Supplemental Online Content

Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw Open*. 2021;4(1):e2033457. doi:10.1001/jamanetworkopen.2020.33457

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Study Sites and Principal Investigators

Study Site	Location	Principal Investigator
QPS MRA Miami Research Associates	Miami, FL, USA	Thomas Wade
Anaheim Clinical Trials	Anaheim, CA, USA	Amina Z. Haggag
Clinilabs	Eatontown, NJ, USA	Magdy Shenouda
Quotient Sciences	Miami, FL, USA	Jeffrey A. Levy
Panax Clinical Research, LLC	Miami, FL, USA	Robert Perry
Translational Research Institute for Metabolism and Diabetes	Orlando, FL, USA	Bret H. Goodpaster
Hassman Research Institute	Berlin, NJ, USA	Michael Hassman
Pennington Biomedical Research Center	Baton Rouge, LA, USA	Steven B. Heymsfield
Simbec Research Limited	Wales, UK	Annelize Koch

eAppendix 2. Inclusion and Exclusion Criteria, Randomization, Sensitivity Analysis

Inclusion Criteria

1. Written informed consent was obtained before any assessment was performed.
2. Male and female, age 18 to 75 years, in stable health condition as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
3. Type 2 diabetes, with an HbA1c between 6.5% and 10% (inclusive) at screening.
4. On one of the following with stable treatment for approximately 3 months prior to randomization: a) metformin monotherapy b) DPP4 inhibitor agent monotherapy c) combination therapy of metformin and/or a DPP4 inhibitor agent d) no anti-diabetes therapy
5. Body mass index (BMI) of 28.0 to 40.0 kg/m^2 (inclusive) at screening.
6. Body weight between 65 and 140 kg (inclusive) at screening, and with a stable body weight (±5 kg) by history (subject report) and stable physical activity within 3 months prior to screening by history (subject report).
7. Able to communicate well with the investigator, understand, and comply with the requirements of the study.

Exclusion Criteria

Conditions related to safety:

1. Pregnant or nursing (lactating) women.
2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant unless they were using highly effective methods of contraception during dosing and for 6 months after stopping of the investigational drug. In the case of oral contraception, women were required to be stable on the same pill for a minimum of 3 months before taking the investigational drug.
3. Any chronic active infection (eg, human immunodeficiency virus, hepatitis B or C, tuberculosis, etc.) or had received anti-hepatitis C virus treatments within the previous 6 months. Patients receiving chemoprophylaxis for latent tuberculosis infection were eligible for the study.
4. History of known hypersensitivity to monoclonal antibodies or drugs like the study drug.
5. History of multiple and recurring allergies or allergy to the investigational compound/compound class used in this study.
6. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the screening or baseline assessments.

Diabetes-related conditions: Diabetes other than type 2, such as type 1 diabetes, surgically induced-diabetes, "brittle" type 2 diabetes as per investigator judgment, history of severe hypoglycemic episodes in the year preceding screening or known hypoglycemic unawareness.

Liver- or pancreas-related conditions:

7. Abnormal liver function tests, such as serum glutamic-oxaloacetic transaminase (SGOT) [aspartate aminotransferase, AST], serum glutamic-pyruvic transaminase (SGPT) [alanine transaminase, ALT], alkaline phosphatase, or serum bilirubin (except Gilbert's disease), or abnormal lipase and/or amylase. The investigator was guided by the following criteria:

- Any single transaminase did not exceed 3x the upper limit of normal (ULN).
- A single parameter elevated up to and including 3x ULN was rechecked as soon as possible, and always prior to enrollment/randomization, to rule out any laboratory error.

- If the total bilirubin concentration was increased above the ULN, total bilirubin was differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin was not expected to exceed a value of 1.6 mg/dL (27 μmol/L).
- Screening or baseline levels of lipase and/or amylase ≥2x ULN were exclusionary. Initial tests in either lipase or amylase of ≥2x ULN were rechecked as soon as possible to confirm laboratory values and were available prior to randomization. Patients with confirmed lipase and/or amylase ≥2x ULN at screening or baseline were excluded.

8. Known history or presence of severe active acute or chronic liver disease (eg, cirrhosis) or conditions with hepatotoxic potential (eg, known gallbladder or bile duct disease, acute or chronic pancreatitis, or exocrine pancreatic insufficiency).

Cardiovascular conditions:

9. History of clinically significant arrhythmias, heart failure, unstable angina, myocardial infarction or stroke, coronary artery bypass graft surgery, or percutaneous coronary intervention (eg, angioplasty or stent placement), deep vein thrombosis/pulmonary embolism, valve disorders or defects, or pulmonary hypertension within 6 months of screening or within 1 year for drug-eluting stents.

10. Tachycardia, defined as pulse rate >100 beats per minute after 5 minutes of resting in the sitting position.

Other conditions:

11. Any medical condition or laboratory finding during screening (eg, an unexplained or clinically significant laboratory result), which, in the opinion of the investigator, could interfere with participation in the study, confound the results of the study, or pose an additional safety risk in administering bimagrumab.
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
13. Active alcohol or drug abuse, or participation in an alcohol or drug treatment program within 1 year prior to screening. Patients who had successfully completed an alcohol or drug treatment program more than 1 year prior to screening with sustained abstinence were eligible.
14. Confirmed diagnosis of current, significant psychiatric disease (eg, dementia, Alzheimer's disease, schizophrenia, depression or bipolar disorder). Individuals with adequately treated depression and stable treatment at least 3 months prior to screening were eligible for enrollment.
15. Chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2).
16. Patients planning to move out of the study area within 12 months or be out of the study area for more than 4 weeks continuously.

17. History of any type of bariatric procedure.

Optional magnetic resonance imaging (MRI) assessment criterion: Patients with a waist circumference >120 cm had given their consent for the optional MRI assessment.

Temporary exclusion criteria:

Patients excluded for one of the temporary medical conditions listed below could be rescreened after a period that was considered enough by the investigator. The subject needed to re-sign the informed consent form and the full screening visit had to be repeated under a new subject number.

1. Use of prohibited medications.
2. Significant acute illness such as urinary tract infection or upper respiratory tract infection that was not resolved within 2 weeks prior to screening.
3. Men with low fasting morning testosterone (<250 ng/dL) at screening. Men receiving testosterone replacement therapy for low testosterone were eligible if they were on a stable dose of testosterone for a

minimum of 3 months and their testosterone level was in the normal range on two consecutive tests at least 1 month apart and not more than 6 months apart, the second one being performed at screening.

4. Systolic blood pressure >180 or <90 mmHg or diastolic blood pressure >100 or <50 mmHg at screening or baseline.
5. Currently enrolled in, or discontinued within the last 30 days (or five half-lives of enrollment or until the pharmacodynamics effect was expected to return to baseline, whichever was longer; or longer if required by local regulations), from a clinical trial involving an investigational drug or off-label use of a drug, or were concurrently enrolled in any other type of medical research judged to be scientifically or medically incompatible with this study.
6. Uncontrolled thyroid disease. Hypothyroid patients with euthyroidism on stable thyroid replacement therapy for at least 3 months prior to screening were allowed.
7. Significant change in cigarette smoking within 3 months of screening, as judged by the investigator.
8. Use of any anti-obesity medications, nutritional supplements or over the counter products for weight loss within 3 months of screening or use of medications known or suspected to induce weight gain, such as some anticonvulsant and psychotropic medications (excluding antidepressant medication), within 3 months of screening.
9. Use of skeletal muscle anabolic agents in any form, such as medications, hormones (except stable testosterone replacement therapy for at least 3 months for hypogonadal men), and over the counter products and nutritional supplements (other than protein) that were labeled as muscle anabolic agents, for 3 months prior to screening.
10. Any dietary intervention, new exercise regimen or lifestyle modifications targeted for weight loss or diabetes control started within 3 months of screening.

Randomization

Treatment was assigned by stratified randomization for two strata based on the patient's baseline BMI. The strata had the following randomization numbers:

- BMI between 28.0 kg/m^2 and 33.0 kg/m^2 (inclusive): 5101-5150
- BMI between 33.1 kg/m^2 and up to 40.0 kg/m^2 (inclusive): 5201-5250

The randomization number was used to identify which strata the patient belonged to at randomization and which treatment the patients were randomized to receive. The patient number assigned to a patient at screening was the unique identifier for the patient throughout the study.

The randomization numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from subjects and investigator staff. A randomization list was produced by and under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio of 1:1. There were two dosing regimens allocated in a 1:1 ratio:

- T01: BYM338 10 mg/kg
- T02: Placebo

BMI was selected as a stratification parameter as it was an important predictor of response on parameters of body composition/body weight and HbA1c (internal data). The expected median value for BMI in this patient population was 33 kg/m^2 (internal data); therefore, two strata above and below/inclusive of the median ensured a balanced representation of patients between placebo and active drug in each strata, i.e. strata of approximately similar size between the two arms. Equal size strata were not enforced, but a minimal size of 10 was required for the smaller stratum in order to ensure adequate precision of treatment effect estimation in both strata.

Sensitivity Analysis

Per the Statistical Analysis Plan, a sensitivity analysis was conducted to gauge the influence of a possible "missingness not-at-random" assumption on the primary endpoint. Using the SAS ® procedure for multiple imputation, Proc MI, we conducted a "tipping point analysis" for the fat mass endpoint, as described in Yuan (2014).[1]

Initially, 25 imputed, complete data sets were generated by imputing the missing changes from baseline in fat mass measurements at weeks 24 and 48 under an assumption of monotonicity and missingness at random (MAR). Next, a tuning parameter was used to upweight the imputed differences in the placebo group (making negative differences more negative) and similarly down-weight the differences in the treatment group (shrinking differences from baseline towards zero). The primary analysis was repeated on each imputed data set and the resulting p-values for a treatment effect at weeks 24 and 48 were inspected. For no tipping point parameter of realistic size (between 0 and 100%) did the reported two-sided p values exceed 0.001 at either week 24 or 48.

eAppendix 3. Imaging

Dual-energy X-ray absorptiometry method

Dual-energy X-ray absorptiometry acquisition

For quality assurance, the dual-energy X-ray absorptiometry (DXA) instrument manufacturer and model remained consistent at each site and its calibration using a phantom was monitored throughout the study. Prior to examination, the subject was checked for metal objects on his/her body. The subject was then positioned so that his/her body was straight on the mattress, as measured against the solid longitudinal whole-body lines on the mat, with the head just below the lateral line at the head end of the mattress. The participant's arms were placed at their side, palms down, with a separation from the thigh such that the arms were within the whole-body scan limit lines on the mattress. Caution was also taken so that the participant's feet were within the foot limit line at the foot of the table and a radiolucent foam cushion could be placed beneath the patient's knees for comfort. Positioning, including hand and foot positions, was consistent from scan to scan. If a subject's body exceeded the width of the table, then positioning was adjusted so that the subject's right side fit entirely within the scan limits and whole-body composition was predicted from the half-body DXA scan.[2]

DXA analysis

In order to achieve consistent results, the raw DXA scans were sent to the central reader and loaded into the appropriate DXA manufacturer's software. Anatomic cut-lines were placed according to predefined anatomic landmarks and numbers for lean body mass (LBM), fat body mass (FBM) and bone mineral content (BMC) were generated and reviewed by a United States board-certified radiologist prior to delivery.

Magnetic resonance imaging method

Magnetic resonance imaging acquisition

For each subject, the non-contrast MRI acquisition protocol included a localization sequence for accurate axial slice prescription.

To measure abdominal (subcutaneous and visceral) fat, a Dixon scan was acquired between the diaphragm and femoral heads, producing both a water image and a fat image. In cases where the site did not have a fast Dixon scan that could be acquired in a single breath hold, a three-dimensional spoiled gradient-recalled echo breath hold sequence was acquired to again cover the whole region between the diaphragm and femoral heads. Both approaches have shown very similar results.[3]

To measure the hepatic fat fraction (HFF), a two-dimensional six-echo spoiled gradient-recalled-echo breath hold sequence of the liver was acquired.[4] If the scanner was not capable of acquiring six echoes simultaneously, multiple acquisitions with dual-echo or single-echo breath hold sequences were used. Each subject was scanned wearing a lipid phantom belt made of four phantom vials (corresponding to 0%, 10%, 20% and 30% fat fractions) to calculate HFF.

The same MRI sequence used for abdominal and HFF was used to assess the paravertebral muscle cross-sectional area (CSA) and associated fat contents (intermuscular adipose tissue [IMAT] and muscle fat fraction [mFF] contents) from a single slice. To enable consistency across visits, the slice chosen contained the vertebral body at or below the origin of the celiac artery. Detailed protocols were described in the MRI subject-scanning guide provided to each imaging site.

Image analysis by the central reader

Abdominal fat volumes

The region of subcutaneous adipose tissue was manually delineated from the viscera. The Dixon image was then automatically segmented based on a threshold of the fat fraction of 50%. Any voxel in the viscera that contained more than 50% fat was labeled as visceral adipose tissue. This was then reviewed by a technologist and radiologist. Corrections were made to the segmentation by erasing regions that were clearly not visceral fat, such as regions within the intestines, stomach, vertebra, muscle and other organs. After those regions were removed from the segmentation, volumes were calculated by counting the voxels that corresponded to each region and multiplying by the voxel volume.

Hepatic fat fraction

A fat fraction map was calculated from the six-echo sequence using a multi-interference technique.[4-6] The multi-interference method takes into account the contribution from the individual resonances in the fat spectrum to the observed MRI signal to obtain an accurate estimate of fat. The different resonances arising from different chemical moieties in fat at 1.5T are measurable at 5.3, 4.2, 2.1, 1.3, and 0.9 parts per million (PPM). The observed MRI signal from each image pixel at a given echo time (TE) was modeled as a sum of signals from water and the five measurable fat moieties. For a gradient echo sequence, the observed signal according to this six-component (water and five fat moieties) interference model can be described by:

$$S(\alpha, TE) = k\alpha \left| \rho_w + \rho_f \sum_{n=1}^{5} C_n e^{2\pi i \Delta f_n TE} \right| e^{-\frac{TE}{T_2^*}}; \sum_{n=1}^{5} C_n = 1$$

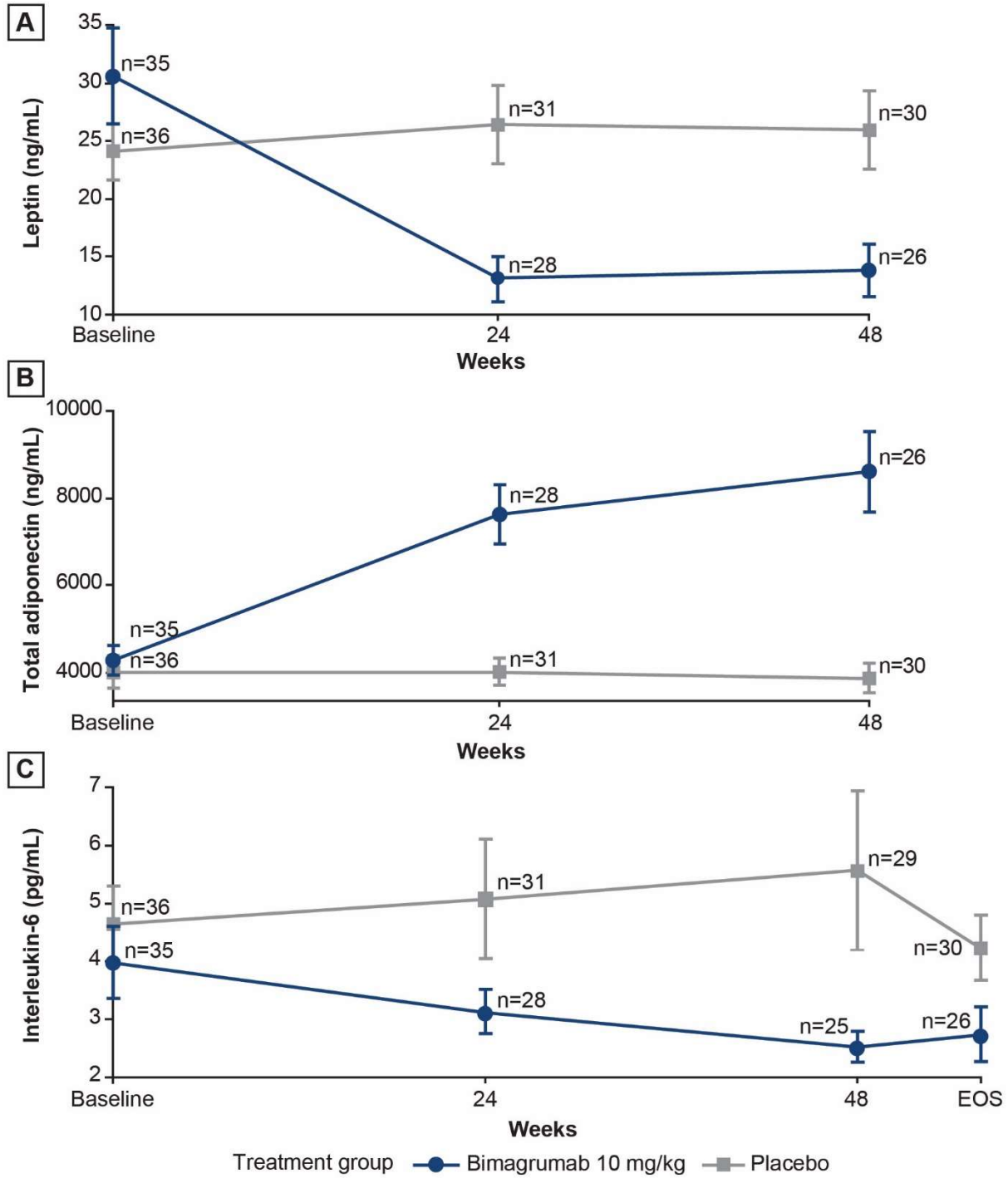
where C_n is the fractional proton density of each fat moiety, and Δf_n is the precession frequency of each fat moiety (at 5.3, 4.2, 2.1, 1.3, and 0.9 PPM relative to tetramethylsilane [TMS]). The terms ρ_w and ρ_w represent proton densities in water and fat, respectively, while α is the flip angle and k is a scanner specific constant. The C_n for fat was obtained from a previously measured proton spectroscopy of human fat. Image intensity data at each pixel for the six echoes (six TEs) were fit to the above equation and the fat and water proton density terms ($k\alpha\rho_f$ and $k\alpha\rho_w$) were estimated. The fat fraction for each pixel was then calculated as fat fraction = $\rho_f/(\rho_f+\rho_w)$ to provide a spatial map of the fat fraction across the whole liver.

The radiologist then identified a circular ROI of a diameter of 1.5 to 2.5 cm within each of the nine Couinaud segments of the liver using the first echo of the six-echo series and excluding blood vessels and the periphery of the liver. Similarly, a circular region within each of the four lipid phantoms was also identified. Following completion of the two region identification tasks, automated tasks generated the HFF as well as the lipid phantom fat fractions.

The whole liver HFF was finally expressed as the mean fat fraction across all nine user-defined ROIs in the liver. The fat fraction phantoms were used to verify that the scanning protocol was implemented correctly and that the calculated fat fraction values for the phantom were in the expected range.

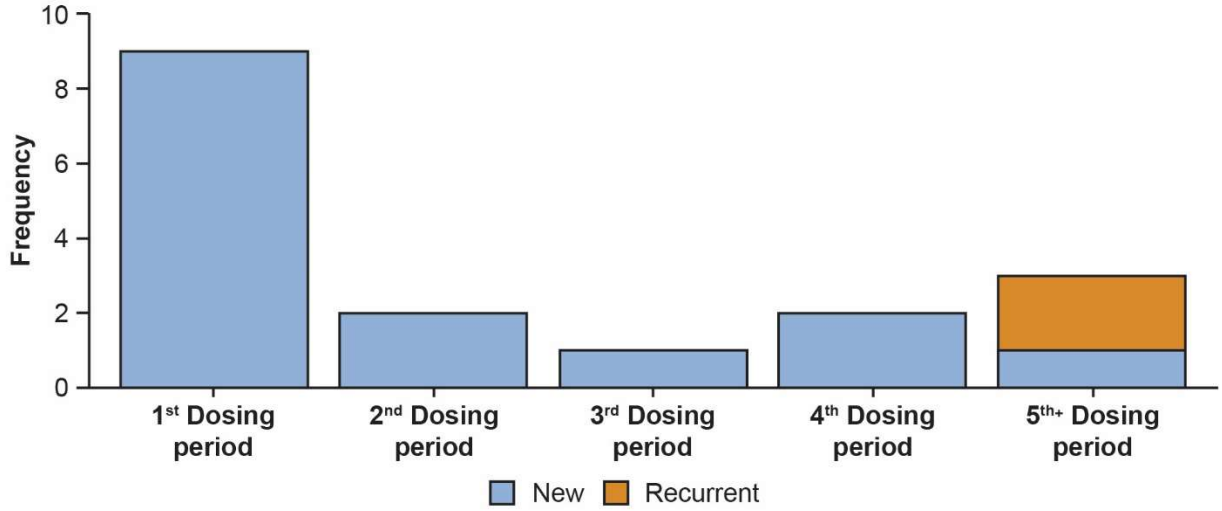
Liver iron content was also calculated using relaxation rate (R2*), where $[Fe]_{R2}^{*} = 0.0254 \times R2^{*} + 0.202$.[7]

eFigure 1. Hormonal and Inflammatory Marker Exploratory End Points



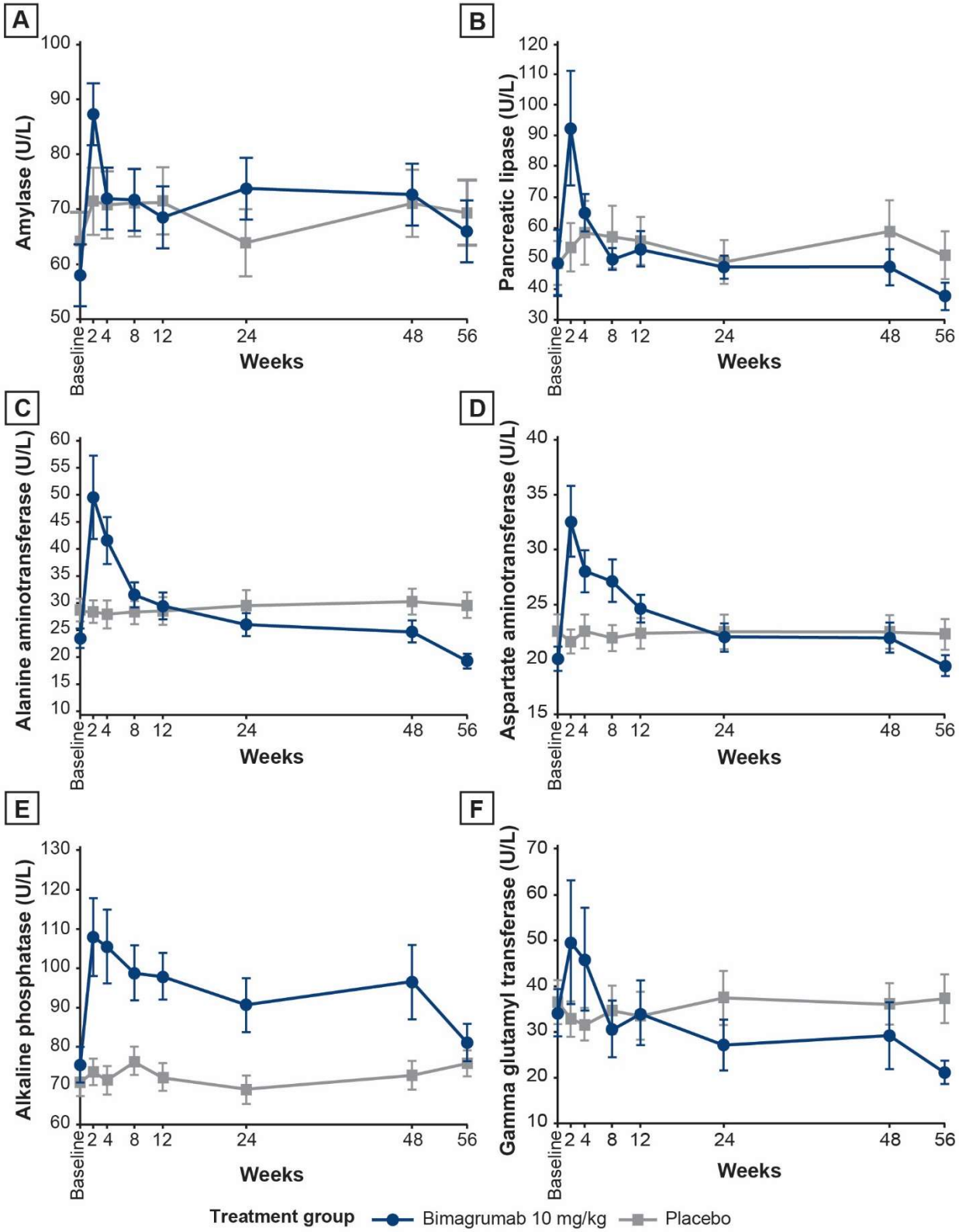
Data shown as mean±SD. End of study (EOS) data were not obtained for leptin and adiponectin. Weeks 48 and 56 are the end of treatment and study visits, respectively. One subject in the placebo group did not complete the end of study visit but did complete the week 48 visit, thus providing data for week 48 biomarker analysis and increasing N for this analysis to 30.

eFigure 2. Frequency of Diarrhea by Treatment Period



Recurrent events refer to those reported by the same patient more than once either within or between treatment periods.

eFigure 3. Biochemistry End Points



Data shown as mean±SD. Weeks 48 and 56 are the end of treatment and study visits, respectively.

eTable 1. Serum Lipids

Endpoint	Visit	Bimagrumab	Placebo
Cholesterol (mmol/L)	Screening	4.88±1.03 [35]	4.73±0.94 [35]
	Week 48	4.85±1.33 [26]	4.63±0.97 [30]
HDL cholesterol (mmol/L)	Screening	1.22±0.29 [35]	1.20±0.28 [35]
	Week 48	1.12±0.19 [26]	1.15±0.19 [30]
LDL cholesterol (mmol/L)	Screening	2.76±0.84 [34]	2.72±0.79 [35]
	Week 48	2.86±1.18 [26]	2.64±0.84 [29]
Triglycerides (mmol/L)	Screening	2.00±1.04 [35]	1.79±0.75 [35]
	Week 48	1.97±0.69 [26]	1.75±0.73 [30]
hsCRP (mg/L)	Baseline	7.67±11.94 [37]	5.15±4.73 [38]
	Week 48	10.39±45.02 [26]	3.95±2.90 [30]

Data shown as mean±SD [n]. No treatment differences at Week 48 achieved statistical significance at a two-sided 5% level. Method: analysis of covariance with a baseline covariate and treatment (Bimagrumab or placebo as main effect). HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LSM, least squares mean; n, number of patients

eTable 2. Hormonal and Inflammatory Markers

Endpoint	Visit	Bimagrumab	Placebo	LSM Difference[a]	P value[a]
Leptin (ng/mL)	Baseline	30.6±24.6 [35]	24.1±14.7 [36]		<0.0001
	Week 48	13.9±11.6 [26]	26.0±18.5 [30]	−12.7	
Adiponectin (ng/mL)	Baseline	4291±2025 [35]	4025±2288 [36]		
	Week 48	8610±4728 [26]	3891±1857 [30]	3604	
Interleukin-6 (pg/mL)	Baseline	4.0±3.7 [35]	4.7±3.9 [36]		
	Week 48	2.5±1.3 [25]	5.6±7.4 [29]		>0.05

Data shown as mean±SD [n]. n, number of patients

[a] LSM difference (Bimagrumab−Placebo) and two-sided P value shown where P value is below 5%. Method: analysis of covariance with a baseline covariate and treatment (Bimagrumab or placebo as main effect).

LSM, least squares mean.

eTable 3. Hand Grip Strength

Endpoint	Visit	Bimagrumab	Placebo
Left hand grip (N)	Baseline	265.3±108.9 [36]	345.1±133.3 [36]
	Week 48	294.2±127.5 [26]	326.2±97.8 [30]
Right hand grip (N)	Baseline	279.2±121.7 [36]	347.9±128.1 [36]
	Week 48	303.3±140.3 [26]	339.6±110.4 [30]

Data shown as mean±SD [n]. N, Newton; n, number of patients
No treatment differences at Week 48 achieved statistical significance at a two-sided 5% level. Method: analysis of covariance with a baseline covariate and treatment (bimagrumab or placebo as main effect).

eTable 4. Pharmacokinetics

Pharmacokinetic Parameter	Profile Day	Bimagrumab
C_{max} (µg/mL)	1	283±32 (11) [36]
	168	292±45 (16) [29]
	308	271±31 (12) [27]
C_{trough} (µg/mL)	84	25.3±6.20 (24.5) [29]
	168	27.5±8.37 (30.4) [29]
	252	31.0±11.2 (36.2) [26]
	308	29.9±11.0 (36.7) [26]
	336	27.8±10.9 (39.2) [25]
T_{max} (hours)	1	0.750 (0.683–0.917) [36]
	168	0.750 (0.750–1.05) [29]
	308	0.750 (0.750–1.38) [27]

Data shown as mean±SD (CV%) [n], except for Tmax, which is shown as median (min–max) [n]. CV% = SD/mean × 100. C_{max}, maximum plasma concentration; C_{trough}, lowest concentration reached by bimagrumab just before the next dose; T_{max}, time to reach maximum concentration; CV, coefficient of variation.

eTable 5. Biochemistry End Points

Endpoint	Visit	Bimagrumab	Placebo
Amylase (U/L)	Baseline	59.6±27.2 [37]	64.8±29.5 [38]
	Week 48	72.6±38.8 [27]	70.5±34.6 [30]
	Week 56	65.2±27.0 [27]	69.7±32.1 [31]
Lipase (U/L)	Baseline	48.2±44.7 [37]	48.3±37.0 [38]
	Week 48	46.9±27.8 [27]	58.9±54.6 [30]
	Week 56	38.0±19.7 [27]	50.3±42.6 [31]
Alanine aminotransferase (U/L)	Baseline	24.2±11.3 [37]	27.6±13.4 [38]
	Week 48	24.9±10.1 [27]	30.2±12.6 [30]
	Week 56	18.8±6.3 [27]	28.2±13.1 [31]
Aspartate aminotransferase (U/L)	Baseline	20.1±6.7 [37]	22.7±9.2 [38]
	Week 48	22.1±7.0 [27]	22.4±8.1 [30]
	Week 56	18.9±5.1 [27]	22.2±7.3 [31]
Alkaline phosphatase (U/L)	Baseline	74.2±20.4 [37]	70.9±19.4 [38]
	Week 48	96.3±47.8 [27]	72.8±19.3 [30]
	Week 56	81.1±24.5 [27]	76.4±18.0 [30]
Gamma glutamyl transferase (U/L)	Baseline	33.5±23.2 [37]	36.1±23.9 [38]
	Week 48	29.9±37.2 [27]	37.0±24.2 [30]
	Week 56	22.3±13.6 [27]	38.0±28.2 [31]
Creatine kinase (U/L)	Baseline	119.3±89.2 [35]	165.1±142.5 [38]
	Week 48	197.7±142.8 [27]	156.6±130.5 [30]
	Week 56	224.5±232.3 [26]	150.7±126.5 [31]
Urate (µmol/L)	Baseline	309.7±86.0 [37]	331.5±83.7 [38]
	Week 48	244.9±84.7 [27]	318.1±68.9 [30]
	Week 56	295.8±85.5 [27]	313.8±76.7 [31]
Follicle stimulating hormone (U/L)	Screening	34.7±28.3 [32]	21.5±22.6 [33]
	Week 48	14.0±8.2 [27]	20.4±21.5 [30]
	Week 56	28.2±21.0 [27]	21.9±23.1 [30]

Data shown as mean±SD [n]. n, number of patients. Weeks 48 and 56 are the end of treatment and study visits, respectively.

eReferences.

1. Yuan Y. Sensitivity Analysis in Multiple Imputation for Missing Data. Paper presented at: Proceedings of the SAS Global Forum 2014.
2. Lundqvist K, Neovius M, Grigorenko A, Nordenström J, Rössner S. Use of dual-energy X-ray absorptiometry in obese individuals: The possibility to estimate whole body composition from DXA half-body scans. *Radiography.* 2009;15(1):12-19.
3. 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.
4. 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.
5. Yokoo T, Bydder M, Hamilton G, et al. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. *Radiology.* 2009;251(1):67-76.
6. Yokoo T, Shiehmorteza M, Hamilton G, et al. Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. *Radiology.* 2011;258(3):749-759.
7. Wood JC, Enriquez C, Ghugre N, et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood.* 2005;106(4):1460-1465.

Main Text 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.
2. Stecker T, Sparks S. Prevalence of obese patients in a primary care setting. *Obesity (Silver Spring).* 2006;14(3):373-376.
3. Kushner RF. Weight Loss Strategies for Treatment of Obesity: Lifestyle Management and Pharmacotherapy. *Prog Cardiovasc Dis.* 2018;61(2):246-252.
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.
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.
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.
7. US Food and Drug Administration. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market. 2020 Feb. Accessed on 3 March 2020. https://wwwfdagov/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.
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.
10. Rooks DS, Laurent D, Praestgaard J, Rasmussen S, Bartlett M, Tanko 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.
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.
12. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA.* 2013;310(20):2191-2194.
13. Hayes C. I Hate to Exercise. 2nd ed. American Diabetes Association, 2006. ISBN-13: 978-1580402538.
14. American Diabetes Association. 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes— 2020. *Diabetes Care.* 2020;43(Supplement 1):S32.

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.
16. Hrebicek J, Janout V, Malincikova J, Horakova D, Cizek 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.
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.
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.
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.
20. Goyal R, Faizy AF, Siddiqui SS, Singhai M. Evaluation of TNF-alpha and IL-6 Levels in Obese and Non-obese Diabetics: Pre- and Postinsulin Effects. *N Am J Med Sci.* 2012;4(4):180-184.
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.
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.
23. US Food and Drug Administration. Developing Products for Weight Management Revision 1. 2007 Feb. Accessed on 28 Feb 2020. *https://wwwfdagov/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.
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.
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.
27. Hotamisligil GS. Molecular mechanisms of insulin resistance and the role of the adipocyte. *Int J Obes Relat Metab Disord.* 2000;24 Suppl 4:S23-27.
28. Dietze D, Koenen M, Rohrig 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.
29. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med.* 2011;364(12):1104-1115.
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.
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.
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).
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.
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.
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.
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.
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.
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.