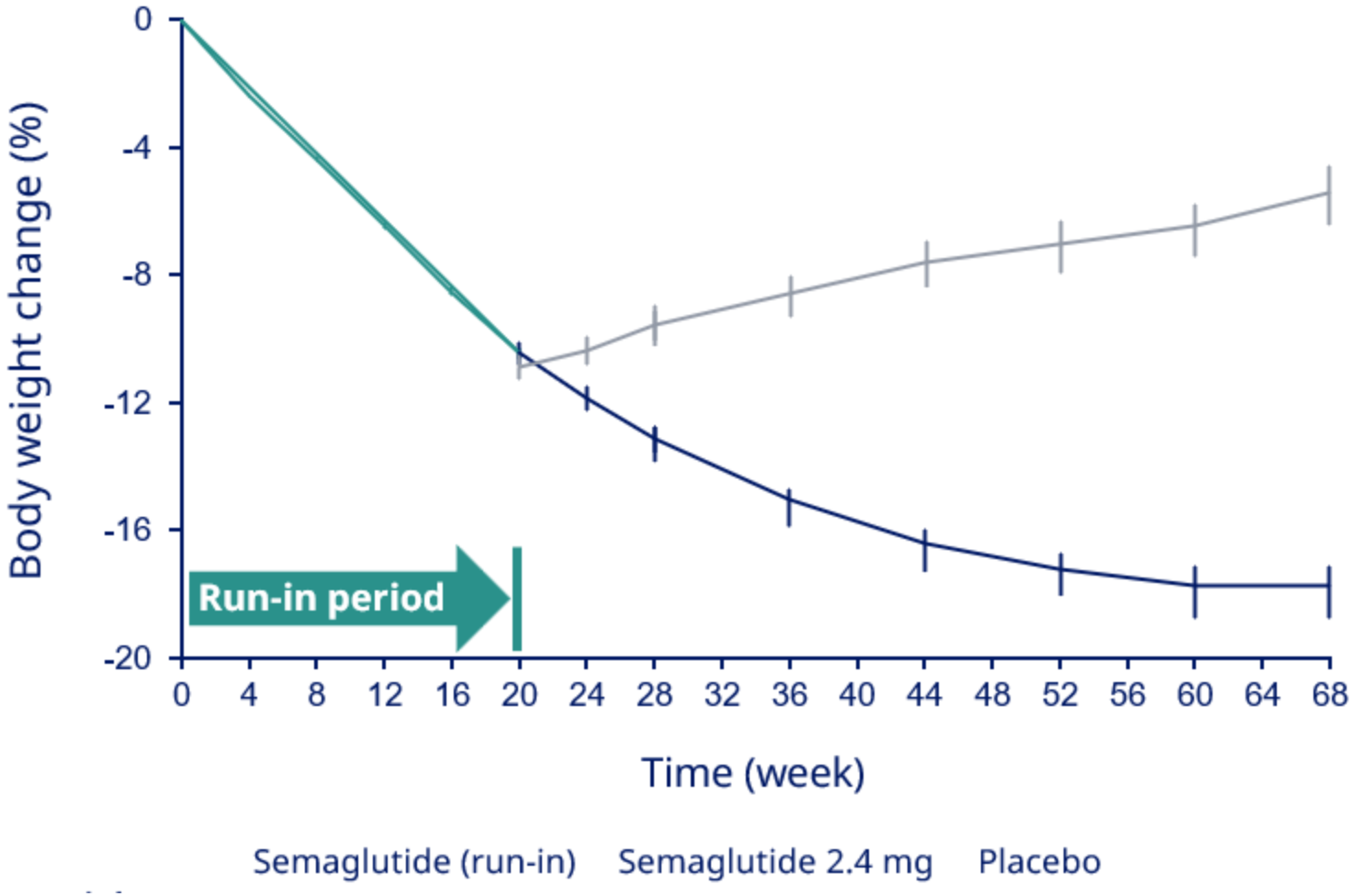
Collaborators, Affiliations + expand

PMID: 33755728 PMCID: PMC7988425 DOI: 10.1001/jama.2021.3224

Conclusions and relevance: Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

Observed body weight change over time

(Mean at week 0: 107.2 kg)



Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP 4 Investigators. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. PMID: 33755728; PMCID: PMC7988425.

STEP PROGRAMME AT A GLANCE

Completed

STEP 1
Weight management

STEP 2
WM in T2D

STEP 3
WM with IBT

STEP 4
Sustained WM

STEP 5
Long-term WM

STEP 6
East Asian trial

STEP 7
WM in China MRCT

STEP 8
H2H vs liraglutide

STEP 9
Semaglutide in knee OA

STEP 10
Reversal of pre-diabetes

STEP 11
WM in Korea/ Thailand

STEP TEENS
WM in adolescents

SELECT
CVOT

STEP HFpEF
Obesity and HFpEF

STEP HFpEF DM
Obesity and HFpEF with T2D

Ongoing

STEP Young
WM in children and adolescents

STEP UP
WM with 7.2 mg

STEP UP T2D
WM with 7.2 mg in T2D

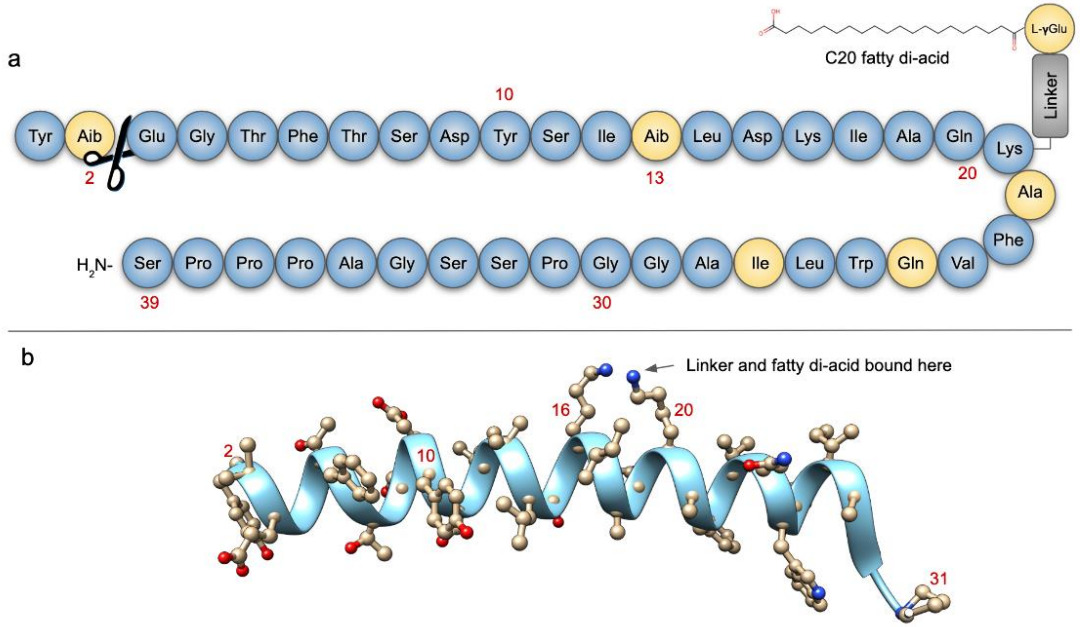
STEP 12
WM in Mainland China and Taiwan

POSEY
US employer trial

STEP 7: China, Brazil, Korea, Hong Kong (left to right) multi-regional clinical trial. CVOT, cardiovascular outcomes trial; HFpEF, heart failure with preserved ejection fraction; H2H, head-to-head; IBT, intensive behavioural therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; WM, weight management. Novo Nordisk A/S. Data on file; Clinicaltrials.gov. ClinicalTrials.gov (Accessed May 2024)

TIRZEPATIDE

- A 39 amino acid , dual hormonal (GLP-1 and GIP)
- FDA approved in 2022 for chronic weight management
- Once weekly injection

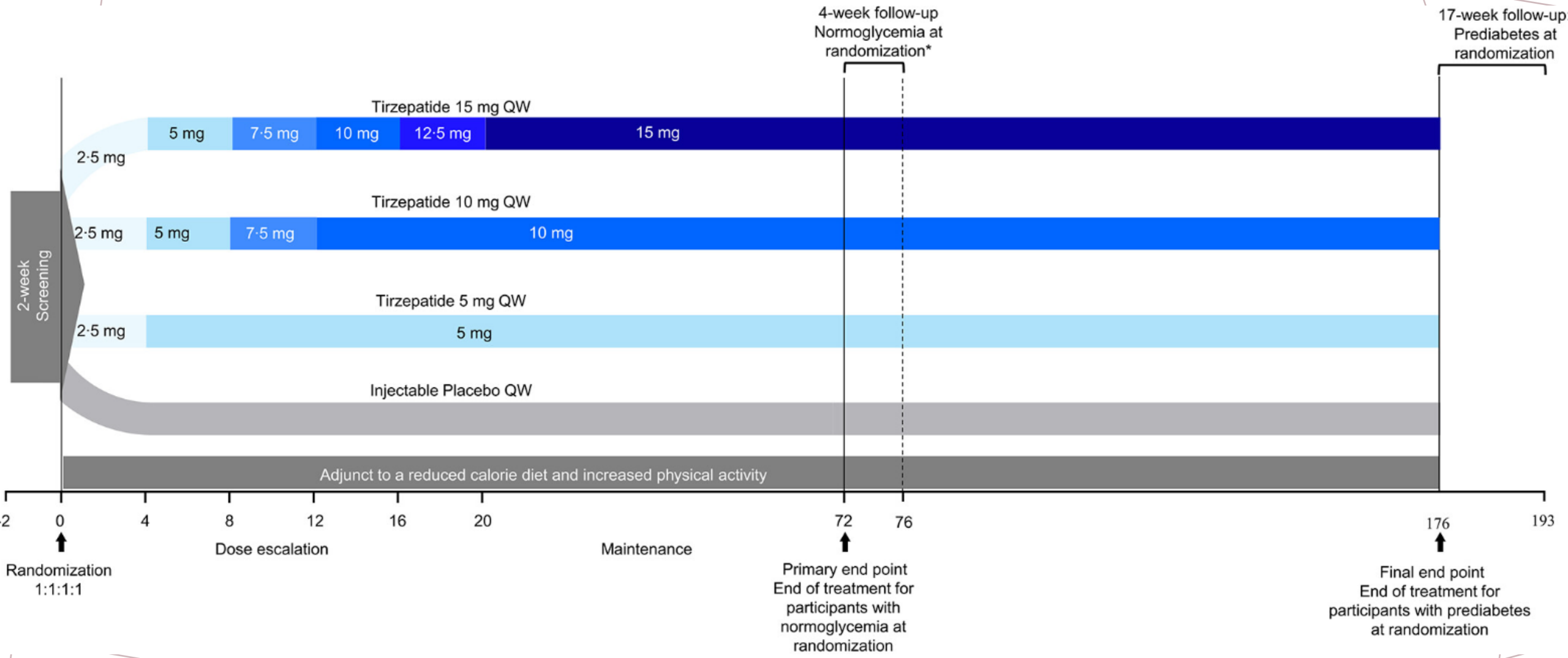


Tirzepatide Once Weekly for the Treatment of Obesity

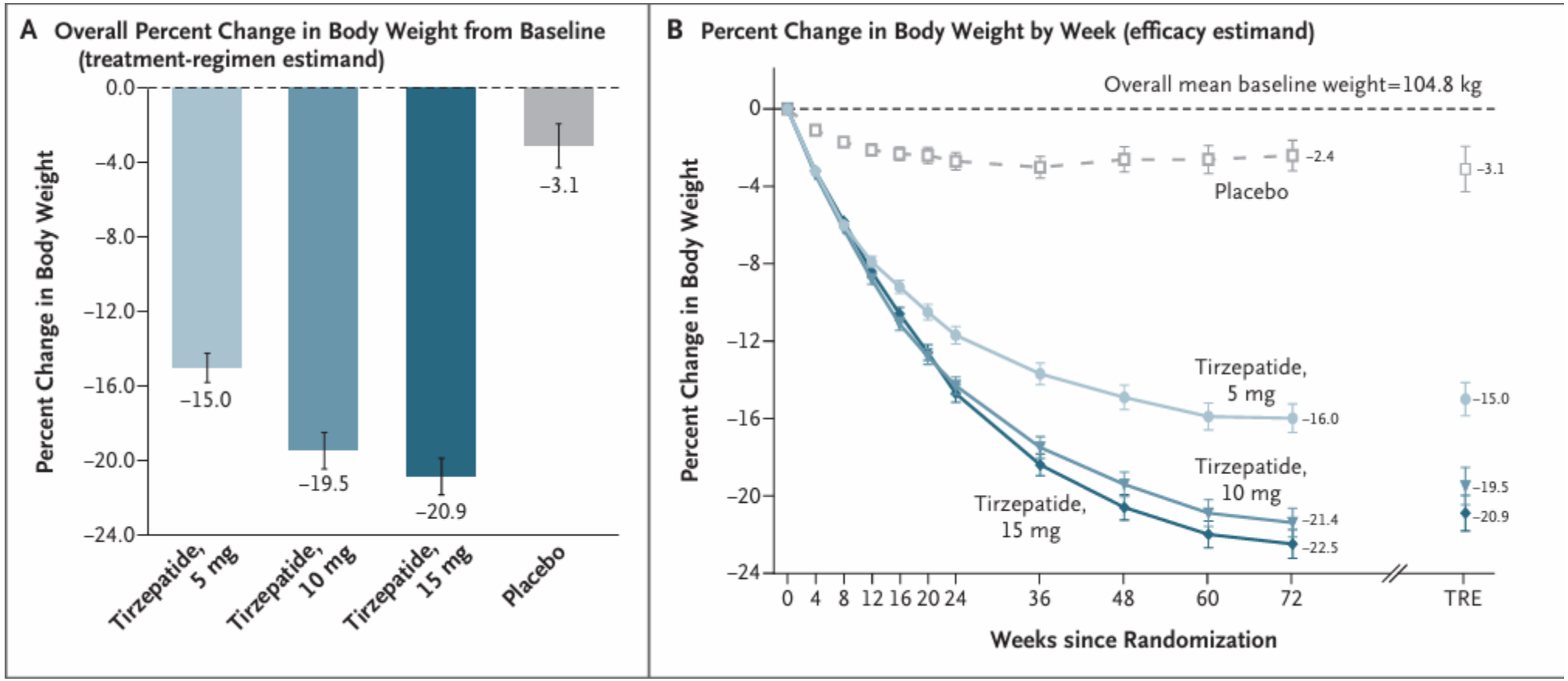
Authors: Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators* Author Info & Affiliations

Published June 4, 2022 | N Engl J Med 2022;387:205-216 | DOI: 10.1056/NEJMoa2206038 | VOL. 387 NO. 3

- Multicentre, 9 countries, randomized, double-blind, parallel, placebo-controlled trial
- Aimed to determine the efficacy and safety of Tirzepatide in participants without T2DM
- Primary endpoint – pooled Tirzepatide vs. placebo, in achieving >5% weight loss
- Participants > 18 yrs, BMI: ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 comorbidity without T2DM



le Roux CW, Zhang S, Aronne LJ, et al. Tirzepatide for the treatment of obesity: Rationale and design of the SURMOUNT clinical development program. *Obesity (Silver Spring)*. 2023; 31(1): 96-110. doi:10.1002/oby.23612



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End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Variable	Tirzepatide, 5 mg (N = 630)	Tirzepatide, 10 mg (N = 636)	Tirzepatide, 15 mg (N = 630)	Placebo (N = 643)
	number (percent)			
Adverse events of special interest				
Hepatic events§	2 (0.3)	2 (0.3)	0	0
Cancer	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Major adverse cardiovascular events (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders¶	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious gastrointestinal events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease§	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events§	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Major depressive disorder or suicidal ideation§	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‖	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dl)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)
Other adverse events of interest that emerged during treatment period†				
Cholelithiasis	7 (1.1)	9 (1.4)	4 (0.6)	6 (0.9)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction‡	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)

SUMMARY

New generation anti-obesity medications are powerful tools that changed the plane field of fighting obesity and for the first time achieved two-digit weight loss that are comparable to bariatric surgery

Needs comprehensive multidisciplinary care when prescribing these medications

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- **https://pdb101.rcsb.org/global-health/diabetes-mellitus/drugs/incretins/drug/tirzepatide/tirzepatide**

THANK YOU