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Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial

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A list of authors and their affiliations appears at the end of the paper

In the STEP-HFpEF trial, semaglutide improved symptoms, physical limitations and exercise function and reduced body weight in patients with obesity phenotype of heart failure and preserved ejection fraction (HFpEF). This prespecified analysis examined the effects of semaglutide on dual primary endpoints (change in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and body weight) and confirmatory secondary endpoints (change in 6-minute walk distance (6MWD), hierarchical composite (death, HF events, change in KCCQ-CSS and 6MWD) and change in C-reactive protein (CRP)) across obesity classes I–III (body mass index (BMI) 30.0–34.9 kg m^{-2}, 35.0–39.9 kg m^{-2} and ≥40 kg m^{-2}) and according to body weight reduction with semaglutide after 52 weeks. Semaglutide consistently improved all outcomes across obesity categories (*P* value for treatment effects × BMI interactions = not significant for all). In semaglutide-treated patients, improvements in KCCQ-CSS, 6MWD and CRP were greater with larger body weight reduction (for example, 6.4-point (95% confidence interval (CI): 4.1, 8.8) and 14.4-m (95% CI: 5.5, 23.3) improvements in KCCQ-CSS and 6MWD for each 10% body weight reduction). In participants with obesity phenotype of HFpEF, semaglutide improved symptoms, physical limitations and exercise function and reduced inflammation and body weight across obesity categories. In semaglutide-treated patients, the magnitude of benefit was directly related to the extent of weight loss. Collectively, these data support semaglutide-mediated weight loss as a key treatment strategy in patients with obesity phenotype of HFpEF. ClinicalTrials.gov identifier: NCT04788511.

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing worldwide, and there are few effective treatments[1,2]. Approximately 60% of patients with HFpEF have the obesity phenotype[3], which is a pathophysiologically distinct form of HFpEF characterized by greater symptom severity, poorer exercise capacity, more adverse hemodynamics and greater risk for HF hospitalization than those with HFpEF without obesity[3–10]. In the STEP-HFpEF trial, treatment with 2.4 mg of the glucagon-like peptide-1 receptor agonist semaglutide weekly produced substantial improvements in symptoms, physical limitations and exercise function and reduced inflammation and resulted in greater weight loss compared to placebo[11,12].

However, it is not known if the observed effects of semaglutide in STEP-HFpEF vary by obesity class. Obesity is traditionally defined as body mass index (BMI) of 30 kg m^{-2} or greater, but, within this broad

e-mail: mkosiborod@saint-lukes.org

definition, there is substantial variation in the amount of excess adiposity. In the United States, approximately one-third of patients with the obesity phenotype of HFpEF have class III obesity, defined by BMI ≥40 kg m^{-2}, whereas 40% of patients have class I obesity (BMI 30–34.9 kg m^{-2}) (ref. 3). In cross-sectional studies, symptom severity, exercise limitations and hemodynamic abnormalities in the obesity phenotype of HFpEF worsen as BMI increases[6–8], suggesting the possibility that beneficial effects from semaglutide could be mostly confined to individuals with HFpEF and very high BMI. Furthermore, it is unclear whether the magnitude of body weight reduction after treatment with semaglutide is related to the extent of clinical improvement in symptom severity, exercise function or systemic inflammation.

This prespecified analysis of STEP-HFpEF investigated the efficacy of semaglutide versus placebo in patients with HFpEF across the different classes of obesity, as it pertains to the primary endpoints (change in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and body weight) and confirmatory secondary endpoints (change in 6-minute walk distance (6MWD), hierarchical composite endpoint (comprising all-cause death, HF events, several thresholds of change in KCCQ-CSS and change in 6MWD ≥30 m) and change in C-reactive protein (CRP)), and it tested whether the degree of body weight reduction achieved on treatment with semaglutide was related to the improvements in the key trial endpoints.

Results

Patient characteristics

A total of 817 patients were screened, and, of this group, 529 fulfilled eligibility criteria and were enrolled and randomized between 19 March 2021 and 9 March 2022 (Extended Data Fig. 1). Among the 529 STEP-HFpEF participants, 263 and 266 were randomized to semaglutide versus placebo, respectively; the median BMI was 37.0 kg m^{-2} (33.7, 41.4) at baseline, 180 (34.0%) had class I obesity, 171 (32.3%) had class II obesity and 178 (33.7%) had class III obesity. Compared to patients who had less severe obesity, those with greater severity of obesity were more likely to be women and younger, with lower N-terminal pro-brain type natriuretic peptide (NTproBNP) levels but more severe impairments in HF symptoms, physical limitations and exercise function as reflected by lower KCCQ-CSS and 6MWD and higher New York Heart Association (NYHA) class and CRP levels (Table 1). No differences were observed in systolic blood pressure (SBP) or medical therapy for HF, except that patients with lower obesity class were more likely to be treated with sodium-glucose co-transporter-2 (SGLT2) inhibitors, and patients with higher obesity class were more likely to receive loop diuretics at higher dose. No differences were observed in the prevalence of hypertension, atrial fibrillation or sleep apnea by obesity class, but patients with increased severity of obesity were less likely to have history of coronary artery disease.

In regression analyses, increase in BMI was associated with lower KCCQ-CSS and 6MWD and higher CRP at the time of baseline assessment, after adjusting for age, sex, NYHA class, history of atrial fibrillation and history of coronary disease (Supplementary Table 1).

Treatment effects by baseline obesity class

As compared to placebo, treatment with semaglutide improved KCCQ-CSS and reduced body weight across all obesity categories (Fig. 1). Semaglutide also improved 6MWD, resulted in a greater number of wins versus placebo for the composite hierarchical endpoint and reduced systemic inflammation assessed by CRP in each obesity class, with no heterogeneity of treatment benefits (Fig. 2). These findings were observed in both the intention-to-treat analyses and the on-treatment analyses.

Semaglutide effects and weight change

Among patients who were treated with semaglutide and had a recorded body weight at week 52, body weight reduction was <5% in 33 (13.4%) participants, 5–<10% in 51 (20.7%) participants, 10–<15% in 54 (22.0%) participants, 15–<20% in 50 (20.3%) participants and >20% in 58 (23.6%) participants. Increased degree of body weight reduction was associated with increased magnitude of improvements in KCCQ-CSS and 6MWD and reduction in CRP. These dose–response relationships between the amount of weight loss and treatment benefits were observed when body weight change was analyzed both as an ordinal (Fig. 3) and as a continuous variable, after adjusting for age, sex, NYHA class, history of atrial fibrillation and coronary artery disease, baseline CRP and NTproBNP at baseline (Table 2). Results were consistent between the intention-to-treat and on-treatment analyses, except for 6MWD where dose–response relationship was observed in the intention-to-treat, but not in the on-treatment, analysis (Extended Data Fig. 2).

Based on the linear regression slopes (Table 2), each 10% reduction in body weight with semaglutide was associated with a 6.4-point (95% confidence interval (CI): 4.1, 8.8) increase in KCCQ-CSS, a 14.4-m (95% CI: 5.5, 23.3) increase in 6MWD and a 28% (95% CI: 16, 37) decrease in CRP, after adjusting for baseline age, sex, body weight, endpoint value, NYHA class, coronary artery disease, atrial fibrillation, CRP (log-transformed) and NTproBNP (log-transformed).

Safety and tolerability

There were fewer serious adverse events reported among participants randomized to semaglutide versus placebo within each obesity class, with no evidence of heterogeneity in safety or tolerability (Table 3). A similar (and small) number of patients discontinued study medication due to serious adverse events in the semaglutide and placebo groups. The number of deaths in the semaglutide and placebo groups, respectively, were 2 and 0 in obesity class I, 0 and 2 in obesity class II and 1 and 2 in obesity class III.

Discussion

In this prespecified analysis from the STEP-HFpEF trial, semaglutide as compared to placebo improved HF-related symptoms, physical limitations and exercise function and reduced body weight and inflammation across the spectrum of obesity categories. Furthermore, in patients treated with semaglutide, increased degree of weight loss was associated with increased magnitude of improvements in symptoms, physical limitations and inflammation, even after adjusting for relevant baseline characteristics that might influence treatment response, including age, sex and baseline body weight. These data demonstrate that the effects of semaglutide-induced weight loss are not restricted to individuals with very high BMI but apply across the entire spectrum of obesity. In addition, the relationships between the magnitude of weight reduction and clinical efficacy provide mechanistic evidence supporting the importance of weight reduction as an effective treatment for patients with the obesity phenotype of HFpEF.

Patients with the obesity phenotype of HFpEF display distinct pathophysiologic characteristics compared to patients with other phenotypes of HFpEF, including greater volume expansion, higher cardiac filling pressures, more severe right-sided HF and increases in epicardial fat that amplify external constraint on the heart[6]. It has been shown that patients with the obesity HFpEF phenotype are younger and have lower natriuretic peptide levels[3,6,7] but present with higher NYHA class[4,7], greater symptom severity, poorer exercise capacity[7,8] and greater systemic inflammation than patients without obesity[7]. These relationships with obesity severity in patients with HFpEF were again observed in the present analysis, supporting the validity and generalizability of these data from the STEP-HFpEF trial.

Previous studies showed direct linear relationships between body weight and symptom severity, exercise limitation and hemodynamic abnormalities in patients with the obesity phenotype of HFpEF[6–8]. These relationships might support a hypothesis that only those individuals with HFpEF and the most severe obesity phenotypes would benefit from weight loss treatments. However, in this analysis, we

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Table 1 | Baseline characteristics of trial participants across obesity categories[a]

Characteristic	BMI <35 kg m^{-2} (*n*=180)	BMI 35–<40 kg m^{-2} (*n*=171)	BMI ≥40 kg m^{-2} (*n*=178)	*P* value
Female, *n* (%)	91 (50.6)	88 (51.5)	118 (66.3)	0.0027
Age, years	72 (64, 78)	70 (63, 74)	67 (60, 73)	<0.0001
Ethnicity, *n* (%)[b]				0.8115
Hispanic or Latino	13 (7.2)	9 (5.3)	14 (7.9)	
Not Hispanic or Latino	167 (92.8)	162 (94.7)	164 (92.1)	
Race, *n* (%)[b]				0.1237
Black/African American	10 (5.6)	2 (1.2)	9 (5.1)	
White	170 (94.4)	169 (98.8)	168 (94.4)	
Other	0 (0.0)	0 (0.0)	1 (0.6)	
Body weight, kg	91.6 (84.1, 100.2)	105.8 (93.7, 117.5)	123.1 (110.0, 137.7)	<0.0001
BMI, kg m^{-2}[c]	32.6 (31.3, 33.8)	37.1 (36.1, 38.4)	43.5 (41.3, 47.6)	[d]
Waist circumference, cm	110.0 (105.0, 116.8)	120.0 (113.0, 127.0)	129.0 (121.0, 141.0)	<0.0001
SBP, mmHg	132.0 (120.0, 141.5)	135.0 (122.0, 148.0)	132.0 (121.0, 140.0)	0.5912
NT-proBNP, pg ml^{-1}	531.1 (278.7, 1083.8)	449.9 (205.5, 1058.8)	385.2 (181.0, 926.9)	0.0201
LVEF, %	56.0 (50.0, 60.0)	57.0 (50.0, 60.0)	58.0 (54.0, 61.0)	0.0206
LVEF stratification, *n* (%)				0.0928
45–49%[e]	33 (18.3)	31 (18.1)	21 (11.8)	
≥50%	147 (81.7)	140 (81.9)	157 (88.2)	
KCCQ-CSS score	61.7 (46.9, 76.0)	60.9 (46.9, 72.9)	51.6 (34.9–65.6)	<0.0001
6MWD, m	351.0 (260.5, 402.5)	340.0 (261.3, 400.0)	272.0 (207.6, 347.8)	<0.0001
CRP, mg L^{-1}	2.6 (1.5, 5.9)	3.8 (2.0, 7.4)	5.2 (2.8, 10.2)	<0.0001
HF hospitalization within 1 year, *n* (%)	32 (17.8)	20 (11.7)	29 (16.3)	0.6926
Comorbidities at screening, *n* (%)				
Atrial fibrillation	97 (53.9)	88 (51.5)	90 (50.6)	0.5283
Hypertension	143 (79.4)	141 (82.5)	149 (83.7)	0.2950
Coronary heart disease	80 (44.4)	51 (29.8)	49 (27.5)	0.0007
Obstructive sleep apnea	24 (13.3)	15 (8.8)	27 (15.2)	0.6033
NYHA functional class, *n* (%)				0.0001
Class II	136 (75.6)	119 (69.6)	95 (53.4)	
Class III	44 (24.4)	51 (29.8)	83 (46.6)	
Class IV	0 (0.0)	1 (0.6)	0 (0.0)	
Concomitant medications, *n* (%)				
Diuretics	143 (79.4)	137 (80.1)	147 (82.6)	0.4520
Loop diuretics	109 (60.6)	95 (55.6)	125 (70.2)	0.0602
Loop diuretic dose (mg)[f]	40 (20, 40)	40 (20, 40)	40 (40, 80)	0.0002
Thiazides	33 (18.3)	31 (18.1)	26 (14.6)	0.3489
MRAs	56 (31.1)	58 (33.9)	70 (39.3)	0.1029
ACE/ARB (ARNI)	129 (71.7)	132 (77.2)	136 (76.4)	0.2992
ARNI	11 (6.1)	9 (5.3)	7 (3.9)	0.3492
Beta-blockers	150 (83.3)	132 (77.2)	136 (76.4)	0.1070
SGLT2i	10 (5.6)	7 (4.1)	2 (1.1)	0.0243

Percentages may not equal 100% due to rounding. Two-sided *P* values for continuous variables are from a Jonckheere–Terpstra trend test, for binary variables from a Cochran–Armitage trend test and for multinomial variables from a Cochran–Mantel–Haenszel test. [a]Data are median (Q1, Q3) unless otherwise stated and are from the full analysis set. [b]Race and ethnic group were reported by the investigator. [c]BMI is the weight in kilograms divided by the square of the height in meters. [d]Not relevant. [e]Includes one participant with LVEF of 33%. [f]Reported in furosemide equivalents per day. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; Q, quartile; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

observed similar treatment benefits of semaglutide for all primary and confirmatory secondary endpoints across the spectrum of obesity categories. These findings have important clinical implications, as approximately 40% of patients with the obesity phenotype of HFpEF have only mild obesity (class I), and the present analyses indicate that these patients benefit just as much as patients with more severe obesity[3]. The relationship observed between reductions in body weight and improvements in symptoms and physical limitations supports the

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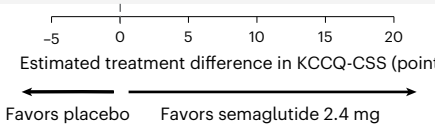
a Effects of semaglutide on symptoms & physical limitations by obesity class

Subgroup	Semaglutide 2.4 mg *n*	Semaglutide 2.4 mg Change from baseline to week 52	Placebo *n*	Placebo Change from baseline to week 52	ETD (95% CI)	*P* value	Interaction *P* value
Intention-to-treat							
All patients	243	16.6	237	8.7	7.8 (4.8, 10.9)	<0.0001	
BMI, kg m^{-2}							
<35	80	15.9	83	7.4	8.5 (3.2, 13.8)	0.0018	0.2122
≥35–<40	81	15.4	78	11.3	4.1 (–1.2, 9.4)	0.1331	
≥40	82	18.5	76	7.7	10.8 (5.5, 16.1)	<0.0001	
On-treatment							
All patients	202	19.1	206	10.3	8.8 (5.9, 11.7)	0.0001	
BMI, kg m^{-2}							
<35	61	18.3	71	8.1	10.2 (5.1, 15.3)	0.0001	0.5505
≥35–<40	67	18.7	68	12.2	6.5 (1.4, 11.6)	0.0125	
≥40	74	20.3	67	10.8	9.6 (4.6, 14.6)	0.0002	



b Effects of semaglutide on body weight by obesity class

Subgroup	Semaglutide 2.4 mg *n*	Semaglutide 2.4 mg Change from baseline to week 52	Placebo *n*	Placebo Change from baseline to week 52	ETD (95% CI)	*P* value	Interaction *P* value
Intention-to-treat							
All patients	246	–13.3	242	–2.6	–10.7 (–11.9, –9.4)	<0.0001	
BMI, kg m^{-2}							
<35	81	–10.7	84	–1.1	–9.6 (–11.8, –7.4)	<0.0001	0.4902
≥35–<40	83	–13.8	78	–2.5	–11.3 (–13.5, –9.0)	<0.0001	
≥40	82	–15.4	80	–4.1	–11.3 (–13.4, –9.1)	<0.0001	
On-treatment							
All patients	203	–15.1	211	–2.4	–12.7 (–13.9, –11.5)	<0.0001	
BMI, kg m^{-2}							
<35	61	–13.2	73	–0.8	–12.4 (–14.5, –10.3)	<0.0001	0.9371
≥35–<40	68	–15.5	69	–2.6	–12.9 (–15.0, –10.8)	<0.0001	
≥40	74	–16.6	69	–3.8	–12.9 (–14.9, –10.8)	<0.0001	

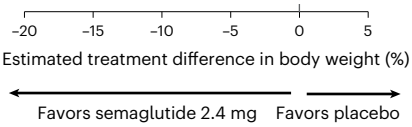


Fig. 1 | Effects of semaglutide compared to placebo across different obesity classes on HF symptoms, physical limitations and body weight. a,**b**, There was no evidence of heterogeneity in the effects of semaglutide compared to placebo on the dual primary endpoints of KCCQ-CSS (**a**) or body weight (**b**). Data are point estimates and 95% CIs. Analyses using the intention-to-treat principle employ an F-test for interaction and a Wald test for treatment effect within BMI subgroups, with 1,000 imputations using Rubin's rule. Analyses using on-treatment data employ an F-test for interaction and a *t*-test for treatment effect within BMI subgroups. *P* values are two-sided. ETD, estimated treatment difference.

hypothesis that the obesity phenotype of HFpEF is, in large part, a consequence of increased adiposity and its many sequelae, although there are also likely non-obesity-related contributors to the pathophysiology.

Weight loss in patients with obesity but no HF is associated with effects that would be expected to reduce symptom severity and improve exercise function in patients with HFpEF, including reversal of hypertrophic chamber remodeling, improvement in ventricular mechanics and reductions in hemodynamic congestion[13,14]. The present findings are supported by the results of the SECRET trial, which showed that non-pharmacologic body weight reduction achieved through caloric restriction improved exercise capacity in patients with the obesity phenotype of HFpEF[15]. The present study directly relates the degree of pharmacologically mediated weight loss with the magnitude of clinical benefits observed across the broad range of outcomes, including symptoms and physical limitations (KCCQ-CSS), exercise function (6MWD) and inflammation (CRP). These benefits are not simply ascribable to mechanical effects of body weight reduction, as the STEP-HFpEF trial also showed that semaglutide reduced NTproBNP levels compared to placebo, consistent with a direct benefit on hemodynamic congestion[11].

The findings of this study should be considered in the context of several potential limitations. Most participants in STEP-HFpEF were White, and individuals with diabetes were excluded by design, which may affect the generalizability to non-White populations and people

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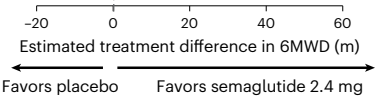
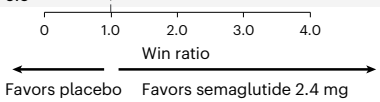
a Effects of semaglutide on exercise function by obesity class

Subgroup	Semaglutide 2.4 mg *n*	Semaglutide 2.4 mg Change from baseline to week 52	Placebo *n*	Placebo Change from baseline to week 52	ETD (95% CI)	*P* value	Interaction *P* value
Intention-to-treat							
All patients	240	21.5	225	1.2	20.3 (8.6, 32.1)	0.0007	
BMI, kg m^{-2}							
<35	79	18.7	79	1.1	17.7 (−2.7, 38.0)	0.0888	0.3063
≥35–<40	82	14.9	73	4.4	10.6 (−9.5, 30.7)	0.3031	
≥40	79	31.1	73	−1.7	32.8 (12.3, 53.3)	0.0017	
On-treatment							
All patients	199	29.0	200	8.3	20.6 (9.5, 31.8)	0.0003	
BMI, kg m^{-2}							
<35	59	31.9	68	5.8	26.1 (6.3, 45.8)	0.0098	0.7429
≥35–<40	68	25.8	65	10.6	15.2 (−4.3, 34.6)	0.1254	
≥40	72	29.7	67	8.8	20.8 (1.8, 39.9)	0.0321	



b Effects of semaglutide on hierarchical composite by obesity class

Subgroup	Semaglutide 2.4 mg *n*	Placebo *n*	W,L,T (semaglutide 2.4 mg) Wins, losses, ties (%)	Win ratio (95% CI)	*P* value	Interaction *P* value
Intention-to-treat						
All patients	263	266	60.1, 34.9, 5.1	1.72 (1.37, 2.15)	<0.0001	
BMI, kg m^{-2}						
<35	89	91	63.0, 32.4, 4.6	1.95 (1.29, 2.92)	0.0015	0.3994
≥35–<40	88	83	54.5, 39.9, 5.6	1.37 (0.94, 1.99)	0.1038	
≥40	86	92	62.2, 32.5, 5.3	1.91 (1.30, 2.81)	0.0010	
On-treatment						
All patients	263	266	63.0, 30.0, 6.9	2.10 (1.67, 2.63)	<0.0001	
BMI, kg m^{-2}						
<35	89	91	66.2, 26.9, 6.9	2.47 (1.65, 3.69)	<0.0001	0.5885
≥35–<40	88	83	60.2, 32.7, 7.1	1.84 (1.25, 2.73)	0.0021	
≥40	86	92	62.4, 30.8, 6.8	2.03 (1.38, 2.98)	0.0004	



c Effects of semaglutide on systemic inflammation by obesity class

Subgroup	Semaglutide 2.4 mg *n*	Semaglutide 2.4 mg Ratio to baseline at week 52	Placebo *n*	Placebo Ratio to baseline at week 52	ETD (95% CI)	*P* value	Interaction *P* value
Intention-to-treat							
All patients	241	0.56	243	0.93	0.61 (0.51, 0.72)	<0.0001	
BMI, kg m^{-2}							
<35	79	0.54	84	0.87	0.61 (0.46, 0.83)	0.0013	0.2321
≥35–<40	83	0.46	78	0.90	0.51 (0.38, 0.68)	<0.0001	
≥40	79	0.73	81	1.01	0.73 (0.54, 0.98)	0.0362	
On-treatment							
All patients	199	0.51	211	0.91	0.56 (0.48, 0.66)	<0.0001	
BMI, kg m^{-2}							
<35	60	0.47	73	0.76	0.62 (0.47, 0.82)	0.0009	0.0938
≥35–<40	68	0.41	69	0.94	0.44 (0.33, 0.57)	<0.0001	
≥40	71	0.69	69	1.07	0.64 (0.49, 0.84)	0.0015	

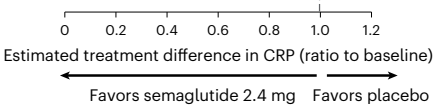


Fig. 2 | Effects of semaglutide compared to placebo across different obesity classes on exercise function, hierarchical composite endpoint and systemic inflammation. a,**b**, There was no evidence of heterogeneity in the effects of semaglutide compared to placebo on the confirmatory secondary endpoints of exercise function assessed by 6MWD (**a**), the hierarchical composite endpoint (**b**) or systemic inflammation assessed by CRP levels. Data are point estimates and 95% CIs. Analyses using the intention-to-treat principle employ an F-test (**a**,**c**) or Cohran's Q-test (**b**) for interaction and a Wald test for treatment effect within BMI subgroups, with 1,000 imputations using Rubin's rule. Analyses using on-treatment data employ an F-test for interaction and a *t*-test for treatment effect within BMI subgroups (**a**,**c**) or Cohran's Q-test (**b**) for interaction and a Wald test for treatment effect within BMI subgroups. *P* values are two-sided. Other abbreviations as in Fig. 1.

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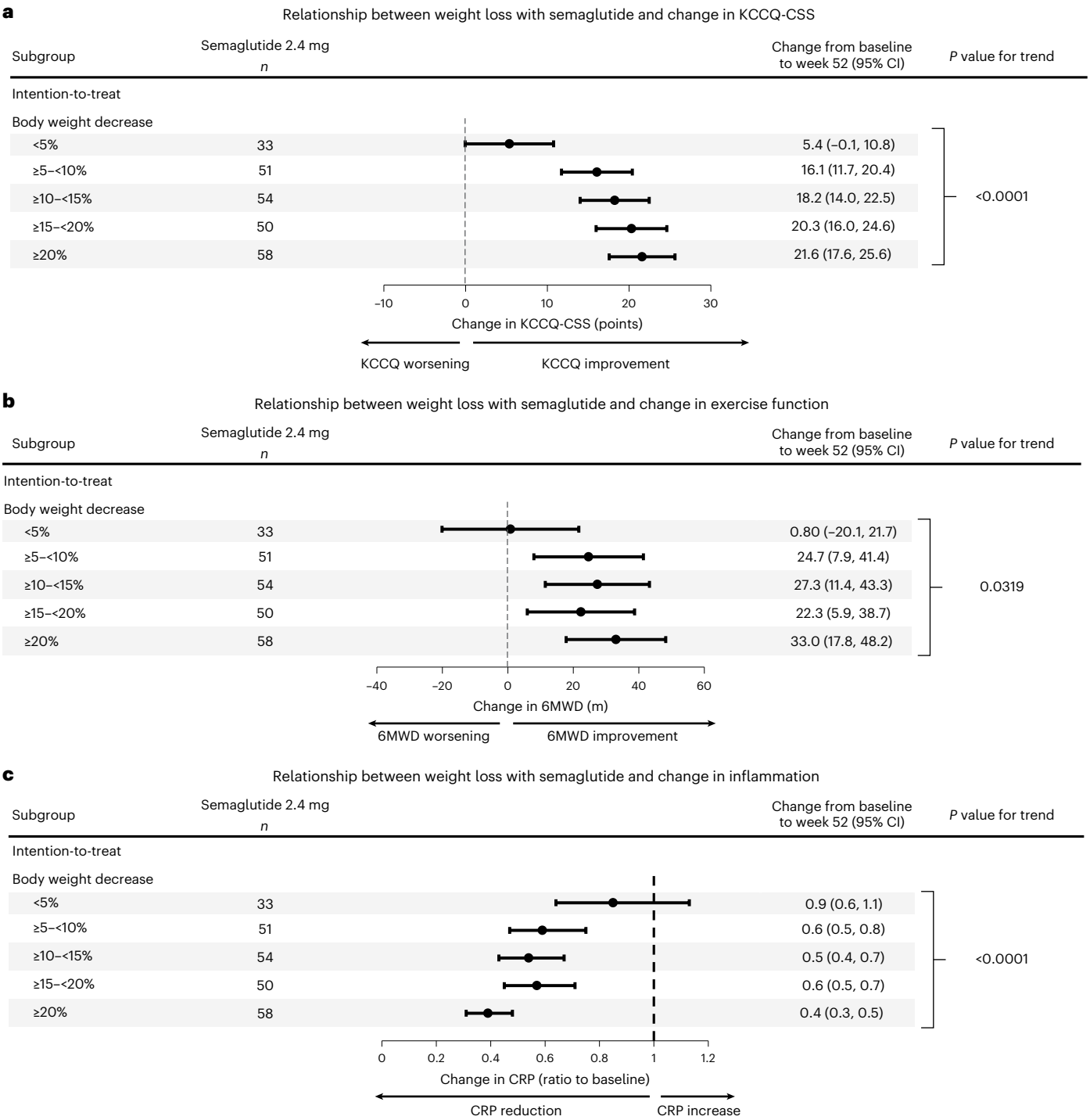

Fig. 3 | Relationship between the magnitude of body weight reduction on semaglutide and primary and confirmatory secondary endpoints. **a**–**c**, Greater body weight reduction with semaglutide was associated with greater improvements in HF symptoms and physical limitations assessed by the KCCQ-CSS (**a**), exercise function assessed by the 6MWD (**b**) and greater reduction in systemic inflammation assessed by CRP levels (**c**). Data are point estimates and 95% CIs. Analyses use the intention-to-treat principle; tests for trend are based on an F-test. *P* values are two-sided. Abbreviations as in Figs. 1 and 2.

with diabetes. A separate, ongoing trial is evaluating the effects of semaglutide in people with the obesity phenotype of HFpEF and type 2 diabetes[12]. The STEP-HFpEF trial was designed to evaluate the effects of treatment on symptoms and physical limitations, exercise function and inflammation, along with body weight, and was, therefore, not powered to assess clinical endpoints such as HF hospitalizations. Power is reduced by focusing on obesity class subgroups as compared to the main analysis, but the findings were consistent across obesity categories with no evidence for heterogeneity of treatment effects. The 52-week duration of treatment was relatively short, and whether the observed effects might have persisted (or become more amplified) with longer evaluation is not known. Use of SGLT2 inhibitors was low in STEP-HFpEF, as patients with diabetes were excluded, and these agents were not yet approved for treatment of HFpEF during the trial conduct. Although semaglutide and SGLT2 inhibitors have complementary and non-overlapping mechanisms of action, the present study cannot

Table 2 | Regression analysis of changes in body weight on semaglutide to efficacy outcomes

	Predicted change per 10% decrease in body weight Model 1		Predicted change per 10% decrease in body weight Model 2	
Endpoint change at 52 weeks	Slope (95% CI)[a]	*P*	Slope (95% CI)[a]	*P*
KCCQ-CSS (points)	5.9 (3.6, 8.3)	<0.0001	6.4 (4.1, 8.8)	<0.0001
6MWD (m)	13.2 (4.4, 22.0)	0.0033	14.4 (5.5, 23.3)	0.0016
CRP (ratio)	0.75 (0.65, 0.86)	<0.0001	0.72 (0.63, 0.84)	<0.0001

Results are shown for the intention-to-treat analysis. Data are point estimates and 95% CIs, computed using multivariable regression analyses. *P* values are two-sided. Model 1 is adjusted for baseline weight and baseline endpoint (baseline KCCQ-CSS, 6MWD or logarithm to CRP). Model 2 is adjusted for baseline values of weight, respective endpoint, age, sex, history of atrial fibrillation, history of coronary artery disease, NYHA class, logarithm to CRP and logarithm to NTproBNP. [a]Change per 10% decrease in body weight on treatment with semaglutide.

Table 3 | Adverse events

	Adverse event rate per 100 patient years					
	Class I obesity (30–34.9 kg m^{-2})		Class II obesity (35–39.9 kg m^{-2})		Class III obesity (≥40 kg m^{-2})	
	Placebo (*n*=91)	Semaglutide (*n*=89)	Placebo (*n*=83)	Semaglutide (*n*=88)	Placebo (*n*=92)	Semaglutide (*n*=86)
Serious adverse events	53.7	32.2	39.0	18.4	56.7	20.4
Deaths	0.0	2.5	3.5	0.0	2.2	1.1
Category of serious adverse event						
Cardiac disorders	19.7	7.4	9.5	1.2	18.9	1.1
Infections and infestations	3.3	3.7	13.0	2.3	8.9	0.0
Gastrointestinal disorders	3.3	2.5	0.0	4.6	5.6	3.4
Nervous system disorders	3.3	6.2	3.5	1.2	1.1	2.3
Renal and urinary disorders	1.1	3.7	1.2	1.2	4.4	3.4
Respiratory, thoracic and mediastinal	6.6	0.0	2.4	0.0	3.3	0.0
Musculoskeletal and connective tissue	1.1	0.0	1.2	3.5	3.3	2.3
Injury, poisoning and procedural	3.3	0.0	2.4	2.3	0.0	2.3
Metabolism and nutrition disorders	2.2	0.0	1.2	2.3	1.1	1.1
Hepatobiliary disorders	2.2	3.7	0.0	0.0	0.0	1.1
General disorders and administration site	0.0	0.0	1.2	0.0	2.2	1.1
Neoplasms benign, malignant and unspecified	1.1	0.0	1.2	0.0	1.1	1.1
Serious adverse event leading to discontinuation	4.4	5.0	1.2	1.2	2.2	2.3

determine whether background therapy with SGLT2 inhibitors might have influenced the treatment benefits observed, which is an important question for future trials. Further insight into the effects of semaglutide in patients who receive background SGLT2 inhibitors will be provided by the STEP-HFpEF DM trial, which includes a greater proportion (32%) of patients taking these agents[12]. BMI is a crude measure of adiposity that does not assess body composition or quantity of visceral fat, which has more deleterious effects in HFpEF[6,16], limiting insight on the effect of semaglutide on visceral fat loss and its association with improvements in KCCQ-CSS and 6MWD outcomes.

In the STEP-HFpEF trial of participants with the obesity phenotype of HFpEF, semaglutide improved symptoms, physical limitations and exercise function and reduced inflammation and body weight across the spectrum of obesity categories. In semaglutide-treated patients, the magnitude of benefit was directly related to the extent of weight loss. Collectively, these data support semaglutide-mediated weight loss as a key treatment strategy in patients with the obesity phenotype of HFpEF.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02526-x.

References

1. Redfield, M. M. & Borlaug, B. A. Heart failure with preserved ejection fraction: a review. *JAMA* **329**, 827–838 (2023).
2. Borlaug, B. A., Sharma, K., Shah, S. J. & Ho, J. E. Heart failure with preserved ejection fraction: JACC Scientific Statement. *J. Am. Coll. Cardiol.* **81**, 1810–1834 (2023).
3. Morgen, C. S. et al. Obesity, cardiorenal comorbidities and risk of hospitalization in patients with heart failure with preserved ejection fraction. *Mayo Clin. Proc.* https://doi.org/10.1016/j.mayocp.2023.07.008 (2023).
4. Dalos, D. et al. Functional status, pulmonary artery pressure, and clinical outcomes in heart failure with preserved ejection fraction. *J. Am. Coll. Cardiol.* **68**, 189–199 (2016).
5. Kitzman, D. W. & Shah, S. J. The HFpEF obesity phenotype: the elephant in the room. *J. Am. Coll. Cardiol.* **68**, 200–203 (2016).
6. Obokata, M., Reddy, Y. N. V., Pislaru, S. V., Melenovsky, V. & Borlaug, B. A. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* **136**, 6–19 (2017).

7. Reddy, Y. N. V. et al. Characterization of the obese phenotype of heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Mayo Clin. Proc.* **94**, 1199–1209 (2019).
8. Reddy, Y. N. V. et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur. J. Heart Fail.* **22**, 1009–1018 (2020).
9. Adamson, C. et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. *Eur. Heart J.* **43**, 4406–4417 (2022).
10. Borlaug, B. A. et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. *Cardiovasc. Res.* **118**, 3434–3450 (2023).
11. Kosiborod, M. N. et al. Once weekly semaglutide in heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* (in the press).
12. Kosiborod, M. N. et al. Design and baseline characteristics of STEP-HFpEF program evaluating semaglutide in patients with obesity HFpEF phenotype. *JACC Heart Fail.* **11**, 1000–1010 (2023).
13. Sorimachi, H. et al. Long-term changes in cardiac structure and function following bariatric surgery. *J. Am. Coll. Cardiol.* **80**, 1501–1512 (2022).
14. Reddy, Y. N. V. et al. Hemodynamic effects of weight loss in obesity: a systematic review and meta-analysis. *JACC Heart Fail.* **7**, 678–687 (2019).
15. Kitzman, D. W. et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* **315**, 36–46 (2016).
16. Sorimachi, H. et al. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur. Heart J.* **42**, 1595–1605 (2021).

Barry A. Borlaug[1], Dalane W. Kitzman[2], Melanie J. Davies[3,4], Søren Rasmussen[5], Eric Barros[5], Javed Butler[6], Mette Nygaard Einfeldt[5], G. Kees Hovingh[5], Daniél Vega Møller[5], Mark C. Petrie[7], Sanjiv J. Shah[8], Subodh Verma[9], Walter Abhayaratna[10], Fozia Z. Ahmed[11], Vijay Chopra[12], Justin Ezekowitz[13], Michael Fu[14], Hiroshi Ito[15], Małgorzata Lelonek[16], Vojtech Melenovsky[17], Julio Núñez[18], Eduardo Perna[19], Morten Schou[20], Michele Senni[21], Peter van der Meer[22], Dirk Von Lewinski[23], Dennis Wolf[24] & Mikhail N. Kosiborod[25] ✉

[1]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA. [2]Department of Cardiovascular Medicine and Section on Geriatrics and Gerontology, Wake Forest University School of Medicine, Winston-Salem, NC, USA. [3]Diabetes Research Centre, University of Leicester, Leicester, UK. [4]NIHR Leicester Biomedical Research Centre, Leicester, UK. [5]Novo Nordisk A/S, Søborg, Denmark. [6]Baylor Scott and White Research Institute, Dallas, TX and Department of Medicine, University of Mississippi, Jackson, MS, USA. [7]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK. [8]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. [9]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Unity Health Toronto, University of Toronto, Toronto, ON, Canada. [10]College of Health and Medicine, The Australian National University, Canberra, ACT, Australia. [11]Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [12]Clinical Cardiology, Heart Failure and Research, Max Super Specialty Hospital, Saket, New Delhi, India. [13]University of Alberta, Edmonton, AB, Canada. [14]Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital-Ostra, Gothenburg, Sweden. [15]Department of General Internal Medicine 3, Kawasaki Medical School, Okayama, Japan. [16]Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland. [17]Institute for Clinical and Experimental Medicine – IKEM, Prague, Czech Republic. [18]Hospital Clínico Universitario de Valencia, INCLIVA, Universidad de Valencia, and CIBER Cardiovascular, Valencia, Spain. [19]Instituto de Cardiologia J. F. Cabral, Corrientes, Argentina. [20]Department of Cardiology, Herlev-Gentofte Hospital, University of Copenhagen, Herlev, Denmark. [21]Cardiovascular Department, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy. [22]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [23]Division of Cardiology, Medical University of Graz, Graz, Austria. [24]Cardiology and Angiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [25]Department of Cardiovascular Disease, Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA. ✉e-mail: mkosiborod@saint-lukes.org

Methods

Study design

STEP-HFpEF (NCT04788511) was a randomized, international, double-blind, placebo-controlled trial that examined the efficacy and safety of semaglutide 2.4 mg once weekly compared to placebo in patients with the obesity phenotype of HFpEF without diabetes[11]. The study design and the primary results were previously published[11,12]. Institutional review board ethics approval was obtained at each study site, and all patients provided informed consent to participate in the trial.

Study patients

Eligible participants were randomized 1:1 to semaglutide 2.4 mg subcutaneously or matching placebo once weekly in addition to standard of care for 52 weeks[12]. For all participants, frequent physical activity of moderate intensity (as tolerated in HFpEF) and limited consumption of salt, red meat, saturated or trans fats, sweets and sugar-sweetened beverages, with restricted calorie intake (goal, 500 kcal deficit per day) were recommended. Smoking cessation was supported, and alcohol consumption was recommended to be limited. Patients were eligible if they had left ventricular ejection fraction (LVEF) ≥45%, NYHA functional class II–IV, BMI ≥30 kg m^{-2}, KCCQ-CSS <90 points and objective evidence of HF based on at least one of the following criteria: (1) elevated left ventricular filling pressures (pulmonary artery wedge pressure or left ventricular end-diastolic pressure ≥15 mmHg at rest or ≥25 mmHg with exercise documented during catheterization or pulmonary artery diastolic pressure measured by implantable monitor ≥15 mmHg, assessed invasively); (2) elevated natriuretic peptide levels (with thresholds stratified based on BMI: ≥220 pg ml^{-1} for patients with BMI <35.0 and sinus rhythm; ≥660 pg ml^{-1} for patients with BMI <35.0 and persistent/permanent atrial fibrillation; ≥125 pg ml^{-1} for patients with BMI ≥35.0 and sinus rhythm; or ≥375 pg ml^{-1} for patients with BMI ≥35.0 and persistent/permanent atrial fibrillation, together with echocardiographic abnormalities (at least one of the following: (i) septal é <7 cm s^{-1} or lateral é < 10 cm s^{-1} or average E/é ≥15; (ii) pulmonary artery systolic pressure >35 mmHg; (iii) left atrial enlargement defined by local laboratory; and (iv) left ventricular hypertrophy with septal thickness or posterior wall thickness ≥1.2 cm)); or (3) hospitalization for HF in the preceding 12 months plus requirement for ongoing diuretics and/or echocardiographic abnormalities (as defined above). Key exclusion criteria were previous or planned bariatric surgery, self-reported change in body weight >11 pounds (5 kg) within 90 d before randomization or SBP >160 mmHg at screening. Patients were excluded from the trial if they had a HbA1c level ≥6.5% or prior medical history of diabetes, because clinical characteristics and response to semaglutide may differ in patients with diabetes. A sister trial (STEP-HFpEF DM) is evaluating the effects of semaglutide in patients with obesity phenotype of HFpEF and diabetes (NCT04916470). The STEP-HFpEF trial was sponsored by Novo Nordisk.

BMI and weight changes

BMI was calculated as body weight in kilograms divided by height in meters squared based on measurements at baseline before randomization. Patients were stratified into BMI categories as obesity class I (BMI 30–34.9 kg m^{-2}), class II (BMI 35–39.9 kg m^{-2}) or class III (BMI ≥40 kg m^{-2}). Relative changes in body weight were expressed as the difference in body weight between baseline and 52 weeks divided by baseline body weight calculated as percentage.

Outcomes

The dual primary endpoints of STEP-HFpEF were change in KCCQ-CSS and percent change in body weight from baseline to 52 weeks[11,12]. Confirmatory secondary endpoints included exercise function assessed by change in 6MWD, overall clinical benefit assessed using a hierarchical composite endpoint (all-cause death, HF events, several thresholds of change in KCCQ-CSS from baseline to 52 weeks and change in 6MWD ≥30 m) and change in CRP from baseline to 52 weeks. All serious adverse events and adverse events leading to premature treatment discontinuation were reported to evaluate safety and tolerability.

Statistical analysis

Baseline characteristics were evaluated according to BMI groups (30–<35, 35–<40 and ≥40 kg m^{-2}), and tests for trend were performed across these groups. Efficacy endpoints for semaglutide compared to placebo, stratified by obesity class at baseline, were assessed using both the full analysis set (all randomized participants according to the intention-to-treat principle, regardless of treatment discontinuation) and the on-treatment data (including only patients receiving allocated study medication). Weight loss 'dose–effect' analyses were performed according to the magnitude of body weight change during the trial confined to the semaglutide group, because the primary objective was to examine the effects of body weight change related to semaglutide treatment rather than spontaneous or other lifestyle-related weight changes (as in the placebo group), using both intention-to-treat (primary) and on-treatment approaches. Subgroup analyses for continuous endpoints in the intention-to-treat were performed using 1,000 multiple imputations using analysis of covariance models, with treatment by BMI groups adjusted for the relevant continuous baseline variable[12]. Estimates from the multiple imputations were derived using Rubin's rule. Subgroups analyses of the hierarchical composite endpoint (win ratio) were performed stratified by the obesity category, based on direct comparisons of each participant randomized to semaglutide versus each participant randomized to placebo within each BMI subgroup. For each of these participant pairs, a 'treatment winner' based on similar observation time was declared based on the endpoint hierarchy (as previously reported[11,12]). The win ratio (that is, the proportion of winners randomized to semaglutide divided by the winners randomized to placebo) was estimated independently within each BMI subgroup using 1,000 imputations. Test for equality of the BMI groups for the win ratio was performed using Cohran's Q-test. Subgroup analyses for continuous endpoints in relation to the secondary hypothetical estimand (on treatment with trial product) were performed using a mixed model with treatment by BMI group adjusted for the relevant continuous baseline variable, all nested within visit, and treatment by BMI groups was evaluated at week 52 using on-treatment data. The hierarchical endpoint was analyzed using prediction (single-imputed) from a mixed model using on-treatment data for each of the components and analyzed stratified as described above. All imputations for the win ratio were pertinent only to KCCQ-CSS and 6MWD, where all-cause death and HF events differed between intention-to-treat and on-treatment approaches due to the collection of events in these two trial periods. Multivariable regression analyses were performed to determine independent relationships between baseline BMI and baseline outcome measures before treatment after adjusting a priori for baseline characteristics that might confound interpretation (age, sex, NYHA class, history of atrial fibrillation and history of coronary artery disease). Multivariable linear regression was also performed to determine relationships between change in body weight and changes in study outcomes with semaglutide unadjusted and after adjusting (a priori) for age, sex, NYHA functional class, history of coronary artery disease, history of atrial fibrillation, baseline CRP and baseline NTproBNP levels. Both unadjusted and adjusted analyses included baseline body weight and relevant continuous baseline variables (for example, baseline KCCQ-CSS, 6MWD or CRP) as covariates. Change in body weight was analyzed both as a continuous variable (% change from baseline) and as an ordinal variable, including the following weight loss categories from baseline to 52 weeks: <5%, 5–<10%, 10–<15%, 15–<20% and ≥20%. A test for linearity was employed for the categorial weight change analyses. All results from statistical analyses are presented with two-sided *P* values and 95% CIs. Safety endpoints were analyzed using

the safety analysis set (all randomized participants exposed to at least one dose of randomized treatment). Further details on the estimands, including specification of intention-to-treat and on-treatment data, statistical analyses and imputation methods to account for missing data, were previously published[12]. The primary estimand quantified the average change from baseline to 52 weeks in KCCQ-CSS and body weight of semaglutide 2.4 mg once weekly relative to placebo, both added to standard of care, in all randomized participants regardless of adherence to randomized treatment. *P* values less than 5% were considered significant, and no adjustment for multiplicity was performed.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Instructions for submitting proposals can be found at https://www.novonordisk-trials.com/. Data will be made available after research completion and approval of the product and product use in the European Union and the United States. Individual participant data will be shared in datasets in a de-identified/anonymized format.

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Author contributions

The academic members (M.N.K., B.A.B., J.B., M.J.D., D.W.K., M.C.P., S.J.S. and S.V.) of the Steering Committee along with the sponsor, Novo Nordisk, conceived and designed the study. The first draft of the manuscript was prepared by B.A.B. and M.N.K. M.N.K. had full access to all study data. All authors interpreted the data, contributed to manuscript writing, approved the final version of the manuscript, vouched for data accuracy and fidelity to the protocol and had final responsibility for the decision to submit for publication.

Competing interests

B.A.B. receives research support from the National Institutes of Health (NIH) and the US Department of Defense as well as research grant funding from AstraZeneca, Axon, GlaxoSmithKline, Medtronic, Mesoblast, Novo Nordisk, Rivus and Tenax Therapeutics. B.A.B. has also served as a consultant for Actelion, Amgen, Aria, Axon Therapies, BD Biosciences, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Eli Lilly, Imbria, Janssen, Merck, Novo Nordisk, NGM Biopharmaceuticals, NXT and VADovations and is named as an inventor (US patent no. 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure. D.W.K. was supported, in part, by the Kermit Glenn Phillips II Chair in Cardiovascular Medicine and NIH grants U01AG076928, R01AG078153, R01AG045551, R01AG18915 and U01HL160272 and reports receiving honoraria as a consultant for Bayer, Corvia Medical, Boehringer Ingelheim, Ketyo, Rivus, Novo Nordisk, AstraZeneca, Pfizer and Novartis; grant funding from Novartis, Bayer, Novo Nordisk, Rivus, Pfizer and AstraZeneca; and stock ownership in Gilead Sciences. M.J.D. has acted as a consultant, advisory board member and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi; an advisory board member and speaker for AstraZeneca; an advisory board member for Pfizer, Medtronic and ShouTi Pharma Inc.; and a speaker for Novartis, Sanofi and Amgen. M.D. has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Sanofi-Aventis, Eli Lilly, Boehringer Ingelheim, Janssen and Novo Nordisk. J.B. is a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Eli Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, 3live and Vifor. M.C.P. has received research grants or consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Napp Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Roche and SQ Innovations; has served on committees for AbbVie, Akero, Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, New Amsterdam, Novo Nordisk, Resverlogix and Teikoku; and is Director of Global Clinical Trial Partners. S.J.S. reports receiving consulting fees from Abbott, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Eli Lilly, Merck, Metabolic Flux, MyoKardia, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya and United Therapeutics. S.V. reports speaking honoraria and/or consulting fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, Novartis, Merck, PhaseBio, HLS Therapeutics, Amarin, Eli Lilly, Janssen, Pfizer, TIMI, Canadian Medical and Surgical Knowledge Translation Research Group. W.A. reports honoraria and/or consulting fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis and Novo Nordisk. F.Z.A. reports honoraria and/or consulting fees from Abbott, AstraZeneca, Medtronic, Novo Nordisk, Occlutech, Pharmacosmos and Vifor. V.C. reports speaker fees from AstraZeneca, Boehringer Ingelheim, Cipla, Dr. Reddy's, Lupin, Novartis, Novo Nordisk, Mankind, Pfizer, Sanofi, Sun Pharma and Torrent. J.E. reports research support for trial leadership from American Regent, Applied Therapeutics, Bayer, Cytokinetics, Merck and Novo Nordisk; honoraria for consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk and Otsuka; and service as an advisor to US2.ai. M.F. reports no conflicts of interest. H.I. reports honoraria and/or consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Mochida, Novartis and Novo Nordisk. M.L. reports honoraria and/or consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Ewopharma, Gedeon Richter, Novartis, Novo Nordisk, Roche and Servier. V.M. reports consulting fees from Bayer, Merck Sharp & Dohme and Novo Nordisk; research grants from Regeneron; and research support from the National Institute for Research of Metabolic and Cardiovascular

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Additional information

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Correspondence and requests for materials should be addressed to Mikhail N. Kosiborod.

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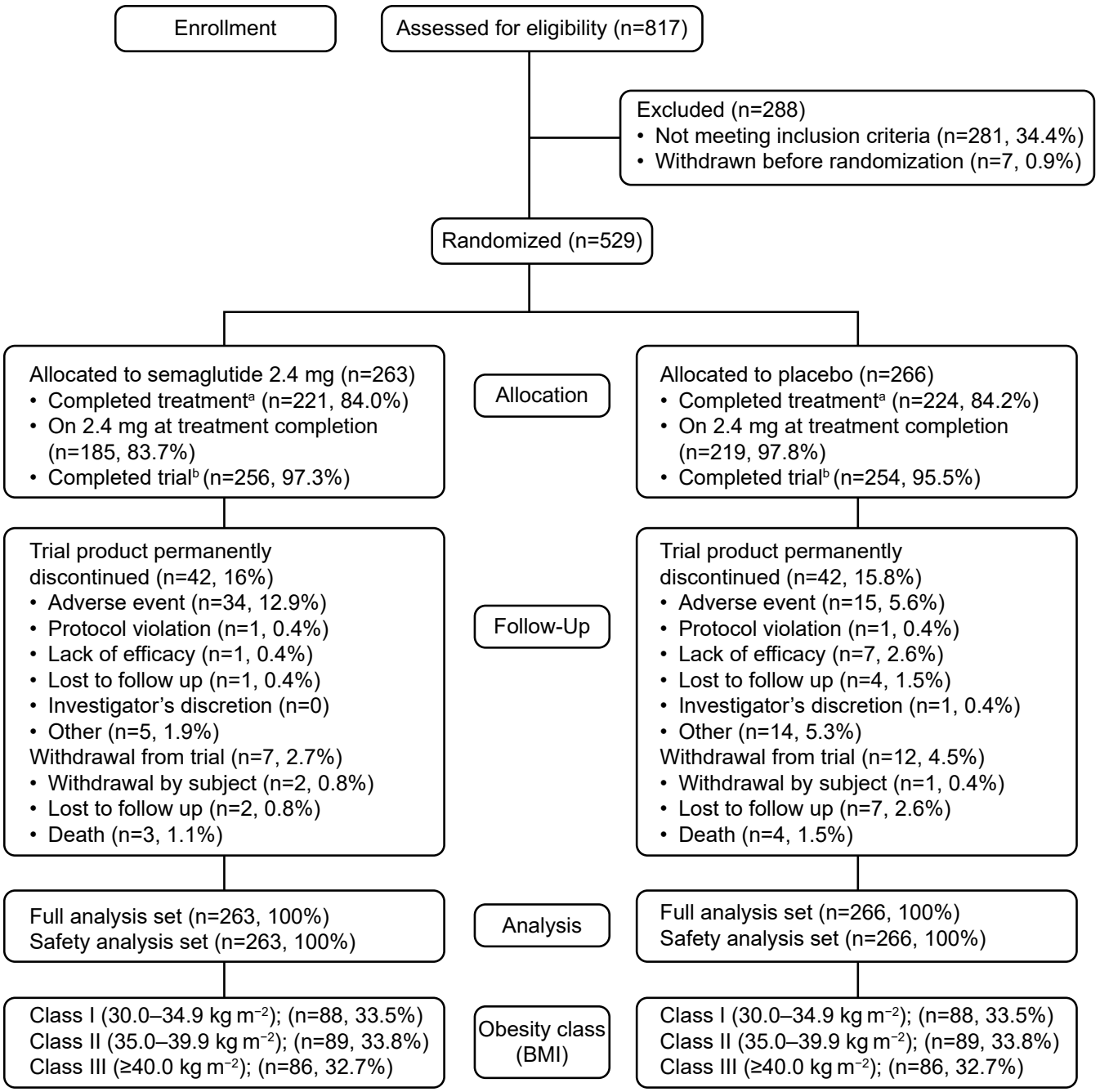
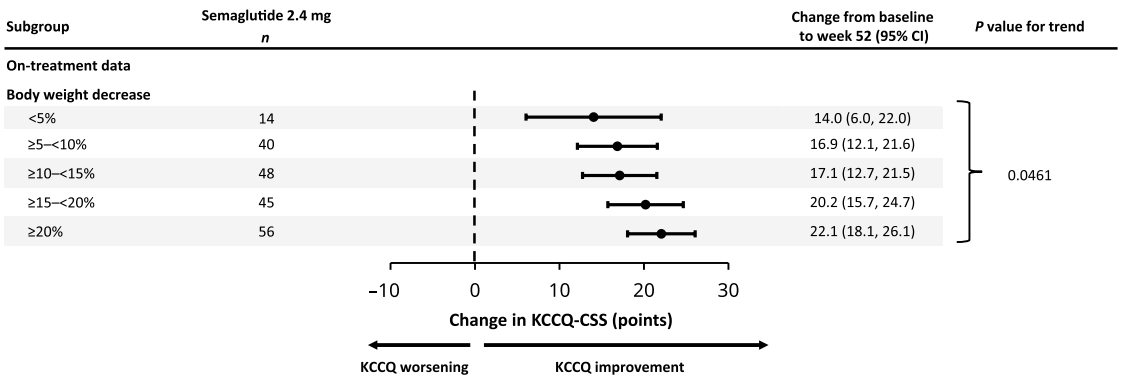


[a]On treatment at week 52. [b]Attended follow up visit at week 57.

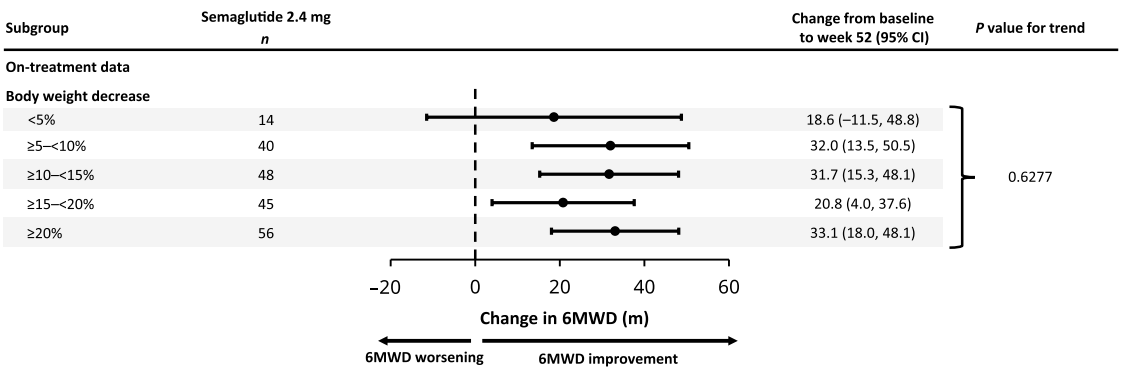
Extended Data Fig. 1 | Participant flow diagram.

https://doi.org/10.1038/s41591-023-02526-x

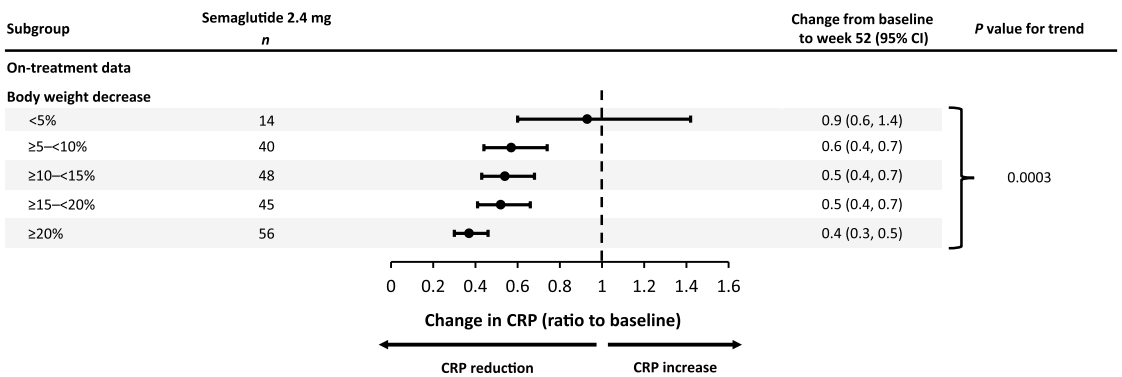
2a Relationship between weight loss with semaglutide and change in KCCQ-CSS



2b Relationship between weight loss with semaglutide and change in exercise function



2c Relationship between weight loss with semaglutide and change in inflammation



Extended Data Fig. 2 | Relationship between the magnitude of body weight reduction on semaglutide with change in KCCQ-CSS (a); 6MWD (b); and ratio of CRP to baseline (c) in the on-treatment (per protocol) analysis. Data are point estimates and 95% CIs. Tests for trend are based on an F-test; *P* values are two-sided.

nature portfolio

Corresponding author(s): Mikhail Kosiborod

Last updated by author(s): 28 July 2023

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☑	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☑	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☑	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☑	A description of all covariates tested
☐	☑	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☑	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☑	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☑	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☑	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☑	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	eCRF (Inform version 7.0.0.1.41); the system for randomization was Calyx Interactive Response Technology (IRT).
Data analysis	Statistics software - SAS V9.4 and R

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion, and approval of the product and product use in the European Union and the USA. Individual participant data will be shared in data sets in a de-identified/anonymized format.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biologic sex was reported for trial participants; information on gender was not collected.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were reported for trial participants.
Population characteristics	Reported in Table 1.
Recruitment	The trial was conducted at 96 sites in 13 countries (Asia, Europe, North and South America). All potentially eligible patients were invited to take part, thereby minimizing any potential self-selection bias.
Ethics oversight	Institutional Review Boards/ethics committees approved the study at all sites. The list of participating sites is in the Supplementary Appendix.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☑ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We estimated that a sample size of 516 participants will provide 90% power for the first dual primary endpoint of change in KCCQ-CSS, and more than 99% power for the second dual primary endpoint of change in body weight, assuming a mean difference of approx. 4.1 points in KCCQ-CSS and approx. 9.9% in body weight between the two treatment groups. final sample size was 529 participants.
Data exclusions	Per the statistical analysis plan, in the on-treatment analyses, data from patients who discontinued study medication prematurely were censored at the time of discontinuation.
Replication	This is an international, randomized, double-blind placebo-controlled trial; thus, replication is not applicable.
Randomization	1:1
Blinding	Participants, care providers, investigators and study staff, and outcomes assessors were blinded to group allocation during data collection and analysis.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing	
Data exclusions	
Non-participation	
Randomization	

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing and spatial scale	
Data exclusions	
Reproducibility	
Randomization	
Blinding	

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	
Location	
Access & import/export	
Disturbance	

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☑	☐ Antibodies
☑	☐ Eukaryotic cell lines
☑	☐ Palaeontology and archaeology
☑	☐ Animals and other organisms
☐	☑ Clinical data
☑	☐ Dual use research of concern
☑	☐ Plants

Methods

n/a	Involved in the study
☑	☐ ChIP-seq
☑	☐ Flow cytometry
☑	☐ MRI-based neuroimaging

Antibodies

Antibodies used	
Validation	

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	
Authentication	
Mycoplasma contamination	
Commonly misidentified lines (See ICLAC register)	

Palaeontology and Archaeology

Specimen provenance	
Specimen deposition	
Dating methods	

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	
Wild animals	
Reporting on sex	
Field-collected samples	
Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04788511
Study protocol	Included with submission
Data collection	The trial was conducated at 96 sites in 13 countries (Asia, Europe, North and South America) between March 19, 2021, and March 9, 2022. All potentially eligible patients were invited to take part, thereby minimizing any potential self-selection bias.
Outcomes	All of the primary and secondary outcomes, and the statistical methodologies used to analyze them, were prespecified in the Statistical Analysis Plan. All statistical analyses performed for all outcomes measures were thus predefined.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☑	☐	Public health
☑	☐	National security
☑	☐	Crops and/or livestock
☑	☐	Ecosystems
☑	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☑	☐	Demonstrate how to render a vaccine ineffective
☑	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☑	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☑	☐	Increase transmissibility of a pathogen
☑	☐	Alter the host range of a pathogen
☑	☐	Enable evasion of diagnostic/detection modalities
☑	☐	Enable the weaponization of a biological agent or toxin
☑	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks

Novel plant genotypes

Authentication

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication.

Files in database submission

Genome browser session
(e.g. UCSC)

Methodology

Replicates

Sequencing depth

Antibodies

Peak calling parameters

Data quality

Software

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Instrument

Software

Cell population abundance

Gating strategy

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Design specifications

Behavioral performance measures

Imaging type(s)

Field strength

Sequence & imaging parameters

Area of acquisition

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software

Normalization

Normalization template

Noise and artifact removal

Volume censoring

Statistical modeling & inference

Model type and settings

Effect(s) tested

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

(See Eklund et al. 2016)

Correction

Models & analysis

n/a	Involved in the study
☑	☐ Functional and/or effective connectivity
☑	☐ Graph analysis
☐	☑ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Graph analysis

Multivariate modeling and predictive analysis

Multivariable regression and multivariable linear regression analyses were performed to determine independent relationships between baseline BMI and baseline outcome measures prior to treatment, and between change in body weight and changes in study outcomes (please see Methods section for further details).