JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Effect of Bimagrumab vs Placebo on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity

A Phase 2 Randomized Clinical Trial

Steven B. Heymsfield, MD; Laura A. Coleman, PhD, RD; Ram Miller, MD; Daniel S. Rooks, PhD; Didier Laurent, PhD; Olivier Petricoul, PhD; Jens Praestgaard, PhD; Therese Swan, PharmD; Thomas Wade, MD; Robert G. Perry, MD; Bret H. Goodpaster, PhD; Ronenn Roubenoff, MD, MHS

Abstract

IMPORTANCE Antibody blockade of activin type II receptor (ActRII) signaling stimulates skeletal muscle growth. Previous clinical studies suggest that ActRII inhibition with the monoclonal antibody bimagrumab also promotes excess adipose tissue loss and improves insulin resistance.

OBJECTIVE To evaluate the efficacy and safety of bimagrumab on body composition and glycemic control in adults with type 2 diabetes and overweight and obesity.

DESIGN, SETTING, AND PARTICIPANTS This double-masked, placebo-controlled, 48-week, phase 2 randomized clinical trial was conducted among adults with type 2 diabetes, body mass index between 28 and 40, and glycated hemoglobin (HbA_{1c}) levels between 6.5% and 10.0% at 9 US and UK sites. The trial was conducted from February 2017 to May 2019. Only participants who completed a full treatment regimen were included in analysis.

INTERVENTIONS Patients were randomized to intravenous infusion of bimagrumab (10 mg/kg up to 1200 mg in 5% dextrose solution) or placebo (5% dextrose solution) treatment every 4 weeks for 48 weeks; both groups received diet and exercise counseling.

MAIN OUTCOMES AND MEASURES The primary end point was least square mean change from baseline to week 48 in total body fat mass (FM); secondary and exploratory end points were lean mass (LM), waist circumference (WC), HbA_{1c} level, and body weight (BW) changes from baseline to week 48.

RESULTS A total of 75 patients were randomized to bimagrumab (n = 37; 23 [62.2%] women) or placebo (n = 38; 12 [31.6%] women); 58 (77.3%) completed the 48-week study. Patients at baseline had a mean (SD) age of 60.4 (7.7) years; mean (SD) BMI of 32.9 (3.4); mean (SD) BW of 93.6 (14.9) kg; mean (SD) FM of 35.4 (7.5) kg; and mean (SD) HbA_{1c} level of 7.8% (1.0%). Changes at week 48 for bimagrumab vs placebo were as follows: FM, −20.5% (−7.5 kg [80% CI, −8.3 to −6.6 kg]) vs −0.5% (−0.18 kg [80% CI, −0.99 to 0.63 kg]) ($P < .001$); LM, 3.6% (1.70 kg [80% CI, 1.1 to 2.3 kg]) vs −0.8% (−0.4 kg [80% CI, −1.0 to 0.1 kg]) ($P < .001$); WC, −9.0 cm (80% CI, −10.3 to −7.7 cm) vs 0.5 cm (80% CI, −0.8 to 1.7 cm) ($P < .001$); HbA_{1c} level, −0.76 percentage points (80% CI, −1.05 to −0.48 percentage points) vs −0.04 percentage points (80% CI, −0.23 to 0.31 percentage points) ($P = .005$); and BW, −6.5% (−5.9 kg [80% CI, −7.1 to −4.7 kg]) vs −0.8% (−0.8 kg [80% CI, −1.9 to 0.3 kg]) ($P < .001$). Bimagrumab's safety and tolerability profile was consistent with prior studies.

CONCLUSIONS AND RELEVANCE In this phase 2 randomized clinical trial, ActRII blockade with bimagrumab led to significant loss of FM, gain in LM, and metabolic improvements during 48 weeks

(continued)

Key Points

Question What are the effects of bimagrumab, an antibody that blocks activin type II receptors and stimulates skeletal muscle growth, on total body fat mass and glycemic control in patients with type 2 diabetes and excess adiposity?

Findings In this phase 2 randomized clinical trial of 75 patients with type 2 diabetes and body mass index between 28 and 40 who received bimagrumab or placebo during 48 weeks along with diet and exercise counseling, those who received bimagrumab had a significantly larger decrease in total body fat mas and glycated hemoglobin and increase in lean mass compared with patients who received placebo.

Meaning These findings suggest that blockade of the activin receptor with bimagrumab could provide a novel pharmacologic approach for managing patients with type 2 diabetes with excess adiposity.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

in patients with overweight or obesity who had type 2 diabetes. ActRII pathway inhibition may provide a novel approach for the pharmacologic management of excess adiposity and accompanying metabolic disturbances.

TRIAL REGISTRATION ClinicalTrials.gov number: NCT03005288

JAMA Network Open. 2021;4(1):e2033457. doi:10.1001/jamanetworkopen.2020.33457

Introduction

Overweight and obesity are present in more than half of patients seen in primary care settings and are often accompanied by insulin resistance, chronic inflammation, and related comorbid diseases.[1,2] Excess adiposity can be successfully managed with lifestyle programs that promote weight loss,[3] although long-term success rates outside of specialized centers remain limited.[4,5] Additionally, only a small percentage of patients with severe obesity are candidates for bariatric surgical procedures.[6]

Combining lifestyle management with pharmacotherapy is increasingly recognized as an effective and safe treatment option for many patients with obesity.[3] Five medications have been approved for long-term use by the US Food and Drug Administration (FDA),[3] with 1 approval rescinded recently,[7] and several new weight loss drugs are in development.[8] A novel potential treatment for obesity and related metabolic disturbances is bimagrumab (BYM338; Novartis), a fully human monoclonal antibody that binds to the activin type II receptor (ActRII) and, through that mechanism, prevents the actions of natural ligands that negatively regulate skeletal muscle growth.[9,10] ActRII blockade in preclinical animal models also promoted actions outside of the skeletal muscles, including effects on brown adipose tissue (BAT) differentiation and activity.[9,10] A single intravenous dose of bimagrumab in human participants not only increased lean mass but significantly reduced total body fat mass (FM) and improved insulin sensitivity compared with placebo during a 10-week study period in healthy volunteers with insulin resistance who were not dieting.[11] These observations suggest that bimagrumab might represent a new approach for the treatment of patients with obesity and related metabolic disturbances. The aim of the current phase 2 study was to determine the efficacy and safety of bimagrumab on body composition and glycemic control in adult patients with overweight or obesity and type 2 diabetes.

Methods

Trial Design and Oversight

This phase 2 randomized clinical trial was conducted at 9 sites in the United States and United Kingdom from February 2017 through May 2019. A list of sites and principal investigators is provided in eAppendix 1 in Supplement 1. Approval was obtained from the institutional review board at each site, and participants provided written informed consent prior to participation. The trial protocol and statistical analysis plan are available in Supplement 2. The study was designed, implemented, and reported in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, in compliance with applicable local regulations, and with the ethical principles established in the Declaration of Helsinki.[12] An external data monitoring committee reviewed safety data from the study at regular intervals. This study is a primary analysis reported in line with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Trial Participants

Patients with type 2 diabetes were eligible for inclusion if they were aged 18 to 75 years; had a glycated hemoglobin (HbA_{1c}) between 6.5% and 10.0% (to convert to proportion of total

hemoglobin, multiply by 0.01), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) between 28 and 40, and stable body weight between 65 and 140 kg; were not taking antidiabetic therapy at the time of screening or were receiving stable metformin monotherapy, dipeptidyl peptidase 4 (DPP4) inhibitor monotherapy, or combination therapy of metformin and a DPP4 inhibitor. These medications were allowed because of their generally weight-neutral effect. The upper limit of body weight was restricted to 140 kg and a capped dose was selected for body weights greater than 120 kg because of the uncertainty of the effect of greater body weight and body composition on the exposure and safety profile of bimagrumab.

Major exclusion criteria included conditions related to safety; diabetes other than type 2 or history of severe hypoglycemic episodes; abnormal liver function tests or abnormal lipase or amylase levels; known history of severe liver disease or conditions with hepatotoxic potential; clinically significant cardiovascular conditions; malignant neoplasms; or history of any type of bariatric surgery. A complete list of inclusion and exclusion criteria is provided in eAppendix 2 in Supplement 1.

Trial Procedures

Eligible patients were randomized in a 1:1 ratio to receive either bimagrumab (10 mg/kg up to a maximum of 1200 mg in 5% dextrose solution) or placebo (5% dextrose solution) via 30-minute intravenous infusion, every 4 weeks for 48 weeks (12 doses) (**Figure 1**A). Allocation was randomized with parallel assignment intervention model and quadruple masking (participant, clinician, investigator, outcomes assessor).

Patients returned to the study site on day 14 for safety and tolerability monitoring and were asked to return for dosing and pharmacokinetic samples on selected days and for efficacy evaluations every 4 weeks during the treatment period (Figure 1A). The treatment period ended approximately 4 weeks after the last dose administration. After completion of the treatment period, patients had a follow-up period of 8 weeks, with regular monitoring for safety and efficacy.

Patients met with a registered dietitian in person at each monthly study visit, beginning with the screening visit and continuing until the end of treatment. Additionally, patients had virtual diet check-in visits in between monthly study visits. At each visit, a 24-hour diet recall was obtained to guide dietary counselling. Patients were advised to follow a calorie-restricted (ie, 500 calorie daily reduction) diet containing approximately 45% to 50% of calories as carbohydrate; 20% to 25%, protein; and 30%, fat. Participants received counselling for physical activity and were encouraged to follow the American Diabetes Association walking program guidelines.[13,14] These interventions were initiated at screening, after eligibility was confirmed.

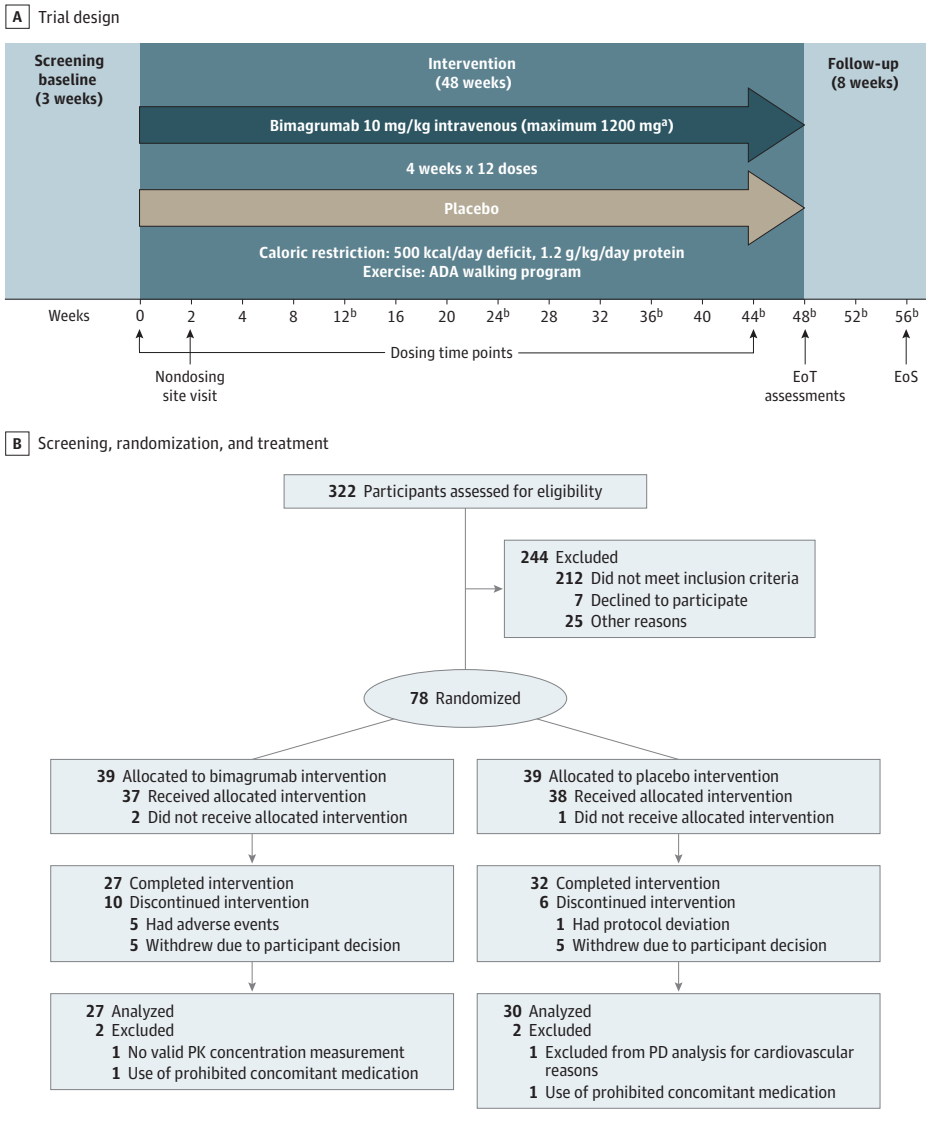
End Points

The primary end point was change from baseline to week 48 in total body FM measured by dual energy x-ray absorptiometry (DXA).[11] The secondary and exploratory efficacy end points at week 48 included change in diabetes status (HbA_{1c} level, homeostatic model assessment [HOMA2], quantitative insulin sensitivity check [QUICKI], and Matsuda Index)[15-17]; body weight and BMI; waist circumference and waist-to-hip ratio; body composition, including DXA-measured bone mineral-free lean mass, magnetic resonance imaging (MRI)–derived hepatic fat fraction,[18] and subcutaneous and abdominal visceral adipose tissue (eAppendix 3 in Supplement 1)[19]; metabolic status,[11,20,21] including the prespecified end points for exploring treatment effects of bimagrumab on metabolic biomarkers and cardiovascular risk factors (serum lipid levels, high-sensitivity C-reactive protein [hsCRP] level, interleukin 6 level, leptin level, adiponectin level, and blood pressure); and physical performance, including hand grip strength by dynamometry.[22] The MRI studies were optional according to patient tolerance and their fit within the imaging system's magnet. Safety and tolerability end points included the frequency and severity of adverse events, vital signs, electrocardiography, clinical laboratory measurements, antibimagrumab antibodies, and immunogenicity.

Statistical Analysis

All primary and secondary analyses were performed using a longitudinal mixed-effects model, with up to 12 measurements per individual in the mixed-effects model. This model had treatment group, time, and time × treatment group interaction as fixed effects. The baseline value of the dependent variable as well as baseline BMI were included in the model as covariates. An unstructured within-patient covariance was used. Missing observations were considered missing at random, and no imputation for missing data was used. Per the statistical analysis plan (Supplement 2), a sensitivity analysis was conducted to gauge the influence of a possible nonrandom missingness assumption on the primary end point (eAppendix 2 in Supplement 1). Least squares mean (LSM) estimates of the difference between treatment and placebo were computed at each point and reported with 2-sided 80% CIs as well as 1-sided *P* values for a treatment difference favoring bimagrumab compared with placebo. The use of the 10% 1-sided level of significance was driven by the study sponsor's internal decision-making and willingness to accept a liberal standard of evidence for declaring success and continuing the drug development effort.

Figure 1. Trial Design, Screening, Randomization, and Treatment



ADA indicates American Diabetes Association; EoS, end of study; EoT, end of treatment; PD, pharmacodynamics; and PK, pharmacokinetic.

[a] Five patients had dosage capped.

[b] PK visits.

A sample size of 68 recruited patients was targeted to enable at least 48 completers, with a maximum dropout rate of 20%. The sample size was chosen to provide 70% power to meet a primary end point at week 48 consisting of 2 criteria: (1) the difference between bimagrumab and placebo in total body FM would have to be significant at a 1-sided level of 10% and (2) the point estimate of the least square difference between bimagrumab and placebo total body FM would have to exceed 5 percentage points measured relative to the mean FM at baseline.

As a supportive analysis, the proportions of patients who reached at least 5% fat and weight loss were presented by treatment group. Statistical analyses were performed with the use of SAS version 9.4 (SAS Institute).

Results

Patients

Study start date was February 1, 2017, and the final data collection date for primary outcome measurement was March 21, 2019. Of the 322 patients screened, 75 were randomized and received in a 1:1 ratio either bimagrumab 10 mg/kg (37 participants) or placebo (38 participants) (Figure 1B). An additional 3 individuals were randomized, but they withdrew from the study prior to receiving the first dose of study medication. Major reasons for screening failure were HbA_{1c} level outside of required range (73 individuals), medical condition or laboratory finding out of range (30 individuals), low serum testosterone in men (27 individuals), and other (17 individuals). Overall, 58 patients (77.3%) completed the study. The reasons for study withdrawal included participant decision (11 individuals), adverse event (4 individuals), lost to follow-up (1 individual), and protocol violation (1 individual).

Demographic characteristics (**Table 1**) were similar between the 2 groups, except that 23 participants (62.2%) in the bimagrumab group were women, compared with 12 (31.6%) in the placebo group. As a result, baseline body weight was lower in patients in the bimagrumab vs placebo groups (mean [SD], 90.1 [14.2] kg vs 96.9 [15.0] kg). Baseline BMI, total body FM, and HbA_{1c} levels did not differ between groups. Background diabetes therapy (Table 1) was balanced between groups, with most patients treated with metformin. One exception was that 6 patients (16.2%) in the bimagrumab group were not on background diabetes therapy at study entry vs 2 patients (5.3%) in the placebo group.

Primary Efficacy End Point

At week 48, total body FM decreased 20.5% (−7.49 kg; 80% CI, −8.33 to −6.64 kg) in the bimagrumab group and 0.5% (−0.18 kg; 80% CI, −0.99 to 0.63 kg) in the placebo group, with a difference in total body FM of 7.31 kg (80% CI, −8.48 to −6.14; $P < .001$) (**Table 2** and **Figure 2**). The percentage of patients who lost at least 5% of total body FM in the bimagrumab vs placebo group at week 48 was 96% (25 of 26 patients) vs 21% (6 of 29 patients); at least 10% total body FM, 92% (24 of 26 patients) vs 10% (3 of 29 patients); and at least 15% total body FM, 77% (23 of 26 patients) vs 10% (3 of 29 patients). This difference was significant between treatment groups ($P < .001$).

Secondary, Exploratory, and Supportive End Points

Results for key secondary and exploratory efficacy end points are shown in Table 2. At week 48, the bimagrumab group gained 3.6% of lean mass (1.70 kg; 80% CI, 1.14 to 2.26 kg) compared with −0.8% (−0.4 kg; 80% CI, −1.0 to 0.1 kg) in the placebo group ($P < .001$), and body weight decreased by 6.5% (−5.90 kg; 80% CI, −7.08 to −4.71 kg) compared with a 0.8% decrease (−0.8 kg; 80% CI, −1.9 to 0.3 kg) in the placebo group ($P < .001$). The relatively large between-group total body FM and body weight differences at 48 weeks were accompanied by directionally similar differences in BMI (−2.19 [80% CI, −2.60 to −1.78] vs −0.28 [80% CI, −0.67 to 0.11]; $P < .001$), waist circumference (−9.0 cm [80% CI, −10.3 to −7.7 cm] vs 0.5 cm [80% CI, −0.8 to 1.7 cm]; $P < .001$), waist-to-hip ratio (−0.05 [80% CI, −0.06 to −0.04] vs 0.01 [0.00 to 0.02]; $P < .001$), hepatic fat fraction (−7.00% [80% CI,

−8.58% to −5.43%] vs −2.33% [80% CI, −4.16% to −0.51%]; *P* = .01), subcutaneous adipose tissue (−1.71 L [80% CI, −2.40 to −1.03 L] vs −0.52 L [−1.30 to 0.26 L]; *P* = .07), and abdominal visceral adipose tissue (−1.52 L [80% CI, −2.42 to −0.62 L] vs −0.01 L [−1.05 to 1.03 L]; *P* = .08). At week 48, 17 of 26 patients (65.4%) receiving bimagrumab achieved at least 5% weight loss vs 3 of 29 (10.3%) receiving placebo (2-sided *P* < .001).

Due to the asymmetrical sex distribution in the 2 randomized groups, we conducted a subanalysis for lean mass and FM, comparing treatment and placebo groups for men and women separately. The reduction in FM at week 48 was similar for men and women (placebo-corrected fat loss for women: −18.4%; −6.20 kg; 80% CI, −8.60 to −3.81 kg; *P* = .003; for men: −22.1%; −7.53 kg; 80% CI, −8.94 to −6.13 kg; *P* < .001.) The placebo-corrected change in lean mass in patients treated with bimagrumab was greater for men (5.1%; 2.76 kg; 80% CI, 1.66 to 3.85 kg; *P* = .002) vs women (2.5%; 0.98 kg; 80% CI, −0.15 to 2.11 kg; *P* = .26).

Significant improvements in metabolic markers were observed in the bimagrumab group vs the placebo group (48-week HbA_{1c} level: −0.76% [80% CI, −1.05% to −0.48%] vs 0.04% [80% CI, −0.23% to 0.31%]; *P* = .005; 36-week QUICKI: 0.01 [80% CI, 0.01 to 0.01] vs 0.00 [80% CI, 0.00 to 0.00]; *P* = .03). The difference between the bimagrumab and placebo group for 36-week HOMA2 and 48-week Matsuda Index were not significant (Table 2). We did not observe any significant changes in the use of background diabetes medications (metformin or DPP4 inhibitor).

Treatment with bimagrumab did not result in significant changes in serum lipid or hsCRP levels from baseline to week 48 (eTable 1 in Supplement 1). Serum leptin and interleukin 6 levels decreased and adiponectin levels increased in patients treated with bimagrumab compared with those who received placebo (eTable 2 and eFigure 1 in Supplement 1). Hand grip strength was lower in the bimagrumab group at baseline, as expected because of the imbalance in the groups by sex, and there

Table 1. Baseline Characteristics of the Patients[a]

Characteristic	No. (%)		
	Bimagrumab (n = 37)	Placebo (n = 38)	Total (N = 75)
Age, mean (SD) [range], y	60.7 (7.5) [46-73]	60.2 (8.0) [42-76]	60.4 (7.7) [42-76]
Sex			
Women	23 (62)	12 (32)	35 (47)
Men	14 (38)	26 (68)	40 (53)
Race			
Black or African American	6 (16)	9 (24)	15 (20)
Other	1 (3)	0	1 (1)
White	30 (81)	27 (71)	57 (76)
Asian	0	1 (3)	1 (1)
Unknown	0	1 (3)	1 (1)
Ethnicity			
Hispanic or Latino	27 (73)	25 (66)	52 (69)
Not Hispanic or Latino	9 (24)	12 (32)	21 (28)
Not reported	1 (3)	1 (3)	2 (3)
Weight, mean (SD) [range], kg	90.1 (14.2) [66-115]	96.9 (15.0) [73-131]	93.6 (14.9) [66-131]
Height, mean (SD) [range], cm	165.6 (10.5) [148-188]	170.9 (10.0) [148-190]	168.3 (10.5) [148-190]
BMI, mean (SD) [range]	32.7 (3.2) [28-40]	33.1 (3.5) [28-40]	32.9 (3.4) [28-40]
Waist-to-hip ratio, mean (SD) [range]	0.98 (0.07) [0.84-1.13]	0.99 (0.06) [0.83-1.10]	0.99 (0.07) [0.83-1.13]
HbA_{1c} level, mean (SD) [range], %	7.99 (1.03) [6.6-10.1]	7.66 (0.95) [6.4-10.2]	7.82 (1.00) [6.4-10.2]
Body FM, mean (SD) [range], kg	35.6 (7.6) [21-49]	35.3 (7.5) [23-58]	35.4 (7.5) [21-58]
Background therapy			
Metformin only	31 (84)	34 (89)	65 (87)
DPP4 inhibitor only	0	0	0
Metformin and DPP4 inhibitor	0	2 (5)	2 (3)
No medication	6 (16)	2 (5)	8 (11)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP4, dipeptidyl peptidase-4; FM, fat mass; HbA_{1c}, glycated hemoglobin.

SI conversion factor: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Safety analysis set.

was no treatment effect (eTable 3 in Supplement 1). Dietary intake based on 24-hour recall did not change from baseline to week 48 in either treatment group. Pharmacokinetic results are reported in eTable 4 in Supplement 1.

Table 2. Major End Points

End Point	Change (80% CI) [Participants, No.][a]			
	Bimagrumab[b]	Placebo[b]	Difference[b]	*P* value
Primary				
FM, kg	−7.49 (−8.33 to −6.64) [26]	−0.18 (−0.99 to 0.63) [29]	−7.31 (−8.48 to −6.14)	<.001
Secondary				
Lean mass, kg	1.70 (1.14 to 2.26) [26]	−0.44 (−0.97 to 0.09) [29]	2.14 (1.36 to 2.93)	<.001
Body weight, kg	−5.90 (−7.08 to −4.71) [26]	−0.79 (−1.92 to 0.33) [30]	−5.10 (−6.74 to −3.47)	<.001
BMI	−2.19 (−2.60 to −1.78) [26]	−0.28 (−0.67 to 0.11) [30]	−1.91 (−2.48 to −1.34)	<.001
Waist circumference, cm	−9.00 (−10.3 to −7.68) [26]	0.45 (−0.79 to 1.69) [30]	−9.46 (−11.3 to −7.64)	<.001
Waist-to-hip ratio	−0.05 (−0.06 to −0.04) [26]	0.01 (0.00 to 0.02) [30]	−0.06 (−0.08 to −0.04)	<.001
HbA_{1c}, %	−0.76 (−1.05 to −0.48) [26]	0.04 (−0.23 to 0.31) [30]	−0.80 (−1.20 to −0.41)	.005
HOMA2, week 36	−0.09 (−0.44 to 0.25) [25]	0.57 (0.24 to 0.90) [27]	−0.66 (−1.14 to −0.18)	.08
QUICKI, week 36	0.01 (0.01 to 0.01) [26]	0.00 (0.00 to 0.00) [30]	0.01 (0.00 to 0.01)	.03
Matsuda Index	3.15 (2.39 to 3.91) [26]	1.78 (1.05 to 2.51) [28]	1.37 (0.31 to 2.43)	.01
Exploratory				
Hepatic fat fraction, %				
Week 24	−4.60 (−6.07 to −3.12) [18]	0.23 (−1.61 to 2.08) [11]	−4.83 (−7.20 to −2.46)	.006
Week 48	−7.00 (−8.58 to −5.43) [5]	−2.33 (−4.16 to −0.51) [5]	−4.67 (−7.09 to −2.25)	.01
Abdominal SAT, L				
Week 24	−0.97 (−1.37 to −0.56) [18]	−0.14 (−0.65 to 0.37) [11]	−0.83 (−1.48 to −0.18)	.05
Week 48	−1.71 (−2.40 to −1.03) [5]	−0.52 (−1.30 to 0.26) [4]	−1.19 (−2.23 to −0.15)	.07
Abdominal VAT, L				
Week 24	−1.49 (−1.69 to −1.29) [18]	0.22 (−0.03 to 0.48) [11]	−1.71 (−2.04 to −1.39)	<.001
Week 48	−1.52 (−2.42 to −0.62) [5]	−0.01 (−1.05 to 1.03) [4]	−1.51 (−2.87 to −0.14)	.08

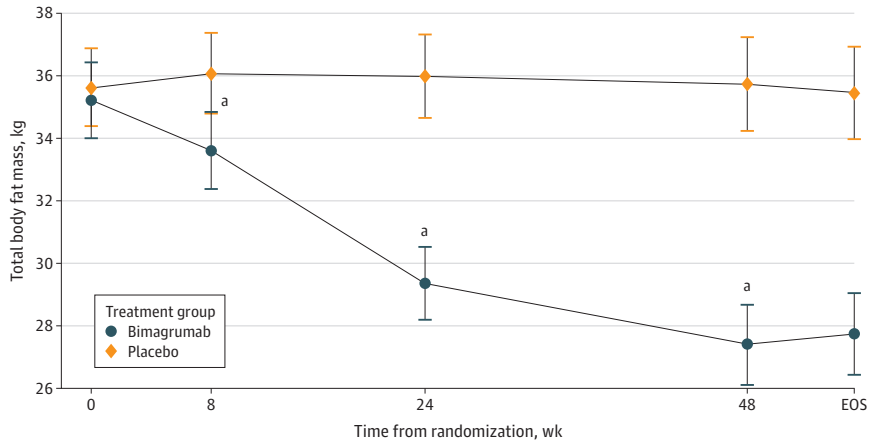
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FM, body fat mass; HbA_{1c}, glycated hemoglobin; HOMA2, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index (calculated as 1/[log{fasting insulin, μU/mL}] + log{fasting glucose, mg/dL}); SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

SI conversion factor: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Change from baseline to week 48, unless otherwise noted, in the end point.

[b] This model has change from baseline FM in kilograms as the dependent variable and treatment group, time, and a time × treatment group interaction as fixed effects. Baseline FM and baseline BMI values were included in the model as covariates. Time was modeled as a categorical variable. An unstructured within-participant covariance was used.

Figure 2. Effect of Bimagrumab on Total Body Fat Mass



1 participant in the bimagrumab group did not have a week 48 or end of study (EOS) dual-energy x-ray absorptiometry scan performed.

[a] *P* < .001.

Safety and Adverse Events

Nine serious adverse events were reported in 6 patients: 2 events in 1 patient in the bimagrumab group (elevated lipase and epigastric pain with normal pancreas and no evidence of acute pancreatitis on imaging, later diagnosed as cholelithiasis), 2 events in 2 patients in the placebo group (cellulitis and thermal burn in 1 patient; acute coronary syndrome and acute myocardial infarction in the other), 1 event each in 2 patients in the bimagrumab group (pancreatitis and pneumonia), and 1 event in 1 patient in the placebo group (worsening gastroparesis) (**Table 3**). The patient with pancreatitis was hospitalized, and the event was considered serious by the investigator.

Adverse events were reported by 31 of 37 patients (83.8%) in the bimagrumab group and 31 of 38 (81.6%) in the placebo group. Mild diarrhea and muscle spasms were the most frequently reported adverse events by patients in the bimagrumab group. The frequency of diarrhea was highest after the first dose (9 patients) and diminished thereafter (eFigure 2 in Supplement 1). Only 1 patient in the bimagrumab group and none in placebo group reported the development of acne, although this adverse event has been identified in some prior studies with bimagrumab.[10,22]

Overall, 8 adverse events leading to study discontinuation occurred in 5 patients in the bimagrumab group and none in the placebo group. Pancreatitis occurred in 1 patient, *Helicobacter pylori* infection occurred in 1 patient, muscle spasms occurred in 2 patients, and 1 patient experienced an increase in serum lipase (reported twice) along with upper abdominal pain and cholelithiasis. Treatment with bimagrumab resulted in no clinically meaningful changes from baseline to week 48 in vital signs, electrocardiogram findings, or mean values of most hematology and biochemistry measures. Patients treated with bimagrumab had decreased levels of follicle stimulating hormone and urate and increased levels of creatine kinase (eTable 5 in Supplement 1). Early, transient elevations were observed in levels of serum lipase (10.8% increase in bimagrumab vs 5.3% in placebo), amylase (5.4% increase in bimagrumab vs 0% in placebo), alanine aminotransferase (2.7% increase in bimagrumab vs 0% in placebo), aspartate aminotransferase (2.7% increase in bimagrumab vs 0% in placebo), alkaline phosphatase (2.7% increase in bimagrumab vs 0% in placebo), and γ-glutamyl transferase (2.7% increase in bimagrumab vs 0% in placebo) (eTable 5 and eFigure 3 in Supplement 1). Two patients from the bimagrumab group had drug-induced, nonneutralizing antidrug antibodies without impact on the exposure level of bimagrumab.

Discussion

The current study confirms and extends earlier reports showing that antibody blockade of ActRII with bimagrumab in human participants leads to a marked loss in FM, an increase in lean mass, and

Table 3. Adverse Events[a]

Adverse event	Patients, No. (%)	
	Bimagrumab group	Placebo group
Death	0	0
Serious adverse events	3 (8)	3 (8)
Any adverse event	31 (84)	31 (82)
Adverse event leading to study discontinuation	5 (14)	0
Most frequent adverse events[b]		
Diarrhea	15 (41)	4 (11)
Muscle spasms	15 (41)	1 (3)
Upper respiratory tract infection	6 (16)	5 (13)
Lipase level increased	4 (11)	2 (5)
Headache	0	5 (13)
Hypertension	3 (8)	1 (3)
Nausea	4 (11)	0
Rash	2 (5)	2 (5)

[a] Adverse events were any untoward medical occurrence in a patient who provided written informed consent for participation in the study until the end of study visit.

[b] Incidence greater than 5%.

improvement in a range of metabolic biomarkers.[11,22] In the current study, patients with type 2 diabetes who had overweight or obesity lost 20.5% of their total body FM, had a 3.6% increase in lean mass, and had a decrease of 0.76 percentage points in their HbA_{1c} levels following 48 weeks of monthly bimagrumab doses combined with a lifestyle intervention. By contrast, patients receiving placebo who also received the lifestyle intervention had an increase in total body FM of 0.5%, a lean mass reduction of 0.8%, and a decrease of 0.04 percentage points in HbA_{1c} levels. The combined loss in total body FM and gain in lean mass led to a net 6.5% reduction in body weight in patients receiving bimagrumab compared with a 0.8% weight gain in their counterparts receiving placebo. Relative to placebo, weight loss with bimagrumab was greater than 7%, a level greater than the 1-year FDA threshold of 5% for registration of new medicines for treating obesity and overweight.[23]

The specific mechanisms linking ActRII inhibition with marked reductions in FM are largely unknown, although the receptor is recognized as present on adipocytes in addition to myocytes.[9,24] No white adipose tissue reduction was detected in preclinical studies involving multiple species, indicating that this pathway behaves differently in humans.[9] However, ActRII inhibition in a rodent model regulated BAT differentiation and activated myoglobin and peroxisome proliferator-activated receptor γ coactivator coregulators, leading to mitochondrial enhancement and an increase in energy expenditure.[9] Garito et al[11] extended these observations in a small sample of human participants without diabetes but with insulin resistance who were evaluated 10 weeks after a single dose of bimagrumab (n = 10) or placebo (n = 6). Compared with placebo, total body FM decreased significantly by 7.9%, BAT volume decreased (although not significantly), and thermogenic capacity remained stable in patients treated with bimagrumab. These early studies need to be extended with larger samples and the exploration of other potential mechanisms that could account for the marked effects of ActRII blockade on FM.

The mechanisms of improved insulin sensitivity, as observed with ActRII inhibition by bimagrumab in the current study, are also largely unknown. Both myostatin knockout and sequestration by soluble ActRII improved insulin sensitivity in preclinical animal models.[25,26] Insulin sensitivity improved by approximately 20% (by hyperinsulinemic-euglycemic clamp) to 40% (by intravenous glucose tolerance test) in the patients with insulin resistance treated with bimagrumab in the study by Garito et al.[11] Effects on adipose tissue and ectopic fat compartments (eg, hepatic fat), known to be associated with insulin resistance, combined with increments in skeletal muscle mass, as observed in the current and earlier clinical studies,[27,28] may account for some of the beneficial anatomic changes (eg, waist circumference, waist-to-hip ratio) and improvements in biomarkers of insulin sensitivity (eg, QUICKI and HOMA2) brought about with bimagrumab treatment. The 0.76 percentage point reduction in HbA_{1c} level in the current study is higher or similar to that observed with other antidiabetic medicines, such as pioglitazone (0.2 percentage points)[29] and dapagliflozin (0.58-0.89 percentage points).[30]

A novel feature of bimagrumab is the expansion of the lean mass (ie, skeletal muscle) compartment in the presence of negative energy balance and weight loss. Decrements in lean mass are typically observed with low calorie dieting, partially offset only when the weight loss program includes a moderate or high intensity exercise prescription.[31,32] An important goal of obesity treatment is that there should be minimal loss of lean tissues and their associated functions. Diets, exercise programs, and weight loss medications are often judged in the context of the relative loss of lean tissues they impose. Some diets are accompanied by large losses of lean components and severe functional deficits, even sudden death.[33] Uniquely, ActRII blockade with bimagrumab not only limited the loss of lean mass but also increased the mass of this compartment by nearly 4% after 4 monthly doses. Additional studies are needed to gain insights into the functional implications of lean mass expansion during the course of weight loss and weight maintenance programs.

Because under usual circumstances the proportion of weight loss brought about by behavioral means alone or with medications is approximately 25% lean mass,[34] bimagrumab efficacy for weight loss cannot be judged in the usual FDA context. Total body FM loss with bimagrumab alone was 8.3% of body weight and, combined with a projected lean loss (assuming one-fourth of weight loss is

composed of lean mass)[34] rather than gain, would approach 10%. A weight loss of this magnitude at 48 weeks would meet or exceed the levels currently recognized for medications approved for treating obesity and overweight and exceeds that of several popular weight loss diets.[35,36] Moreover, the distribution of body fat loss in patients treated with bimagrumab was highly favorable, with reduction of abdominal visceral adipose tissue and waist circumference that was nearly twice that observed in a recently published study of patients with type 2 diabetes treated with an intensive lifestyle program and the glucagon-like peptide 1 agonist liraglutide.[37] These observations highlight the importance of moving away from body weight as a primary efficacy marker of drugs to more metabolically relevant end points, such as total body FM.

Overall, adverse effects and events were balanced between the bimagrumab and placebo groups, although more patients in the bimagrumab group experienced transient elevations of pancreatic and liver enzymes, which tended to subside after the first dose of bimagrumab. The etiology of these elevations is unclear but could be related to mobilization of adipocyte triglycerides and amino acids as a new metabolic equilibrium is reached during early bimagrumab dosing. Further studies are needed to determine whether weekly administration of an available subcutaneous formulation may alleviate these transient elevations by permitting a more gradual achievement of a new steady state. Regarding pancreatitis, more than 1000 adults have been enrolled in the clinical program, with a total of 2 cases of acute pancreatitis reported, 1 from the current study and the other unpublished. Additional studies are needed to explore the etiology of pancreatitis.

Limitations

This study has limitations. The sample size in this phase 2, proof-of-concept study was modest, and the protocol was limited to patients with type 2 diabetes who had overweight or obesity. Moreover, there was a gender imbalance across the groups, with more women randomized to bimagrumab and more men to placebo. However, if anything, this imbalance may have led to an underestimation of the lean mass gain in the bimagrumab treatment group. The completion rate in our study was 77%; this is higher than that of many randomized clinical trials using pharmacotherapy for treating obesity, in which, on average, up to one-half of participants discontinue participation by 1 year.[38]

The possibility exists that the lean mass gains we observed in participants who received bimagrumab were caused by fluid or water accumulation rather than muscle protein accretion. Although we did not measure total body water or muscle water content, we are unaware of any effects of bimagrumab on water balance in this study or in earlier related studies. We thus view our lean mass estimates as representing normally hydrated skeletal muscle, and this assumption can be tested in future in-depth phase 2 studies. Additionally, the etiology of the changes in energy balance underlying the weight loss remains unknown.

Conclusions

In this study, 48 weeks of exposure to bimagrumab, an antibody inhibitor of ActRII, was safe and effective for treating the excess adiposity and metabolic disturbances of adult patients with obesity and type 2 diabetes. While antibody blockade or knockout of ActRII in animal models is accompanied by marked increases in skeletal muscle mass, this study confirms that inhibition of this receptor in human participants leads to not only increases in lean mass but profound decreases in body fat, along with improvements in glycemic control. Inhibition of ActRII may provide a novel pathway for the pharmacologic management of excess adiposity and accompanying metabolic disturbances.

ARTICLE INFORMATION

Accepted for Publication: November 22, 2020.

Published: January 13, 2021. doi:10.1001/jamanetworkopen.2020.33457

Corresponding Author: Steven B. Heymsfield, MD, Pennington Biomedical Research Center, Louisiana State University System, 6400 Perkins Rd, Baton Rouge, LA 70808 (Steven.Heymsfield@pbrc.edu).

Author Affiliations: Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge (Heymsfield); Translational Medicine, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts (Coleman, Miller, Rooks, Praestgaard, Swan); Translational Medicine, Novartis Institutes for BioMedical Research, Basel, Switzerland (Laurent, Petricoul, Roubenoff); QPS-Miami Research Associates, Miami, Florida (Wade); Panax Clinical Research, Miami, Florida (Perry); Advent Health Research Institute, Orlando, Florida (Goodpaster).

Author Contributions: Dr Coleman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Coleman, Rooks, Laurent, Petricoul, Roubenoff.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Heymsfield, Coleman, Laurent, Praestgaard, Wade.

Critical revision of the manuscript for important intellectual content: Heymsfield, Coleman, Miller, Rooks, Laurent, Petricoul, Praestgaard, Swan, Perry, Goodpaster, Roubenoff.

Statistical analysis: Praestgaard.

Obtained funding: Roubenoff.

Administrative, technical, or material support: Heymsfield, Miller, Rooks, Laurent, Petricoul, Swan, Wade.

Supervision: Heymsfield, Coleman, Miller, Laurent, Swan, Wade, Perry, Roubenoff.

Conflict of Interest Disclosures: Dr Heymsfield reported receiving personal fees from Tanita and Medifast outside the submitted work. Drs Coleman, Miller, Rooks, Roubenoff, Laurent, Praestgaard, Petricoul, and Swan reported being employees of Novartis Institutes for BioMedical Research during the conduct of the study. Drs Coleman and Roubenoff reported having a patent for PAT058683-US-PSP pending with Novartis. Drs Rooks and Roubenoff reported being coauthors of a patent for use of bimagrumab in other indications that is no longer being developed. Dr Goodpaster reported receiving personal fees from Novartis for work performed during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was funded by Novartis Pharmaceuticals.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Partial results of this study were presented at Obesity Week; November 4, 2019; Las Vegas, Nevada.

Data Sharing Statement: See Supplement 3.

Additional Contributions: The authors thank Shyamashree Dasgupta, PhD (Novartis Healthcare Private Limited), for formatting, referencing, preparing tables and figures, incorporating the authors' revisions, and submission, all under the direction of the authors. Dr Dasgupta was compensated for their time. The final responsibility for the content lies with the authors. The authors acknowledge BioTel Research (Rochester, New York) for medical imaging support. BioTel Research was compensated for their contribution.

REFERENCES

1. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a disease: the Obesity Society 2018 position statement. *Obesity (Silver Spring)*. 2019;27(1):7-9. doi:10.1002/oby.22378

2. Stecker T, Sparks S. Prevalence of obese patients in a primary care setting. *Obesity (Silver Spring)*. 2006;14(3):373-376. doi:10.1038/oby.2006.49

3. Kushner RF. Weight loss strategies for treatment of obesity: lifestyle management and pharmacotherapy. *Prog Cardiovasc Dis*. 2018;61(2):246-252. doi:10.1016/j.pcad.2018.06.001

4. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT randomized controlled trial. *Obesity (Silver Spring)*. 2020;28(3):529-536. doi:10.1002/oby.22726

5. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(7):434-447. doi:10.7326/0003-4819-155-7-201110040-00006

6. Telem DA, Jones DB, Schauer PR, et al. Updated panel report: best practices for the surgical treatment of obesity. *Surg Endosc*. 2018;32(10):4158-4164. doi:10.1007/s00464-018-6160-x

7. US Food and Drug Administration. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market. Published February 13, 2020. Accessed March 3, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market

8. Srivastava G, Apovian C. Future pharmacotherapy for obesity: new anti-obesity drugs on the horizon. *Curr Obes Rep*. 2018;7(2):147-161. doi:10.1007/s13679-018-0300-4

9. Fournier B, Murray B, Gutzwiller S, et al. Blockade of the activin receptor IIb activates functional brown adipogenesis and thermogenesis by inducing mitochondrial oxidative metabolism. *Mol Cell Biol*. 2012;32(14):2871-2879. doi:10.1128/MCB.06575-11

10. Rooks DS, Laurent D, Praestgaard J, Rasmussen S, Bartlett M, Tankó LB. Effect of bimagrumab on thigh muscle volume and composition in men with casting-induced atrophy. *J Cachexia Sarcopenia Muscle*. 2017;8(5):727-734. doi:10.1002/jcsm.12205

11. Garito T, Roubenoff R, Hompesch M, et al. Bimagrumab improves body composition and insulin sensitivity in insulin-resistant individuals. *Diabetes Obes Metab*. 2018;20(1):94-102. doi:10.1111/dom.13042

12. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

13. Hayes C. *I Hate to Exercise*. 2nd ed. American Diabetes Association, 2006.

14. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: *Standards of Medical Care in Diabetes-2020. Diabetes Care*. 2020;43(suppl 1):S32-S36. doi:10.2337/dc20-S003

15. Yokoyama H, Emoto M, Fujiwara S, et al. Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment are useful indexes of insulin resistance in type 2 diabetic patients with wide range of fasting plasma glucose. *J Clin Endocrinol Metab*. 2004;89(3):1481-1484. doi:10.1210/jc.2003-031374

16. Hrebícek J, Janout V, Malincíková J, Horáková D, Cízek L. Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. *J Clin Endocrinol Metab*. 2002;87(1):144-147. doi:10.1210/jc.87.1.144

17. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;22(9):1462-1470. doi:10.2337/diacare.22.9.1462

18. Mashhood A, Railkar R, Yokoo T, et al. Reproducibility of hepatic fat fraction measurement by magnetic resonance imaging. *J Magn Reson Imaging*. 2013;37(6):1359-1370. doi:10.1002/jmri.23928

19. Fallah F, Machann J, Martirosian P, Bamberg F, Schick F, Yang B. Comparison of T1-weighted 2D TSE, 3D SPGR, and two-point 3D Dixon MRI for automated segmentation of visceral adipose tissue at 3 Tesla. *MAGMA*. 2017;30(2):139-151. doi:10.1007/s10334-016-0588-6

20. Goyal R, Faizy AF, Siddiqui SS, Singhai M. Evaluation of TNF-α and IL-6 Levels in obese and non-obese diabetics: pre- and postinsulin effects. *N Am J Med Sci*. 2012;4(4):180-184. doi:10.4103/1947-2714.94944

21. Rossi AP, Fantin F, Zamboni GA, et al. Predictors of ectopic fat accumulation in liver and pancreas in obese men and women. *Obesity (Silver Spring)*. 2011;19(9):1747-1754. doi:10.1038/oby.2011.114

22. Rooks D, Praestgaard J, Hariry S, et al. Treatment of sarcopenia with bimagrumab: results from a phase ii, randomized, controlled, proof-of-concept study. *J Am Geriatr Soc*. 2017;65(9):1988-1995. doi:10.1111/jgs.14927

23. US Food and Drug Administration. Developing products for weight management revision 1. Published February 2007. Accessed February 28, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-products-weight-management-revision-1

24. Lach-Trifilieff E, Minetti GC, Sheppard K, et al. An antibody blocking activin type II receptors induces strong skeletal muscle hypertrophy and protects from atrophy. *Mol Cell Biol*. 2014;34(4):606-618. doi:10.1128/MCB.01307-13

25. Guo T, Jou W, Chanturiya T, Portas J, Gavrilova O, McPherron AC. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. *PLoS One*. 2009;4(3):e4937. doi:10.1371/journal.pone.0004937

26. Camporez JP, Petersen MC, Abudukadier A, et al. Anti-myostatin antibody increases muscle mass and strength and improves insulin sensitivity in old mice. *Proc Natl Acad Sci U S A*. 2016;113(8):2212-2217. doi:10.1073/pnas.1525795113

27. Hotamisligil GS. Molecular mechanisms of insulin resistance and the role of the adipocyte. *Int J Obes Relat Metab Disord*. 2000;24(suppl 4):S23-S27. doi:10.1038/sj.ijo.0801497

28. Dietze D, Koenen M, Röhrig K, Horikoshi H, Hauner H, Eckel J. Impairment of insulin signaling in human skeletal muscle cells by co-culture with human adipocytes. *Diabetes*. 2002;51(8):2369-2376. doi:10.2337/diabetes.51.8.2369

29. DeFronzo RA, Tripathy D, Schwenke DC, et al; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104-1115. doi:10.1056/NEJMoa1010949

30. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-2224. doi:10.2337/dc10-0612

31. Jo E, Worts PR, Elam ML, et al. Resistance training during a 12-week protein supplemented VLCD treatment enhances weight-loss outcomes in obese patients. *Clin Nutr*. 2019;38(1):372-382. doi:10.1016/j.clnu.2017.12.015

32. Willoughby D, Hewlings S, Kalman D. Body composition changes in weight loss: strategies and supplementation for maintaining lean body mass, a brief review. *Nutrients*. 2018;10(12):E1876. doi:10.3390/nu10121876

33. Rayner JJ, Abdesselam I, Peterzan MA, et al. Very low calorie diets are associated with transient ventricular impairment before reversal of diastolic dysfunction in obesity. *Int J Obes (Lond)*. 2019;43(12):2536-2544. doi:10.1038/s41366-018-0263-2

34. Heymsfield SB, Gonzalez MC, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes Rev*. 2014;15(4):310-321. doi:10.1111/obr.12143

35. Ge L, Sadeghirad B, Ball GDC, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ*. 2020;369:m696. doi:10.1136/bmj.m696

36. Singh AK, Singh R. Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs. *Expert Rev Clin Pharmacol*. 2020;13(1):53-64. doi:10.1080/17512433.2020.1698291

37. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE Insulin randomized controlled trial. *Diabetes Care*. 2020;43(5):1085-1093. doi:10.2337/dc19-1745

38. Delahanty LM, Riggs M, Klioze SS, Chew RD, England RD, Digenio A. Maximizing retention in long-term clinical trials of a weight loss agent: use of a dietitian support team. *Obes Sci Pract*. 2016;2(3):256-265. doi:10.1002/osp4.57

SUPPLEMENT 1.

eAppendix 1. Study Sites and Principal Investigators
eAppendix 2. Inclusion and Exclusion Criteria, Randomization, Sensitivity Analysis
eFigure 1. Hormonal and Inflammatory Marker Exploratory End Points
eFigure 2. Frequency of Diarrhea by Treatment Period
eFigure 3. Biochemistry End Points
eTable 1. Serum Lipids
eTable 2. Hormonal and Inflammatory Markers
eTable 3. Hand Grip Strength
eTable 4. Pharmacokinetics
eTable 5. Biochemistry End Points
eReferences.

SUPPLEMENT 2.

Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 3.

Data Sharing Statement