JACC: HEART FAILURE VOL. ■, NO. ■, 2023

ORIGINAL RESEARCH PAPER

Design and Baseline Characteristics of STEP-HFpEF Program Evaluating Semaglutide in Patients With Obesity HFpEF Phenotype

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ABSTRACT

BACKGROUND The majority of patients with heart failure with preserved ejection fraction (HFpEF) have the obesity phenotype, but no therapies specifically targeting obesity in HFpEF exist.

OBJECTIVES The aim of this study was to describe the design and baseline characteristics of 2 trials of semaglutide, a glucagon-like peptide-1 receptor agonist, in patients with the obesity HFpEF phenotype: STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF; NCT04788511) and STEP-HFpEF DM (Semaglutide Treatment Effect in People with obesity and HFpEF and type 2 diabetes; NCT04916470).

METHODS Both STEP-HFpEF and STEP-HFpEF DM are international multicenter, double-blind, placebo-controlled trials that randomized adults with HFpEF and a body mass index ≥30 kg/m^2 to once-weekly semaglutide at a dose of 2.4 mg or placebo. Participants were eligible if they had a left ventricular ejection fraction (LVEF) ≥45%; New York Heart Association (NYHA) functional class II to IV; a Kansas City Cardiomyopathy Questionnaire (KCCQ)-Clinical Summary Score (CSS) <90 points; and ≥1 of the following: elevated filling pressures, elevated natriuretic peptides plus structural echocardiographic abnormalities, recent heart failure hospitalization plus ongoing diuretic use, and/or structural abnormalities. The dual primary endpoints are the 52-week change in the KCCQ-CSS and body weight.

RESULTS In STEP-HFpEF and STEP-HFpEF DM (N = 529 and N = 617, respectively), nearly half were women, and most had severe obesity (median body mass index of 37 kg/m^2) with typical features of HFpEF (median LVEF of 57%, frequent comorbidities, and elevated natriuretic peptides). Most participants received diuretic agents and renin-angiotensin blockers at baseline, and approximately one-third were on mineralocorticoid receptor antagonists. Sodium-glucose cotransporter-2 inhibitor use was rare in STEP-HFpEF but not in STEP HFpEF DM (32%). Patients in both trials had marked symptomatic and functional impairments (KCCQ-CSS ~59 points, 6-minute walking distance ~300 m).

CONCLUSIONS In total, STEP-HFpEF program randomized 1,146 participants with the obesity phenotype of HFpEF and will determine whether semaglutide improves symptoms, physical limitations, and exercise function in addition to weight loss in this vulnerable group. (J Am Coll Cardiol HF 2023;■:■–■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2023.05.010

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CRP = C-reactive protein

6MWD = 6-minute walking distance

AE = adverse event

GLP-1RA = glucagon-like peptide-1 receptor agonist

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular events

NP = natriuretic peptide

NT-proBNP = N-terminal pro-B-type natriuretic peptide

QOL = quality of life

SBP = systolic blood pressure

SGLT2 = sodium-glucose cotransporter-2

T2D = type 2 diabetes

Heart failure with preserved ejection fraction (HFpEF) represents more than half of all heart failure (HF) cases,[1] is a leading cause of morbidity and mortality, and is associated with a high burden of symptoms and physical limitations.[2] The prevalence of HFpEF is increasing because of population aging and rising prevalence of obesity and type 2 diabetes (T2D)[3]; yet, despite this rapidly increasing economic and health care burden, few treatments have been shown to improve outcomes.[4,5]

HFpEF is commonly a consequence of obesity and associated metabolic and hemodynamic derangements.[3,6-12] Patients with the obesity phenotype represent the majority of those with HFpEF and have a unique phenotype.[12-15] Compared with the nonobese phenotype, individuals with the obese phenotype of HFpEF display increased plasma volume and stressed blood volume, more concentric left ventricular remodeling and high prevalence of hypertension (which in itself is an important factor for the development and progression of HFpEF), more right ventricular dysfunction, increased epicardial fat thickness, and higher total epicardial heart volume,[12,16] leading to greater symptom burden, poorer functional capacity, and more severely impaired quality of life (QOL).[17,18]

One of the likely reasons for the lack of effective therapies in HFpEF is that no currently used HF therapies directly target the most fundamental derangement leading to HFpEF (ie, obesity). In patients with the obesity phenotype of HFpEF, caloric restriction led to 7% weight loss and improved exercise capacity and health status as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[6] Observational studies have shown that clinically meaningful weight loss may result in substantial reductions in filling pressures and improvements in cardiac function, which would be expected to improve symptoms, physical limitations, and QOL and reduce clinical events.[19,20]

No previous clinical trials have examined pharmacotherapy for weight loss as a potential intervention for the obesity phenotype of HFpEF. The emergence of potent long-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs) represents a unique opportunity to develop a novel treatment option for the obesity phenotype of HFpEF.[21,22] In previous studies, semaglutide once weekly produced substantial weight loss in individuals with overweight and obesity with and without T2D with associated improvements in multiple cardiometabolic risk factors (including systolic blood pressure [SBP] and diastolic blood pressure).[21,23,24] In addition, in individuals with T2D, semaglutide significantly reduced the risk of major adverse cardiovascular events (MACE).[25]

Collectively, these findings highlight that obesity is a key driver of HFpEF development and progression. We describe the design and baseline characteristics of the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF) program in which we aim to test the hypothesis that treatment with once-weekly subcutaneous semaglutide at a dose of 2.4 mg will improve symptoms, physical limitations, and exercise function as measured by the KCCQ and the 6-minute walking distance (6MWD), along with promoting weight loss, in individuals with the obesity phenotype of HFpEF.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT POPULATION. The STEP-HFpEF program includes 2 randomized, international, multicenter, double-blind, placebo-controlled trials in individuals with the obesity phenotype of HFpEF: STEP-HFpEF (Semaglutide

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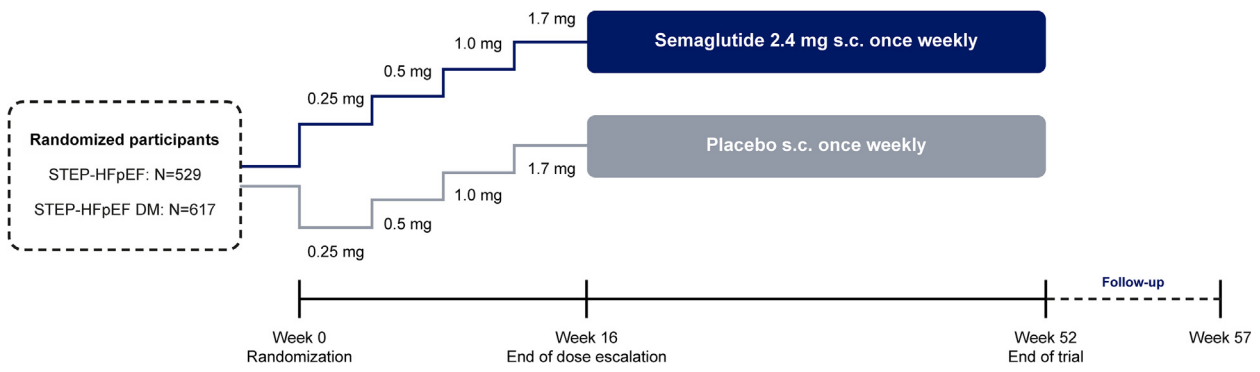
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 16, 2023; revised manuscript received May 15, 2023, accepted May 15, 2023.

FIGURE 1 **STEP-HFpEF Trial Program Design**



STEP-HFpEF = Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction; STEP-HFpEF DM = Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction and type 2 diabetes; s.c. = subcutaneous.

Treatment Effect in People with obesity and HFpEF; NCT04788511) (among those with obesity and HFpEF and without diabetes) and STEP-HFpEF DM (Semaglutide Treatment Effect in People with obesity and HFpEF and type 2 diabetes; NCT04916470) (among those with obesity, HFpEF, and T2D). In both trials, eligible participants were randomized 1:1 to receive either semaglutide 2.4 mg administered subcutaneously or matching placebo once weekly as an add-on to standard of care (**Figure 1**). Randomization was stratified by baseline body mass index (BMI) (<35.0 kg/m^2 or ≥35.0 kg/m^2). Both trials included a screening visit to assess eligibility followed by a randomization visit for those who were found to be eligible and agreed to participate. After randomization, there was a 16-week dose escalation period designed to minimize gastrointestinal adverse events (AEs) with a dose increase every fourth week until the maximally tolerated dose was reached. Hereafter, a study visit took place every eighth week until the end of treatment (week 52), with a follow-up period of 5 weeks after the end of treatment.

The full inclusion and exclusion criteria are shown in Supplemental Table 1. Participants in both trials were eligible if they had a left ventricular ejection fraction (LVEF) ≥45%; NYHA functional class II to IV; KCCQ-Clinical Summary Score (CSS) <90 point; and ≥1 of the following: 1) elevated filling pressures (based on right heart catheterization or remote pulmonary artery pressure sensor technology); 2) elevated natriuretic peptide (NP) levels (with thresholds stratified by baseline BMI) plus echocardiographic abnormalities; or 3) HF hospitalization in the previous 12 months plus requirement for ongoing diuretic agents and/or echocardiographic abnormalities. Key exclusion criteria were prior or planned bariatric surgery; self-reported change in body weight >11 lbs (5 kg) within 90 days before randomization, a recent (within previous 30 days) adverse cardiovascular event or HF hospitalization, or SBP >160 mm Hg at screening. Patients were excluded from STEP-HFpEF if they had a glycated hemoglobin level ≥6.5% and from STEP-HFpEF DM if their glycated hemoglobin was >10%.

A subset of randomized participants underwent echocardiography assessment at randomization and during follow-up and was included in the echocardiography substudy.

STUDY GOVERNANCE. The STEP-HFpEF trial program is sponsored by Novo Nordisk. The design and protocols of both trials were developed and study procedures operationalized through a close collaboration between the academic members of the steering committee and the trial sponsor. The steering committee, which included academic leaders and representatives from Novo Nordisk, is also primarily responsible for the trial-related academic publications. A global expert panel provided academic, medical, and operational input at a country level. An external, independent, and blinded events committee oversaw the adjudication of predefined clinical events.

Both trials were approved by the regulatory authorities and ethics committees in each participating country/institution as applicable. Informed consent was obtained from all participating individuals before the initiation of study procedures. The trials were conducted in accordance with the International Council for Harmonisation E6(R1) Guidelines of Good Clinical Practice and the Declaration of Helsinki.

TABLE 1 Primary and Secondary Endpoints for the STEP-HFpEF and STEP-HFpEF DM Trials

Primary endpoints
Change in KCCQ-CSS
Change in body weight
Secondary endpoints
Change in 6MWD
Hierarchical composite of • Time to all-cause death • Number of HF events requiring hospitalization or urgent HF visit • Time to first HF event requiring hospitalization or urgent HF visit • Difference at least 15 in KCCQ-CSS change from baseline to 52 wks • Difference at least 10 in KCCQ-CSS change from baseline to 52 wks • Difference at least 5 in KCCQ-CSS change from baseline to 52 wks • Difference at least 30 m in 6MWD change from baseline to 52 wks (assessed by the win ratio)
Change in C-reactive protein
Supportive secondary endpoints
Subjects achieving ≥10%, ≥15%, or ≥20% weight loss
Subjects improving ≥5 or ≥10 points in KCCQ-CSS
Change in KCCQ overall summary score
Subject achieving threshold for clinically meaningful within-subject change in KCCQ-CSS
Subject achieving threshold for clinically meaningful within-subject change in 6MWD
Change in SBP
Change in waist circumference
Exploratory endpoints
Change in antihypertensive medication
Change in loop diuretic medication
Change in NT-proBNP
Change in EQ-5D-5L score
Subject worsening by ≥5 or ≥10 points in KCCQ-CSS
Subject improving by ≥5 or ≥10 or ≥15 points in KCCQ-CSS
Subject worsening by ≥5 or ≥10 points in KCCQ overall summary score
Change in subscales of KCCQ (total symptom score, physical limitations score, social limitations score, and health-related quality of life)
Subject experiencing deterioration in NYHA functional class
Time to first HF event (hospitalization or urgent visit)

6MWD = 6-minute walking distance; CSS = Clinical Summary Score; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-brain type natriuretic peptide; SBP = systolic blood pressure; STEP-HFpEF = Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction; STEP-HFpEF DM = Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction and type 2 diabetes.

OUTCOMES. A full listing of the primary, confirmatory secondary, supportive secondary, and exploratory endpoints is provided in Table 1.

Primary objective and endpoints. The primary objective of the study is to investigate the effects of once-weekly semaglutide 2.4 mg on physical function, symptoms, and body weight compared with placebo, both added to standard of care, in participants with the obesity phenotype of HFpEF. The corresponding dual primary endpoints are: 1) a change in the KCCQ-CSS from baseline to 52 weeks; and 2) a percent change in body weight from baseline to 52 weeks.

The KCCQ is a standardized 23-item, self-administered instrument that quantifies HF-related symptoms (frequency, severity, and recent change), physical function, QOL, and social function.[26] For each domain, the validity, reproducibility, responsiveness, and interpretability have been independently established for both HF with reserved ejection fraction and HFpEF populations.[27] Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status.[28] The KCCQ-CSS includes the symptom and physical function domains of the KCCQ.

Confirmatory secondary objectives and endpoints. The confirmatory secondary objectives of the program are to investigate the effects of once-weekly semaglutide 2.4 mg on the overall clinical benefit, 6MWD, and inflammation as reflected by C-reactive protein (CRP). The corresponding confirmatory secondary endpoints are listed in Table 1 and include the hierarchical composite endpoint of the total clinical benefit (comprising all-cause death, HF events, several thresholds for change in the KCCQ-CSS from baseline to 52 weeks, and a change in the 6MWD of 30 m or more from baseline to 52 weeks), the change in the 6MWD from baseline to 52 weeks, and the change in CRP from baseline to 52 weeks.

Supportive secondary and exploratory objectives and endpoints. The supportive secondary and exploratory objectives include the effects of semaglutide on various thresholds of weight loss and the KCCQ-CSS, 6MWD, effects on other domains of the KCCQ and additional patient-reported outcomes, change in blood pressure and waist circumference, change in diuretic and blood pressure medications, HF biomarkers, and effects on HF events. The corresponding confirmatory secondary and exploratory endpoints are listed in Table 1.

Safety events. The following safety events were collected: all serious AEs and the following AEs irrespective of seriousness: AEs leading to premature treatment discontinuation, AEs of special interest, and AEs related to COVID-19. All deaths and all HF events (hospitalizations and urgent visits) were adjudicated.

Echocardiographic substudy. A list of echocardiographic substudy endpoints as well as a comprehensive listing of echocardiographic variables assessed (per the imaging protocol) are included in the Supplemental Methods.

STATISTICAL CONSIDERATIONS. Sample size and power calculations. For the STEP-HFpEF trial, it is estimated that a sample size of 516 participants will provide 90% power for the first dual primary endpoint of change in the KCCQ-CSS and more than 99% power for the second dual primary endpoint of change in body weight, assuming a mean difference

of ~4.1 points in the KCCQ-CSS and ~9.9% in body weight between the 2 treatment groups and with other assumptions as specified in Supplemental Table 2. Power calculations for the confirmatory secondary endpoints are also listed in Supplemental Table 2 and reveal sufficient power for all of these outcomes. The corresponding power calculations for STEP-HFpEF DM are shown in Supplemental Table 2, for which the planned sample size of 610 patients would provide sufficient power for all primary and confirmatory secondary endpoints.

Planned statistical approach. A strong control of the type I error rate will be applied in testing the dual primary and confirmatory secondary efficacy endpoints for each trial. First, the dual primary endpoints will be tested; for these 2 endpoints (KCCQ-CSS and body weight), the alpha split with 1% allocation for weight change and 4% for change in the KCCQ-CSS. The tests for the multiple endpoints will follow the weighted Holm-Bonferroni procedure such that if 1 of the 2 endpoints is superior, then the full alpha can be recycled for the other endpoint, and, hence, the remaining primary endpoint will be tested at the 5% significance level (2-sided) (**Figure 2**).

The confirmatory secondary endpoints will be tested as specified in **Figure 2**. All primary and secondary efficacy endpoints will be analyzed based on a treatment policy estimand, with a composite (estimand) strategy for cardiovascular deaths (and HF events) in relation to the KCCQ-CSS and 6MWD. The primary analysis model for change in the KCCQ-CSS (points) or change in body weight (%) is a linear regression analysis of covariance model with randomized treatment and with the baseline KCCQ-CSS (points) and baseline body weight (kg), respectively, as covariates. The BMI category ($<$35.0 kg/m^2 vs $\geq$35.0 kg/m^2) is included in the model because it is used as a stratification variable in the randomization scheme.

The estimated treatment difference between semaglutide and placebo will be reported together with the associated 2-sided 95% CI and the corresponding *P* value. The imputation approach is listed in the Supplemental Methods.

The analysis of the hierarchical composite endpoint will be based on direct comparisons of each participant randomized to semaglutide vs each participant randomized to placebo within each stratum.[29] For each of these participant pairs, a "treatment winner" based on a similar observation time will be declared based on the endpoint hierarchy (Supplemental Figure 1). The win ratio (ie, the proportion of winners randomized to semaglutide divided by the winners randomized to placebo) will be reported together with the associated 2-sided 95% CI and the corresponding *P* value. Furthermore, the contribution of wins and ties from each individual component of the hierarchical composite endpoint will be summarized.

Full details of all analyses including an "on-treatment" approach using mixed models (a hypothetical estimand), the approach to analyze the supportive secondary and exploratory endpoints, details of the imputation model, and the multiple testing strategy will be provided in a statistical analysis plan that will be completed before the end of the trial, before unblinding of the results. Analyses of the primary and confirmatory secondary endpoints will be validated by a sponsor-independent statistician.

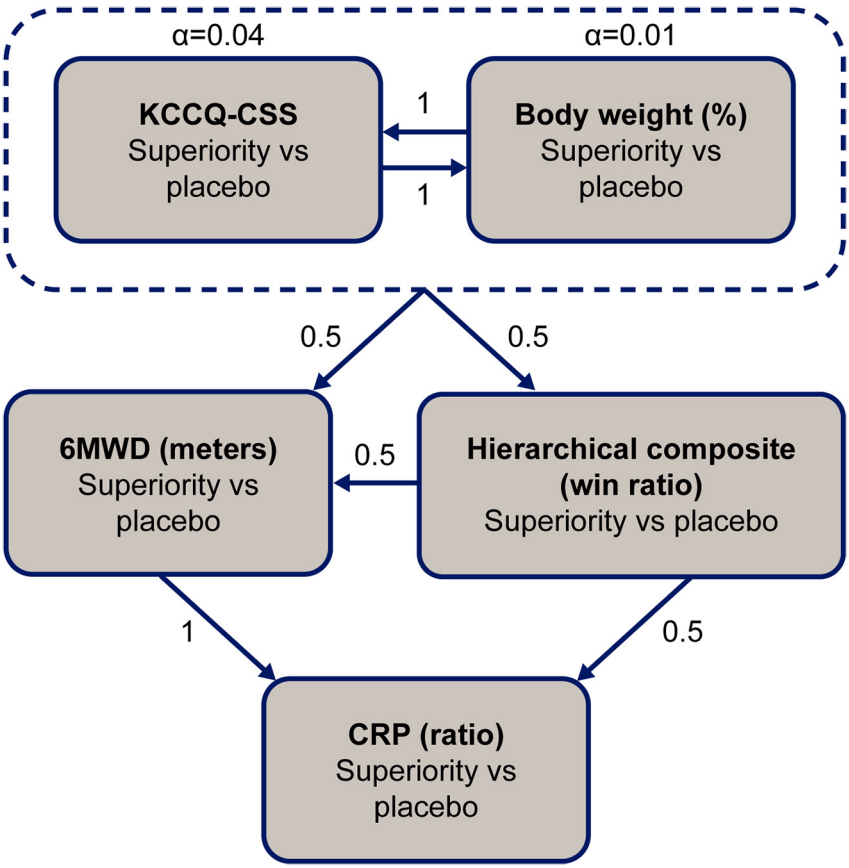
CURRENT STATUS AND BASELINE CHARACTERISTICS. Both STEP-HFpEF and STEP-HFpEF DM trials are fully enrolled and currently in the follow-up phases. In STEP-HFpEF, 529 participants were randomized across 83 sites in 13 countries between March 16, 2021, and February 24, 2022 (Supplemental Figure 2). In STEP-HFpEF DM, 617 participants were randomized across 108 sites in 16 countries between June 15, 2021, and August 19, 2022.

Baseline characteristics of participants in both trials are shown in **Table 2**. In both trials, approximately half of the participants were women, and the majority were White. In both trials, 75% of participants had HFpEF (ejection fraction $\geq$50%), and 25% had HF with mildly reduced ejection fraction (ejection fraction 45%-49%). The median BMI was ~37 kg/m^2, and comorbidities were common, including hypertension, coronary disease, and atrial fibrillation. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were elevated at baseline in both trials. The majority of participants in both trials were treated with beta-blockers, renin-angiotensin blockers, and diuretics, and about one-third received mineralocorticoid receptor antagonists. Although the use of a sodium-glucose cotransporter-2 (SGLT2) inhibitor was rare in STEP-HFpEF, nearly one-third of participants in the STEP-HFpEF DM trial were on an SGLT2 inhibitor at baseline. Importantly, patients in STEP-HFpEF and STEP-HFpEF DM had marked impairments in symptoms, physical limitations, and exercise function, with a baseline KCCQ-CSS of ~59 in both trials and a 6MWD of 320 m and 280 m, respectively.

DISCUSSION

HFpEF accounts for the majority of all HF,[1,2] and its prevalence is expected to continue increasing by ~1% per year.[30] Patients living with HFpEF experience a

FIGURE 2 **Tests of Superiority for the Primary and Confirmatory Secondary Endpoints**



If superiority is confirmed for both primary endpoints, the confirmatory secondary endpoint will be tested. The 5% alpha will be split between the 6-minute walking distance (6MWD) and the hierarchical composite endpoint. The hierarchical composite endpoint will be tested at the 2.5% significance level, and if superiority is confirmed, the 6MWD will be tested at the 3.75% significance level. If superiority is not confirmed for the hierarchical composite endpoint, the 6MWD will be tested at the 2.5% significance level. If superiority is confirmed for both, C-reactive protein (CRP) will be tested at the 5% significance level. If only 6MWD is confirmed, CRP will be tested at the 2.5% significance level. If only the hierarchical composite is confirmed, CRP will be tested at the 1.25% significance level. KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

high burden of symptoms and physical limitations and poor QOL. The extent of these limitations is more pronounced in individuals with HFpEF than those with HF with reserved ejection fraction.[31] Improving health status and exercise function is a key goal of management in patients with HFpEF and is increasingly emphasized by the practice guidelines and regulators.[32-34] To date, there has been a dearth of treatments shown to improve these important outcomes in patients with HFpEF, highlighting a major unmet clinical need.

One of the key reasons for the rising prevalence of HFpEF is the marked increase in the numbers of individuals living with obesity. A high BMI is an independent predictor of incident HFpEF, and more than 83% of patients with HFpEF are found to have either overweight or obesity.[35] Abundant evidence suggests that adipose tissue plays an overarching, pivotal role in the development, progression, and adverse outcomes in HFpEF. Excess adipose promotes inflammation, hypertension (an important factor in HFpEF development and progression), insulin resistance, and dyslipidemia and impairs diastolic and systolic left ventricular function and arterial, skeletal muscle, and physical function.[36,37] In established HFpEF, those with the obesity phenotype have a distinct clinical profile and hemodynamic features. A higher BMI is an independent predictor of

higher inflammatory markers, more pronounced hypertension, more severe symptoms, exercise intolerance, diastolic dysfunction, expanded plasma and blood volume, reduced venous capacitance, elevations in exercise pulmonary wedge pressures (but paradoxically lower NT-proBNP levels), and adverse hemodynamic response to diuresis.[12,16-18,38,39] Furthermore, the local restrictive effects of adipose accumulations in the pericardium play an important role in promoting hemodynamic derangements.[40]

Despite the fact that obesity is present in the majority of individuals with HFpEF[14,15] and the strong pathophysiologic links that exist between excess adipose, the associated metabolic derangements (including insulin resistance and inflammation), and worse outcomes, obesity is still commonly seen as a comorbidity rather than a root cause and a target for therapeutic intervention. Yet, observational studies evaluating lifestyle intervention-related and surgical weight loss show significant associated improvements in hemodynamics[19,20] and a substantially lower risk of incident HFpEF. In a clinical trial of caloric restriction and an exercise program, individuals with obesity and HFpEF experienced improvements in health status and exercise function along with meaningful weight loss.[6]

No clinical trials have examined weight loss with pharmacologic agents as a potential intervention for the obesity phenotype of HFpEF. In the past, this might have been explained by the lack of highly effective therapies that produce rapid and sustained weight loss without cardiovascular safety concerns. The emergence of potent weight loss treatments, such as long-acting GLP-1RAs, represents a unique opportunity to target body weight as a treatment target in the obese phenotype of HFpEF. Several clinical trials have demonstrated significant, clinically meaningful effects of once-weekly subcutaneous semaglutide at a dose of 2.4 mg on weight loss in individuals with overweight and obesity both with and without T2D (placebo-adjusted reduction of 14.4% and 7.6% in body weight at 68 weeks [trial product estimands], respectively).[21,23] Beyond weight loss, semaglutide has favorable effects on multiple metabolic and hemodynamic derangements common in the obesity phenotype of HFpEF, including insulin resistance, dysglycemia, inflammation, and hypertension, and in individuals with T2D, semaglutide reduces the risk of MACE, demonstrating not just its cardiovascular safety but also its cardiovascular superiority (**Central Illustration**).[25] Even larger cardiovascular

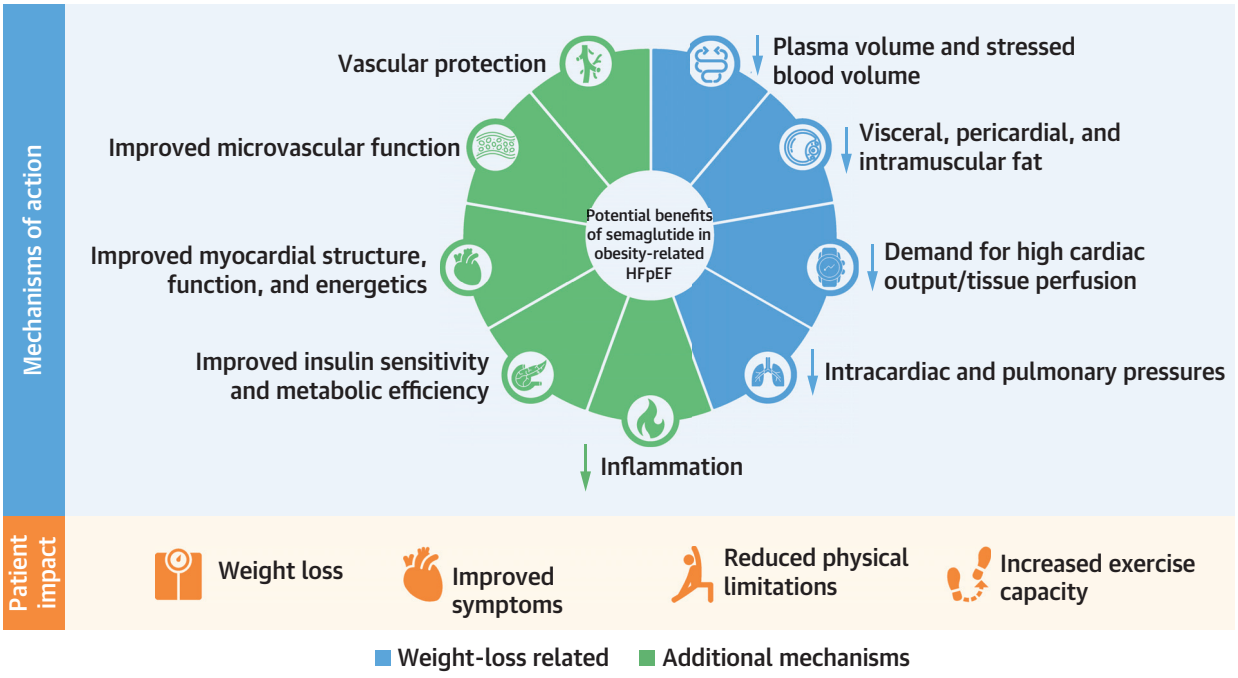
TABLE 2 Baseline Demographics and Clinical Characteristics of the STEP-HFpEF and STEP-HFpEF DM Trial Populations

	STEP-HFpEF (N = 529)	STEP-HFpEF DM (N = 627)
Female	297 (56.1)	274 (44.4)
Age, y	69 (62-75)	69 (63-75)
Ethnicity		
Hispanic or Latino	36 (6.8)	76 (12.3)
Not Hispanic or Latino	493 (93.2)	541 (87.7)
Race		
Asian	–	74 (12.0)
Black or African American	21 (4.0)	18 (2.9)
Other	1 (0.2)	5 (0.8)
White	507 (95.8)	519 (84.1)
Body weight, kg	105.1 (92.4-120.8)	102.7 (90.5-117.7)
BMI, kg/m^2	37.0 (33.7-41.4)	36.9 (33.6-41.4)
Waist circumference, cm	119.4 (110.5-128.0)	120.4 (112.0-130.0)
HbA_{1c}, %	NA	6.8 (6.2-7.6)
Diabetes duration, y	NA	10.5 ± 9.0
SBP, mm Hg	133 (121-144)	135 (125-144)
eGFR, mL/min/1.73 m^2	NA	69.0 (50.0-88.0)
NT-proBNP, pg/mL	452.4 (221.6-1,016)	495.6 (249.5-1,007)
LVEF, %	57.0 (50.0-60.0)	56.0 (50.0-60.0)
KCCQ-CSS	58.9 (41.7-72.9)	59.4 (43.8-72.0)
6MWT, m	320.0 (240.0-389.0)	280.0 (204.0-350.0)
Comorbidities at screening		
Atrial fibrillation	275 (52.0)	243 (39.4)
Hypertension	433 (81.9)	525 (85.1)
Coronary artery disease	180 (34.0)	269 (43.6)
Obstructive sleep apnea	65 (12.3)	51 (8.3)
NYHA functional class		
Class II	350 (66.2)	435 (70.5)
Class III-IV	179 (33.8)	181 (29.3)
Concomitant medications		
CV-related		
Beta-blockers	416 (78.6)	509 (82.5)
SGLT2 inhibitors	15 (2.8)	200 (32.4)
Diuretic agents	427 (80.7)	493 (79.9)
Loop diuretic agents	329 (62.2)	371 (60.1)
MRA	184 (34.8)	198 (32.1)
Thiazides	90 (17.0)	82 (13.3)
ACE inhibitor/ARB (ARNI)	396 (74.9)	492 (79.7)
ARNI	27 (5.1)	31 (5.0)
T2D-related		
Metformin	9 (1.7)[a]	436 (70.7)
Insulins	–	127 (20.6)
DPP-4	–	88 (14.3)
Sulfonylureas	–	103 (16.7)

Values are n (%), median (IQR), or mean ± SD and are from the full analysis set. [a]Participants treated with metformin because of prediabetes, impaired glucose tolerance, or polycystic ovary syndrome.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NA = not available; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Potential Mechanisms of Benefit for Semaglutide in Individuals With the Obesity Phenotype of HFpEF**



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HFpEF = heart failure with preserved ejection fraction.

outcome studies are evaluating the effects of semaglutide on MACE in individuals with overweight and obesity and no T2D,[41] but no previous trials have specifically evaluated the effects of semaglutide in individuals with the obesity phenotype of HFpEF.

The STEP-HFpEF program was specifically designed to address this important knowledge gap. Several design features of STEP-HFpEF should be highlighted. First, recognizing the well-described, inverse relationship between a higher BMI and lower NT-proBNP levels, we developed 3 distinct pathways in which patients could qualify for participation. Two of these pathways—documented elevated filling pressures (based on invasive measurements with right heart catheterization or remote sensor technology) and recent HF-related hospitalization combined with a continued need for diuretic therapy and/or structural echocardiographic abnormalities—allowed individuals with a clearly established clinical HFpEF syndrome to be enrolled regardless of NP levels. Furthermore, for those who qualified based on NT-proBNP levels and structural abnormalities, the NP thresholds were stratified by the baseline BMI (with still elevated but lower levels for those with a higher BMI).[42] Second, we selected a higher threshold of LVEF than most other HFpEF trial programs, recognizing that individuals with HFpEF and a higher BMI tend to have a higher ejection fraction[43] and that those with a higher LVEF represent a population in great need for additional efficacious treatments because most tested therapies (with a notable exception of SGLT2 inhibitors)[15,44,45] have previously failed to show significant benefits in this patient group.[46–53] Third, by focusing on patients with both a high BMI and KCCQ <90 points, we sought to identify a group with a substantial burden of symptoms and physical limitations because of the obesity HFpEF phenotype. Fourth, we designed the program that incorporates 2 parallel trials (in individuals with HFpEF with and without T2D) to establish whether the effects of semaglutide in the obesity HFpEF phenotype are consistent across the entire range of metabolic derangements and dysglycemia because the presence of diabetes may affect the metabolic and

weight loss response to GLP-1RA therapy. Finally, we captured a broad range of relevant key outcomes, including symptoms, physical limitations, and exercise function but also the total clinical benefit (captured in the hierarchical composite endpoints, which included clinical events) along with body weight and markers of inflammation. A number of supportive and exploratory endpoints will also allow us to evaluate the effects of semaglutide on a broad range of cardiometabolic and hemodynamic factors, including SBP, waist circumference, NP, NYHA functional class, and loop diuretic agent use, among others.

STUDY LIMITATIONS. STEP-HFpEF Program has some limitations. First, while approximately half of all participants are women, the proportion of nonwhite individuals is low. Second, the trials are primarily intended to evaluate the effects of semaglutide on symptoms, physical limitations and exercise function, rather than clinical events such as heart failure hospitalizations and urgent visits.

CONCLUSIONS

Patients with the obesity phenotype represent a growing majority of those with HFpEF and experience an especially high burden of symptoms and physical limitations. STEP-HFpEF is the first clinical trial program to specifically address obesity as a treatment target and, if successful, will likely change the therapeutic approach in this vulnerable patient group.

ACKNOWLEDGMENTS The development and formatting of the figures was provided by OPEN Health, funded by Novo Nordisk. The authors thank Søren Rasmussen (Novo Nordisk) for statistical support.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The STEP-HFpEF and STEP-HFpEF DM trials were funded by Novo Nordisk. Dr Kosiborod served as a consultant or on an advisory board for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received research grants from AstraZeneca and Boehringer Ingelheim; holds stocks in Artera Health and Saghmos Therapeutics; has received honorarium from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; and has received other research support from AstraZeneca. Dr Abildstrøm is employed by Novo Nordisk; and has shares in Novo Nordisk. Dr Borlaug has received research support from the National Institutes of Health and the United States Department of Defense; has received research grant funding from AstraZeneca, Axon, GlaxoSmithKline, Medtronic, Mesoblast, Novo Nordisk, Rivus, and Tenax Therapeutics; has served as a consultant for Actelion, Amgen, Aria, Axon Therapies, BD, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Eli Lilly, Imbria, Janssen, Merck, Novo Nordisk, NGM, NXT, and VADovations; and is named inventor (U.S. patent number 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure. Dr Butler 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, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, 3live, and Vifor. Dr Christensen is employed by Novo Nordisk; and has shares in Novo Nordisk. Dr Davies has acted as a consultant, advisory board member, and speaker for Boehringer Ingelheim, Lilly, Novo Nordisk, and Sanofi; is an advisory board member and speaker for AstraZeneca; is an advisory board member for Pfizer, Medtronic, and ShouTi Pharma Inc; is a speaker for Novartis, Sanofi, and Amgen; and has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Sanofi-Aventis, Eli Lilly, Boehringer Ingelheim, Janssen, and Novo Nordisk. Dr Hovingh is employed by Novo Nordisk and The Amsterdam University Medical Center; and has shares in Novo Nordisk. Dr Kitzman has served as a paid consultant for Novo Nordisk; and his institution has received grant awards from Novo Nordisk. Dr Lindegaard is employed by Novo Nordisk; and has shares in Novo Nordisk. Dr Møller is employed by Novo Nordisk; and has shares in Novo Nordisk. Dr Shah has been supported by research grants from the National Institutes of Health (U54 HL160273, R01 HL107577, R01 HL127028, R01 HL140731, and R01 HL149423); and 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, Lilly, Merck, Metabolic Flux, MyoKardia, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and United Therapeutics. Dr Treppendahl is employed by Novo Nordisk; and has shares in Novo Nordisk. Dr Verma has received 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, and Canadian Medical and Surgical Knowledge Translation Research Group. Dr Petrie has received research grants or consultancy fees from SQ Innovations, AstraZeneca, Roche, Boehringer Ingelheim, Pharmacosmos, Eli Lilly, Napp Pharmaceuticals, Novartis, and Novo Nordisk; has served on committees for AbbVie, Akero, Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Resverlogix, Teikoku, New Amsterdam, and Novo Nordisk; and is director of Global Clinical Trial Partners.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The obesity phenotype of HFpEF is common, but whether specifically targeting obesity can improve HFpEF outcomes is unknown.

TRANSLATIONAL OUTLOOK: STEP-HFpEF is the first trial program targeting the obesity phenotype of HFpEF and will determine whether treatment with semaglutide can improve symptoms, physical limitations, and exercise function in addition to weight loss in this group.

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KEY WORDS 6-minute walking distance, health status, HFpEF, Kansas City Cardiomyopathy Questionnaire, obesity, semaglutide, weight loss

APPENDIX For an expanded Methods section as well as supplemental tables, figures, and references, please see the online version of this paper.