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ORIGINAL RESEARCH

Effects of Epeleuton, a Novel Synthetic Second-Generation n-3 Fatty Acid, on Non-Alcoholic Fatty Liver Disease, Triglycerides, Glycemic Control, and Cardiometabolic and Inflammatory Markers

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BACKGROUND: Epeleuton is 15-hydroxy eicosapentaenoic acid ethyl ester, a second-generation synthetic n-3 fatty acid derivative of eicosapentaenoic acid. The primary objective was to assess the effect of epeleuton on markers of nonalcoholic fatty liver disease (NAFLD) with post hoc analyses of cardiometabolic markers.

METHODS AND RESULTS: In a multicenter, randomized, double-blind, placebo-controlled trial, 96 adults with nonalcoholic fatty liver disease and body mass index 25 to 40 were randomized in a 1:1:1 ratio to receive epeleuton 2 g/day, epeleuton 1 g/day, or placebo for 16 weeks. A total of 27% of patients had diabetes mellitus. Primary end points of changes in alanine aminotransferase and liver stiffness did not improve at week 16. Secondary and post hoc analyses investigated changes in cardiometabolic markers. Epeleuton 2 g/day significantly decreased triglycerides, very-low-density lipoprotein cholesterol, and total cholesterol without increasing low-density lipoprotein cholesterol. Despite a low mean baseline hemoglobin A1C (HbA_{1C}; 6.3±1.3%), epeleuton 2 g/day significantly decreased HbA_{1c} (–0.4%; P=0.026). Among patients with baseline HbA_{1c} >6.5%, epeleuton 2 g/day decreased HbA_{1c} by 1.1% (P=0.047; n=26). Consistent dose-dependent reductions were observed for fasting plasma glucose, insulin, and insulin resistance indices. Epeleuton 2 g/day decreased circulating markers of cardiovascular risk and endothelial dysfunction. Epeleuton was well tolerated, with a safety profile not different from placebo.

CONCLUSIONS: While epeleuton did not meet its primary end points on alanine aminotransferase or liver stiffness, it significantly decreased triglycerides, HbA_{1C}, plasma glucose, and inflammatory markers. These data suggest epeleuton may have potential for cardiovascular risk reduction and nonalcoholic fatty liver disease by simultaneously targeting hypertriglyceridemia, hyperglycemia, and systemic inflammation. Further trials are planned.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02941549.

Key Words: 15-HEPE ■ DS102 ■ epeleuton ■ n-3 fatty acid

Nonalcoholic fatty liver disease (NAFLD) is becoming the most common cause of liver disease globally and results from the buildup of fat within the liver commonly in the setting of weight gain and insulin resistance.[1] There are no approved therapies for the treatment of NAFLD, and thus patients can suffer

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CLINICAL PERSPECTIVE

What Is New?

- In this phase IIa randomized, double-blind, placebo-controlled trial, epeleuton, a second-generation synthetic n-3 fatty acid derivative of eicosapentaenoic acid, did not decrease the primary end points, liver stiffness, or alanine aminotransferase levels in patients with obesity and nonalcoholic fatty liver disease.
- Post hoc analysis revealed hypothesis-generating findings that epeleuton decreased triglycerides, inflammatory markers, insulin resistance indices, and meaningfully decreased hemoglobin A_{1C}, a novel finding for an n-3 fatty acid.

What Are the Clinical Implications?

- Future trials will be necessary to determine whether epeleuton may have meaningful potential for cardiovascular risk reduction and nonalcoholic fatty liver disease by simultaneously targeting hypertriglyceridemia, hyperglycemia, and systemic inflammation, and to assess the full therapeutic potential of epeleuton.

Nonstandard Abbreviations and Acronyms

15(S)-HEPE	15-hydroxy eicosapentaenoic acid
Adipo-IR	adipose insulin resistance
AE	adverse event
ALT	alanine aminotransferase
BMI	body mass index
EPA	eicosapentaenoic acid
HbA_{1C}	hemoglobin A_{1C}
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment for insulin resistance
hsCRP	high-sensitivity C-reactive protein
LDL-C	low-density lipoprotein cholesterol
mITT	modified intention-to-treat
NAFLD	nonalcoholic fatty liver disease
RLP-C	remnant lipoprotein cholesterol
VLDL-C	very-low-density lipoprotein cholesterol

from progressive liver fibrosis and decompensation. Alongside the development of liver disease, many patients with NAFLD are at increased risk of type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, and cardiovascular disease.[1] Indeed, cardiovascular disease remains the leading cause of morbidity and mortality globally, with persistently high rates of ischemic events reported in many populations.[2]

Despite the prevalent use of statins; blood pressure control; and therapeutic counseling for smoking abstinence, weight management, and physical activity, ischemic heart disease remains the leading cause of premature adult mortality worldwide.[3] Recent advances in primary and secondary prevention of cardiovascular events provide hope that new therapies targeting various cardiovascular risk factors including elevated triglycerides, inflammation, and hyperglycemia will produce benefits additional to current prevention strategies including low-density lipoprotein cholesterol (LDL-C) management with statins.[4–7] While the novel glucose-lowering medications for patients with type 2 diabetes mellitus may lessen cardiovascular risk largely independent of glucose lowering per se, there is evidence for cardiovascular benefits of glucose lowering, and Mendelian randomization studies support this.[8–10]

Results from the JELIS (Japan Eicosapentaenoic Acid Lipid Intervention Study) and the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) demonstrated superior cardiovascular outcomes with the experimental intervention. In addition, complementary results from several recent epidemiologic and Mendelian randomization studies have advanced treatment of hypertriglyceridemia specifically with higher-dose eicosapentaenoic acid (EPA) as a potential paradigm for cardiovascular risk reduction.[5,11–15] Indeed, in the primary analyses of the aforementioned trials, the risk of major adverse cardiovascular events was reduced by 19% and 25%, respectively, compared with the control arms following treatment with EPA's ethyl ester, icosapent ethyl, in patients on optimized statin therapy.[5,11] These findings contrast with results from other medications that reduce triglycerides, including low-dose n-3 fatty acid combination products (EPA plus docosahexaenoic acid), fibrates, and niacin, where reductions in cardiovascular events have not been significant in the statin era.[16,17] Cumulatively, this may suggest that the JELIS and REDUCE-IT studies do not establish a purely triglyceride-based paradigm for cardiovascular risk reduction but instead support specific cardiovascular benefits of actions at the EPA axis.

Similarly, recent cardiovascular outcome trials of antihyperglycemic medications have shown that in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, antihyperglycemic agents can reduce the risk of future cardiovascular events.[18–20] Glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have emerged as therapeutic classes that significantly reduce the risk of major adverse cardiovascular events in secondary prevention cohorts.[4]

However, a recent meta-analysis did not show similar favorable effects of sodium-glucose cotransporter-2 inhibitors for primary prevention of ischemic events in patients without established atherosclerotic cardiovascular disease.[21] Furthermore, cardiovascular outcome trials of dipeptidyl peptidase 4 inhibitors have not shown any cardiovascular benefits.[22] Together, these results indicate that new antihyperglycemic agents that have additional cardiovascular benefits may provide incremental improvements in outcomes compared with current antihyperglycemic therapeutic classes.

Epeleuton is 15-hydroxy eicosapentaenoic acid (15(S)-HEPE) ethyl ester, a second-generation synthetic n-3 fatty acid derivative of EPA. 15(S)-HEPE, at much lower concentrations, is an endogenous downstream 15-lipoxygenase metabolite of EPA that has been associated with potent anti-inflammatory and antiproliferative effects in nonclinical studies.[23,24] The therapeutic effects of 15(S)-HEPE are thought to be induced by pleiotropic modes of action. We postulated that because of the expected increase in fatty acid oxidation and basal metabolic rate following n-3 fatty acid treatment,[25] and the observed improvement of NAFLD histology, hepatic fat content, alanine aminotransferase (ALT) and markers of fibrosis in preclinical testing, epeleuton may exert a beneficial treatment effect in patients with NAFLD.

This phase 2a trial was designed to investigate the efficacy and safety of 2 doses of epeleuton; 1 and 2 g/day compared with placebo in patients with NAFLD, a body mass index (BMI) between 25.0 and 40.0 kg/m^2, and elevated serum ALT. Because of the high prevalence of metabolic syndrome, type 2 diabetes mellitus, and dyslipidemia in patients with NAFLD,[1] secondary and post hoc analyses were undertaken to compare the lipid-lowering, antihyperglycemic, and anti-inflammatory effects of epeleuton 1 g/day and epeleuton 2 g/day with placebo. On the basis of nonclinical pharmacology studies, we hypothesized that epeleuton may exert superior triglyceride-lowering and anti-inflammatory effects than its endogenous precursor EPA and may provide additional therapeutic benefits attributable to its distinct chemical structure.

METHODS

Study Design and Oversight

The data that support the findings of this study may be made available from the corresponding author upon reasonable request. This was a 16-week, multicenter, international, randomized, double-blind, placebo-controlled, phase 2a trial (NCT02941549) of epeleuton in patients with NAFLD and elevated BMI. The trial was approved by the central and local institutional review boards or ethics committees and was conducted according to the provisions of the International Conference on Harmonization for Good Clinical Practice, the World Health Organization Declaration of Helsinki, and all applicable regulatory requirements. All participants provided written informed consent before participation in the trial.

Study Participants and Study Conduct

Patients were assigned to trial treatment in accordance with the randomization schedule in permuted blocks stratified according to trial site. Patients meeting all inclusion and no exclusion criteria were randomized in a 1:1:1 ratio to epeleuton 2 g/day (epeleuton 1 g twice daily), epeleuton 1 g/day (epeleuton 500 mg twice daily) or placebo (light liquid paraffin) twice daily.

Eligibility criteria at screening included an age of 18 to 75 years, NAFLD based on the presence of hepatic steatosis on imaging or histology in the absence of secondary causes, BMI between 25.0 and 40.0 kg/m^2, and ALT ≥1.5 times the upper limit of normal and <5 times upper limit of normal. Exclusion criteria included weight change >5% in the 3 months before screening, history of gastric bypass surgery, history of or scheduled orthotopic liver transplant, hemoglobin A1C (HbA_{1c}) ≥9%, decompensated or severe liver disease, or patients requiring antihyperglycemic treatment or lipid-lowering treatment who were not on a stable dose for at least 3 months before screening. Patients were excluded from the trial if they used dietary supplements containing n-3 or n-6 fatty acids in the 4 weeks before baseline. Detailed inclusion and exclusion criteria are provided in Table S1.

End Points

The primary end points were changes from baseline to week 16 in ALT and liver stiffness as measured by transient elastography. This was the first clinical trial of epeleuton in this patient population. A sample size of 32 participants per group was estimated to provide 80% power for each of the primary end points, assuming a 20% difference in the percentage change between each epeleuton treatment group and placebo, a standard deviation of 25%, a 2-sided alpha rate of 0.05 and accounting for a 20% dropout rate. ALT was assessed at baseline and weeks 2, 4, 8, 12, 16, and the week 20 posttreatment follow-up visit. Liver stiffness was assessed at baseline and week 16.

Changes from baseline of hepatic fat as measured by the controlled attenuation parameter,[26] an ultrasound-based method for hepatic steatosis measurement, measured at baseline and week 16; homeostatic model assessment for insulin resistance (HOMA-IR),[27] a surrogate measure of β-cell function and insulin resistance based on fasting plasma glucose and insulin, measured at baseline and weeks 2, 4, 8, 12, 16, and

20; and adipose insulin resistance (Adipo-IR),[28] a measure of impaired suppression of lipolysis in the presence of high insulin levels that has been associated with impaired glucose tolerance and elevated plasma free fatty acid levels, measured at baseline and weeks 2, 4, 8, 12, 16, and 20, were assessed as secondary end points.

Lipid and glycemic values were initially measured as safety parameters in the study at baseline and weeks 2, 4, 8, 12, 16, and 20. Post hoc analyses assessed percentage changes from baseline to week 16 of triglycerides, very-low-density lipoprotein cholesterol (VLDL-C), non–high-density lipoprotein cholesterol (HDL-C), total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), and remnant lipoprotein cholesterol (RLP-C). Non–HDL-C was calculated by subtracting HDL-C from total cholesterol. RLP-C was derived by subtracting LDL-C from non–HDL-C. Changes from baseline of HbA_{1c}, fasting plasma glucose, insulin, free fatty acids, and hsCRP (high-sensitivity C-reactive protein) were also assessed.

High-throughput ultrasensitive serum proteomic analyses (OLINK proximity extension assay platform)[29] were performed to quantify changes from baseline to week 16 of a panel of 364 circulating biomarkers associated with systemic inflammation, fibrosis, endothelial dysfunction, cardiovascular risk, and other biological processes. Analytes and bioanalytical laboratories are detailed in Table S2.

Blood samples for trough plasma total and unesterified 15(S)-HEPE concentrations were collected via direct venipuncture before the first daily dose at baseline; during treatment weeks 2, 4, 8, and 16; and at the week 20 posttreatment follow-up. Plasma unesterified and total 15(S)-HEPE concentrations were determined by Charles River Laboratories (Edinburgh) using a validated liquid chromatography–tandem mass spectrometry method.

Statistical Analysis

The primary population for efficacy analyses was a modified intention-to-treat (mITT) population that consisted of all randomized patients who received at least 1 dose of the study drug and had 1 postbaseline measurement. The safety population consisted of all patients who received at least 1 dose of the study drug.

The primary end points ALT and liver stiffness, and the prespecified secondary end points hepatic fat measured by controlled attenuation parameter, HOMA-IR, and Adipo-IR at each visit were analyzed using a mixed model of repeated measures under missing-at-random assumptions. The mixed model of repeated measures included treatment group, visit, and treatment-by-visit interaction as fixed effects and baseline as well as treatment-by-baseline as interaction terms. Least squares means and corresponding 95% CIs for each treatment group, along with overall and pair-wise *P* values were calculated. A 2-sided $P<0.05$ was considered statistically significant for all comparisons.

Analysis of changes in triglycerides, non–HDL-C, VLDL-C, LDL-C, HDL-C, total cholesterol, and RLP-C were performed using a Wilcoxon rank sum test with the Hodges-Lehmann median and 95% CIs. The Wilcoxon rank-sum test was selected as a nonparametric test that is robust against outliers.

Changes from baseline of HbA_{1c}, fasting plasma glucose, insulin, and hsCRP were analyzed using an ANCOVA model with baseline value as a covariate. The proportion of patients with elevated HbA_{1C} that normalized at end of treatment was analyzed using logistic regression with baseline HbA_{1C} as a covariate. A nonparametric ANCOVA model was applied to fasting plasma glucose and insulin because of the presence of outliers.

For analysis of serum proteomics, normalized protein expression values were modeled using a linear mixed effects model with visit, treatment, and the interaction between them as fixed effects and a random intercept for each patient. Post hoc contrasts were used to estimate the changes with treatment within each treatment group. *P* values of serum proteomics were adjusted for multiple testing using the Benjamini–Hochberg procedure,[30] which controls for false discovery rate.

For all efficacy end points, a hierarchical closed testing procedure was used for comparing each of the epeleuton treatment groups with placebo. Epeleuton 2 g/day versus placebo was tested first. If the test was not significant, the comparison of epeleuton 1 g/day versus placebo was not considered eligible for declaring significance even if the *P* value was <0.05. A pairwise comparison of epeleuton 2 g versus epeleuton 1 g was also conducted and considered as descriptive. No statistical testing of adverse event rates was performed. Analysis of adverse event rates was descriptive.

Statistical analyses of the primary and secondary end points were conducted using SAS Version 9.2 or above. Post hoc analyses were conducted using SAS JMP Version 14.2.

RESULTS

Patient Population

Between December 2016 and January 2019, a total of 96 patients were enrolled and randomized in permuted blocks of 3 to each of the treatment groups. A total of 33 patients were randomly assigned to epeleuton 2 g/day, 32 to epeleuton 1 g/day, and 31 to placebo. Patient disposition including the numbers of patients who were screened, randomized to a treatment group, and included in the mITT population are shown in the

Consolidated Standards of Reporting Trials flow diagram in Figure 1.

Baseline patient characteristics of the mITT population are listed in Table 1. Serum ALT and liver stiffness were higher at baseline in the placebo group, triglycerides were higher in the epeleuton 2 g/day group. Baseline characteristics were otherwise comparable across treatment groups. Median ALT concentrations at baseline were 74.0, 70.5, and 96.5 U/L in the epeleuton 2 g/day, epeleuton 1 g/day, and placebo groups, respectively. Median liver stiffness was 7.90, 8.16, and 8.42 kPa in the epeleuton 2 g/day, epeleuton 1 g/day, and placebo groups, respectively. Median triglyceride levels were 242.0, 146.0, and 150.0 mg/dL in the epeleuton 2 g/day, epeleuton 1 g/day, and placebo groups, respectively. Median LDL-C levels were 133.0, 133.0, and 138.5 mg/dL in the epeleuton 2 g/day, epeleuton 1 g/day, and placebo groups, respectively. Most (88.2%) patients were not on statin therapy before screening. Baseline HbA_{1c} (%) and fasting plasma glucose were comparable across the treatment groups. Mean HbA_{1c} at baseline was 6.2%; 28.0% of patients had an HbA_{1c} >6.5% at baseline, and 18.3% of patients had a HbA_{1c} >7.0% at baseline; and 25.8% of trial participants were on antihyperglycemic medications.

Primary and Secondary End Points

Treatment with epeleuton at 1 and 2 g/day doses did not result in improvements of the primary end points

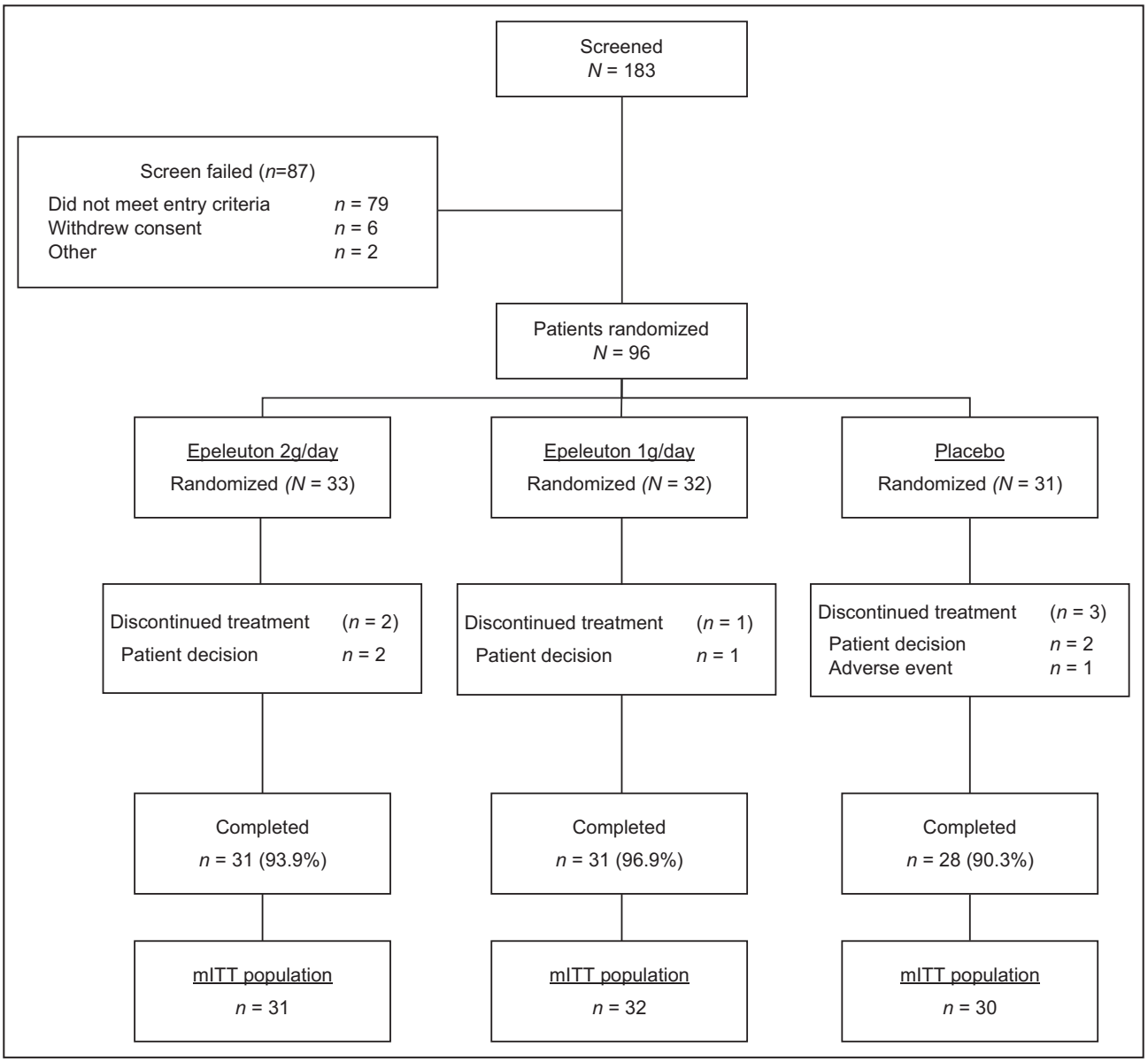

Figure 1. Consolidated Standards of Reporting Trials flow diagram of subject disposition.
mITT indicates modified intention-to-treat.

Table 1. Baseline Patient Characteristics (mITT Population)

	Epeleuton 2 g/d	Epeleuton 1 g/d	Placebo
Characteristic	(N=31)	(N=32)	(N=30)
Sex, n (%)			
Female	10 (32.3)	12 (37.5)	9 (30.0)
Age, y			
Mean (SD)	45.7 (12.0)	50.8 (13.7)	48.8 (11.7)
Race, n (%)			
White	31 (100.00)	30 (93.75)	27 (90.00)
Other	0 (0.00)	2 (6.25)	3 (10.00)
Weight, kg			
Mean (SD)	95.0 (17.8)	98.3 (19.3)	101.2 (16.4)
Body mass index, kg/m^2			
Mean (SD)	31.6 (3.6)	33.4 (4.4)	33.4 (4.8)
Diabetes mellitus, n (%)	9 (29.0)	8 (25.0)	8 (26.7)
Alanine aminotransferase, U/L			
Median (IQR)	74.0 (40.0)	70.5 (46.0)	96.5 (45.0)
Liver stiffness, kPa			
Median (IQR)	7.90 (5.4)	8.16 (3.2)	8.42 (4.5)
HbA_{1c} (%)			
Mean (SD)	6.3 (1.31)	6.2 (1.29)	6.2 (1.02)
HbA_{1c} >6.5%, n (%)	10 (32.3)	9 (28.1)	8 (26.7)
HbA_{1c} >7.0%, n (%)	6 (19.4)	6 (18.8)	5 (16.7)
Fasting plasma glucose, mg/dL			
Mean (SD)	119.1 (42.8)	110.9 (29.9)	120.3 (40.2)
Triglycerides, mg/dL			
Median (IQR)	242.0 (155.0)	146.0 (122.3)	150.0 (94.3)
LDL cholesterol, mg/dL			
Median (IQR)	133.0 (49.0)	133.0 (59.5)	138.5 (59.3)
Statin use, n (%)	3 (9.7)	4 (12.5)	4 (13.3)
Antihyperglycemic use, n (%)	8 (25.8)	9 (28.1)	7 (23.3)

HbA_{1c} indicates hemoglobin A_{1C}; IQR, interquartile range; and LDL, low-density lipoprotein.

of serum ALT and liver stiffness at week 16 compared with placebo (Table 2). A decrease from baseline was observed in all treatment groups for both ALT and liver stiffness, reaching significance in the placebo group (ALT, *P*=0.0008; liver stiffness, *P*=0.0003) where higher median baseline concentrations were observed (Table 1). ALT decreased by 6.9, 10.1, and 16.3 U/L in the epeleuton 1 g/day, epeleuton 2 g/day, and placebo groups, respectively. Liver stiffness decreased by 1.3, 0.7, and 2.2 kPa in the epeleuton 1 g/day, epeleuton 2 g/day, and placebo groups, respectively.

Analysis of subgroups with BMI >30 and BMI <30 was generally consistent with the mITT analysis for liver stiffness. Among patients with baseline BMI <30, epeleuton 1 and 2 g/day-treated patients had higher ALT concentrations at baseline and numerically greater reductions than placebo. Conversely, placebo-treated patients had higher baseline ALT concentrations in the subgroup with BMI >30 and exhibited numerically greater reductions suggesting that changes in ALT were dependent on baseline concentrations (Table S3).

Treatment with epeleuton produced a dose-dependent reduction of hepatic fat assessed by controlled attenuation parameter, greatest in the epeleuton 2 g/day group but the between-group comparison did not reach significance at the week 16 end-of-treatment visit. Hepatic fat decreased by 16.3, 22.4, and 12.3 U/L in the epeleuton 1 g/day, epeleuton 2 g/day, and placebo groups, respectively (Table 2).

In a dose-dependent manner, HOMA-IR improved compared with placebo. Epeleuton 2 g/day reduced least squares mean HOMA-IR significantly compared with placebo (epeleuton 2 g/day –2.04 points versus placebo –0.39 points; *P*=0.006) (Table 3 and Figure 2). A similar pattern of dose-dependent improvement was observed for Adipo-IR. Epeleuton 2 g/day induced a statistically significant least squares mean decrease of Adipo-IR compared with placebo (epeleuton 2 g/day

Table 2. Change in ALT, Liver Stiffness, and Hepatic Fat

	Epeleuton						Placebo (n=30)	
	Epeleuton 2 g/d (n=31)			Epeleuton 1 g/d (n=32)				
	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)	*P* Value (vs Placebo)	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)	*P* Value (vs Placebo)	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)
ALT, U/L	93.3 (47.6)	−10.1 (−36.9, 16.8) *P=0.0737	0.7309	82.7 (33.8)	−6.9 (−34.5, 20.7) *P=0.7347	0.5946	98.1 (35.0)	−16.3 (−44.2, 11.7) * P =0.0008
Liver stiffness, kPa	8.99 (6.74)	−0.73 (−1.55, 0.10) *P=0.1165	0.0058	8.53 (3.50)	−1.31 (−2.11, −0.51) * P =0.0038	0.0763	9.10 (4.12)	−2.23 (−3.07, −1.38) * P =0.0003
Hepatic fat measured by CAP, dB/m	327.8 (31.7)	−22.4 (−43.0, −1.8) * P =0.0093	0.4593	310.3 (49.5)	−16.3 (−36.8, 4.1) *P=0.083	0.7671	332.9 (43.8)	−12.3 (−34.4, 9.9) * P =0.0106

ALT indicates alanine aminotransferase; CAP, controlled attenuation parameter; and LS, least squares.
*Indicates *P* value of within-group change from baseline.

−21.07 points versus placebo +3.66 points; *P*=0.017) (Table 3 and Figure 2).

Effects of Epeleuton on Triglycerides, Non–HDL-C, VLDL-C, and Other Lipid Parameters

Epeleuton significantly decreased triglycerides and other atherogenic lipids from baseline to end-of-treatment (Figure 3, Table 4 and Figure S1). In the mITT population, epeleuton 1 g/day reduced median triglyceride levels by 4.6% (*P*=0.016 versus placebo, *P*=0.94 versus baseline) and epeleuton 2 g/day reduced median triglyceride levels by 13.9% (*P*=0.0001 versus placebo, *P*=0.017 versus baseline). However, median triglyceride levels increased by 24.1% in the placebo group (*P*=0.008). Analysis of subgroups with elevated triglyceride levels at baseline indicated that in both epeleuton treatment groups, patients with higher baseline triglyceride levels exhibited greater improvements, whereas in the placebo group patients exhibited smaller changes from baseline (Table S4). In patients with triglycerides ≥150 mg/dL at baseline (n=52), treatment with epeleuton 1 and 2 g/day resulted in reductions of 20.3% (*P*=0.052 versus placebo) and 22.0% (*P*=0.011 versus placebo) compared with placebo, which exhibited a smaller change from baseline than in the mITT population (+13.9%). Greater reductions from baseline were observed for both epeleuton 1 g/day (−20.6%) and 2 g/day (−25.1%) in patients with triglycerides ≥200 mg/dL at baseline (n = 35), and no increase from baseline was observed for placebo-treated patients (−5.0%).

Epeleuton did not affect LDL-C levels relative to placebo at either dose. Similar to the dose-dependent triglyceride-lowering effect observed, epeleuton 2 g/day produced greater reductions of other lipid parameters than epeleuton 1 g/day. Epeleuton 2 g/day significantly reduced VLDL-C (*P*=0.0003), RLP-C (*P*=0.003) and total cholesterol (*P*=0.028) with no effect on HDL-C. Epeleuton 2 g/day also reduced non–HDL-C (*P*=0.058) (Table 4).

Effects of Epeleuton on Glycemic Control and Insulin Sensitivity

Epeleuton produced a dose-dependent and significant decrease in HbA_{1c} from baseline to end of treatment compared with placebo (Figure 2, Table 3, and Figures S2 and S3). Epeleuton 2 g/day significantly reduced mean HbA_{1C} by 0.42% (*P*=0.026) compared with placebo (−0.08%). Epeleuton 1 g/day did not significantly reduce HbA_{1C} compared with placebo. Analysis of subgroups by baseline HbA_{1c} indicated that patients with higher HbA_{1c} at baseline exhibited greater HbA_{1C} improvements compared with the mITT population (Table 3). In patients with HbA_{1c} >6.5% at baseline (mean baseline HbA_{1c}, 7.9%), treatment with epeleuton 2 g/day resulted in a significant mean HbA_{1c} reduction of 1.13% (*P*=0.047; n=26) compared with placebo (−0.26%). Furthermore, among patients with HbA_{1c} >6.5% at baseline, a significantly greater proportion of patients in the epeleuton 2 g/day group (60.0%) than in the placebo group (12.5%) achieved an HbA_{1c} <6.5% at week 16 (*P*=0.034).

Additionally, epeleuton produced consistent dose-dependent reductions of multiple indicators of glycemic control and insulin sensitivity including fasting plasma glucose, insulin, and plasma free fatty acids, with greater reductions noted in the epeleuton 2 g/day group (Table 3 and Figure 2). Epeleuton 2 g/day significantly decreased fasting plasma glucose (mean

Table 3. Change in HbA_{1c}, Glycemic Parameters, Insulin Resistance Parameters, and hsCRP

	Epeleuton						Placebo (n=30)	
	Epeleuton 2 g/d (n=31)			Epeleuton 1 g/d (n=32)				
	Baseline Value Mean (SD)	Change From Baseline Mean (SD)	*P* Value (vs Placebo)	Baseline Value Mean (SD)	Change From Baseline Mean (SD)	*P* Value (vs Placebo)	Baseline Value Mean (SD)	Change From Baseline Mean (SD)
HbA1c (%)	6.3 (1.31)	−0.42 (0.75)	0.0255	6.2 (1.29)	−0.10 (0.49)	0.6827	6.2 (1.02)	−0.08 (0.44)
Subgroups								
HbA_{1c} (%) >6.5%	7.9 (1.03) n=10	−1.13 (0.91)	0.0474	7.8 (1.25) n=9	−0.33 (0.84)	0.8523	7.6 (0.75) n==8	−0.26 (0.66)
HbA_{1c} (%) >7.0%	8.6 (0.55) n=6	−1.30 (1.06)	0.1044	8.4 (1.1) n=6	−0.58 (0.99)	0.7628	8.1 (0.42) n=5	−0.36 (0.78)
Fasting Plasma Glucose, mg/dL	119.1 (42.8)	−6.5 (24.1)	0.0320	110.9 (29.9)	−2.2 (12.9)	0.3155	120.3 (40.2)	−0.2 (14.9)
Fasting Plasma FFA, mmol/L	0.6 (0.24)	−0.05 (0.18)	0.1245	0.5 (0.27)	−0.02 (0.28)	0.2437	0.5 (0.20)	0.05 (0.24)
Fasting Plasma insulin, uU/L	20.5 (19.6)	−5.15 (22.00)	0.1967	26.1 (21.4)	−3.87 (10.53)	0.3295	21.2 (11.8)	0.06 (11.70)
hsCRP, mg/L	2.7 (2.3)	1.3 (6.3)	0.8524	3.0 (1.9)	0.81 (5.7)	0.9751	3.3 (3.2)	0.07 (3.8)
	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)	*P* Value	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)	*P* Value	Baseline Value Mean (SD)	Change From Baseline LS Mean (95% CI)
HOMA-IR	6.1 (5.6)	−2.04 (−2.9, −1.2)	0.0056	7.6 (7.8)	−0.33 (−1.2, 0.6)	0.9064	6.6 (4.9)	−0.39 (−1.3, 0.5)
Adipo-IR	81.7 (65.5)	−21.07 (−36.4, −5.7)	0.0168	91.2 (70.4)	−10.68 (−26.8, 5.4)	0.1622	75.4 (62.7)	3.66 (−12.5, 19.9)

Adipo-IR indicates adipose tissue insulin resistance; FFA, free fatty acid; HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment for insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LS, least squares.

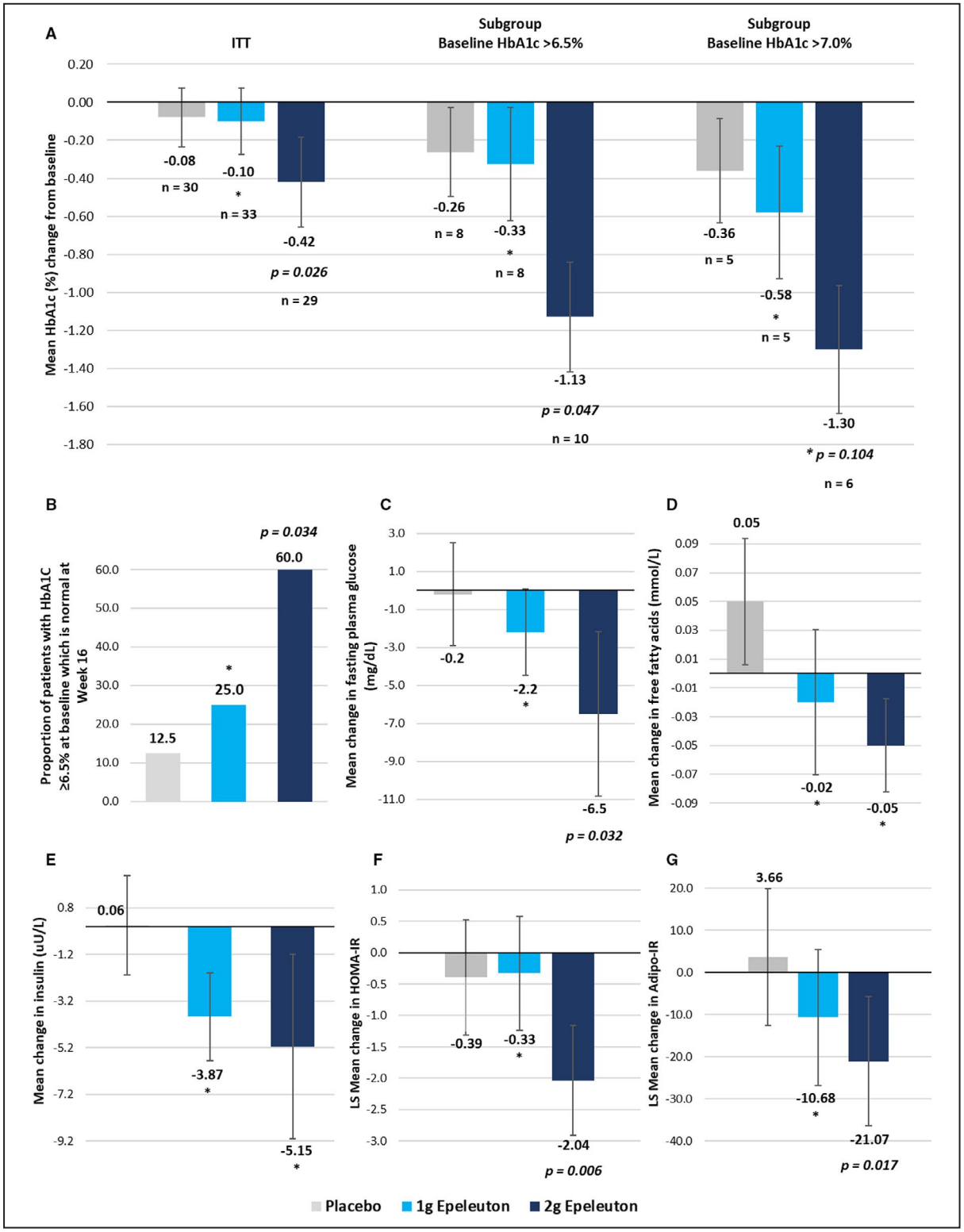

Figure 2. Change in HbA_{1c}, glycemic, and insulin resistance parameters.
A, Change in HbA_{1C} (%) in placebo and epeleuton groups. **B**, Proportion of patients with HbA_{1c} >6.5% at baseline which is normal at week 16. **C**, Change in fasting plasma glucose in placebo and epeleuton groups. **D**, Change in plasma free fatty acids in placebo and epeleuton groups. **E**, Change in insulin in placebo and epeleuton groups. **F**, LS mean change in HOMA-IR in placebo and epeleuton groups. **G**, LS mean change in Adipo-IR in placebo and epeleuton groups. For (**A**, **C**, **D** and **E**) error bars denote standard error. For (**F** and **G**) error bars denote 95% CIs. Adipo-IR indicates adipose tissue insulin resistance; HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment for insulin resistance; and LS, least squares. * denotes nonsignificant *P* values (>0.05) compared with placebo.

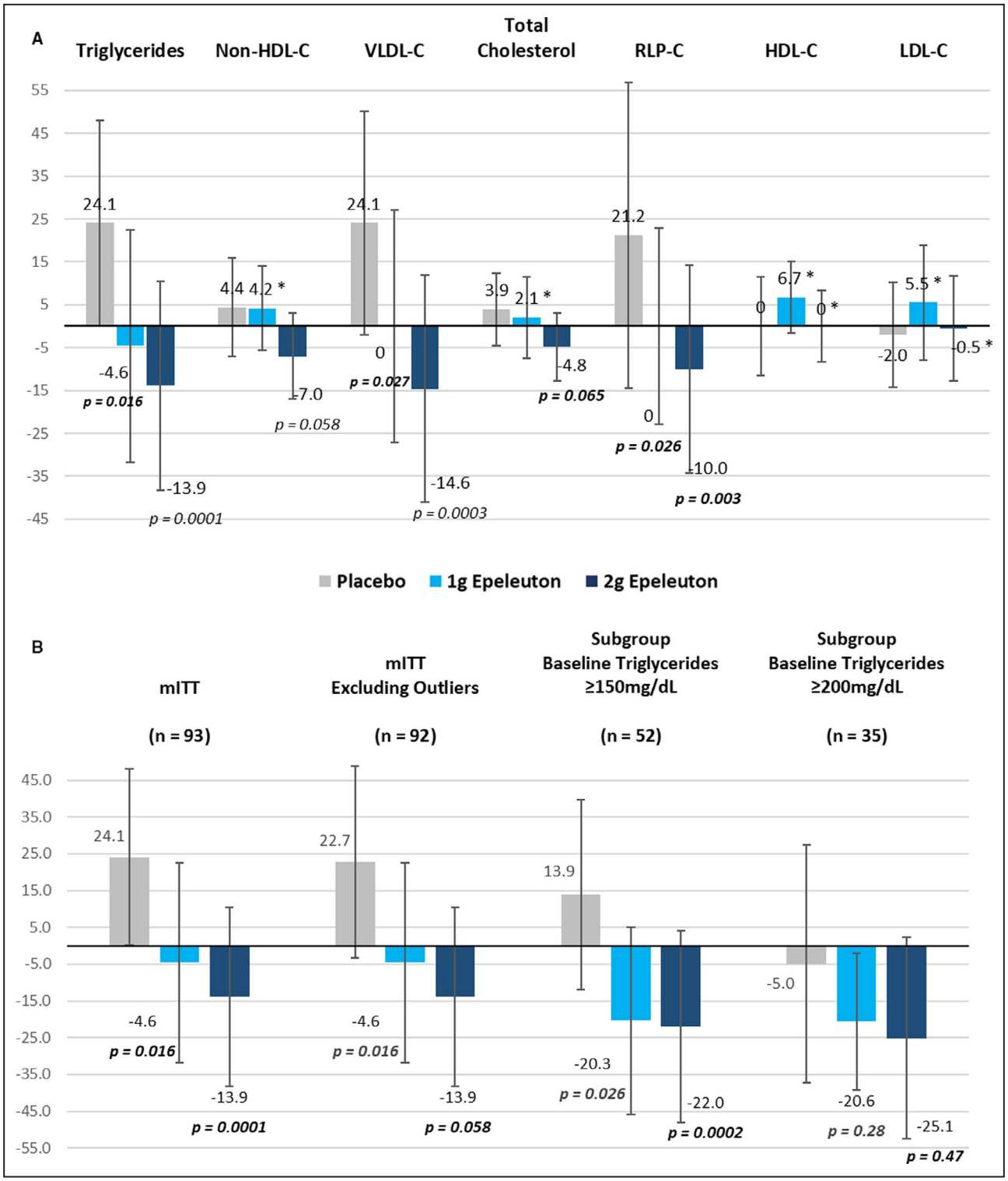

Figure 3. Median percentage change in lipid levels in patients receiving placebo, epeleuton 1 g/day or epeleuton 2 g/day (intention-to-treat population).

A, Changes in lipid levels at week 16. **B**, Changes in triglycerides levels at week 16 in the mITT population and subgroups excluding outliers and with elevated triglycerides at baseline. *P* values are from the Wilcoxon rank-sum test. Error bars denote 95% CIs. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; and VLDL-C, very-low-density lipoprotein cholesterol. *Denotes nonsignificant *P* values (>0.05) compared with placebo.

Table 4. Median Placebo-Corrected Percentage Change in Lipid Levels in Patients Receiving Epeleuton 2 g/day or Epeleuton 1 g/day (Intention-to-Treat Population)

	Epeleuton						Placebo (n=30)		Between-Group Differences	
	Epeleuton 2 g/d (n=31)			Epeleuton 1 g/d (n=32)						
	Baseline Value (mg/dL)	Percent Change From Baseline	*P* Value vs Placebo	Baseline Value (mg/dL)	Percent Change From Baseline	*P* Value vs Placebo	Baseline Value (mg/dL)	Percent Change From Baseline	Epeleuton 2 g/d vs Placebo (%)	Epeleuton 1 g/d vs Placebo (%)
Triglycerides, mg/dL	242.0 (155.0)	−13.9 (48.7) *P=0.017	0.0001	146.0 (122.3)	−4.6 (54.2) *P=0.94	0.0163	150.0 (94.3)	24.1 (47.9) *P=0.008	−40.2 (−60.1, −21.5)	−26.7 (−46.3, −7.1)
VLDL-C, mg/dL	48.0 (30.0)	−14.6 (52.9) *P=0.06	0.0003	28.5 (23.8)	0.0 (54.1) *P=0.89	0.0265	29.5 (18.8)	24.1 (52.2) *P=0.001	−39.4 (−60.2, −18.6)	−25.7 (−45.1, −3.9)
Non–HDL-C, mg/dL	183.0 (95.0)	−7.0 (20.0) *P=0.26	0.0583	165.5 (42.8)	4.2 (19.7) *P=0.13	0.9117	165.0 (61.8)	4.4 (23.1) *P=0.14	−8.1 (−17.5, 0.3)	0.5 (−8.5, 8.8)
RLP-C, mg/dL	45.0 (29.0)	−10.0 (48.4) *P=0.25	0.0031	28.5 (22.5)	0.0 (45.7) *P=0.66	0.0259	25.5 (15.3)	21.2 (71.5) *P=0.003	−34.6 (−57.8, −11.9)	−23.1 (−45.2, −2.8)
Total cholesterol, mg/dL	231.0 (89.0)	−4.8 (15.8) *P=0.18	0.0278	206.0 (42.8)	2.1 (19.0) *P=0.18	0.8382	213.5 (68.0)	3.9 (16.7) *P=0.06	−8.0 (−14.9, −0.8)	−0.7 (−8.7, 6.6)
LDL-C, mg/dL	133.0 (49.0)	−0.5 (24.4) *P=0.92	0.8941	133.0 (59.5)	5.5 (26.8) *P=0.06	0.2366	138.5 (59.3)	−2.0 (24.4) *P=0.76	−0.5 (−9.4, 8.8)	5.8 (−5.1, 15.4)
HDL-C, mg/dL	41.0 (19.0)	0.0 (16.6) *P=0.80	0.8590	43.5 (13.8)	6.7 (16.7) *P=0.0004	0.0686	42.0 (11.0)	0.0 (22.9) *P=0.55	0.2 (−8.6, 8.4)	6.7 (−0.3, 14.3)

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; and VLDL-C, very-low-density lipoprotein cholesterol.

*Indicates *P* value of within-group change from baseline. Baseline values and percent changes from baseline are presented as median (interquartile ranges). Median differences between treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. *P* values are from the Wilcoxon rank-sum test.

change—epeleuton 2 g/day −6.5 mg/dL versus placebo −0.2 mg/dL; *P*=0.032). Epeleuton did not affect blood pressure or body weight (Table S5).

Effects of Epeleuton on Markers of Cardiovascular Risk and Inflammation

HsCRP did not change significantly compared with placebo in either of the epeleuton treatment groups (Table 3). However, epeleuton 2 g/day significantly decreased multiple circulating inflammatory markers including cellular adhesion molecules, chemokines, tumor necrosis factor receptor superfamily members, and other biomarkers of cardiovascular risk and diabetes mellitus (Table S6 and Figures S4 through S8). Epeleuton 1 g/day and placebo did not produce significant decreases of markers of cardiovascular risk and inflammation (Tables S7 and S8).

Plasma 15(S)-HEPE Concentrations

All plasma unesterified 15(S)-HEPE concentrations were below quantifiable limits for predose samples in all treatment groups as well as for most postdose samples for the placebo group. Predose plasma total 15(S)-HEPE concentrations were detectable, were similar for placebo, epeleuton 1 g/day, and epeleuton 2 g/day.

Plasma 15(S)-HEPE concentrations were at pharmacokinetic steady state by 4 weeks and were maintained throughout the 16-week treatment period. Mean plasma unesterified 15(S)-HEPE concentrations across trial weeks 2 through 16 were 43.5 and 62.0 ng/mL for epeleuton 1 and 2 g/day, respectively. Mean plasma total 15(S)-HEPE concentrations across trial weeks 2 through 16 were 355 and 952 ng/mL for epeleuton and 2 g/day, respectively. Concentrations of 15(S)-HEPE generally increased in a dose-dependent manner. Concentration versus time profiles for plasma total and unesterified 15(S)-HEPE in each of the treatment groups are presented in Figures S9 and S10.

Safety

Treatment-emergent adverse events AEs were reported in 15 (45.5%) patients in the epeleuton 2 g/day group, 20 (62.5%) patients in the epeleuton 1 g/day group and 17 (54.8%) patients in the placebo group. Most treatment-emergent AEs were mild-to-moderate in severity and considered unrelated to study drug. The most common treatment-emergent AEs were gastrointestinal disorders which were mild-to-moderate in intensity and occurred in 6 (18.2%) patients in the epeleuton 2 g/day group, 9 (28.1%) patients in the epeleuton 1 g/day group and 7 (22.6%) patients in the placebo group. One patient in the placebo group (3.2%) discontinued treatment because of a treatment-emergent AE. No patients in the epeleuton groups discontinued treatment due to an adverse event. In total, 2 non–study drug–related serious AEs were reported during the trial, a pilonidal cyst in a patient in the placebo group and schizophrenia in a patient in the epeleuton 2 g/day group. No serious AEs were considered related to the study drug. No clinically meaningful adverse changes in laboratory parameters, electrocardiographic parameters, vital signs, or physical examinations were noted.

DISCUSSION

In this phase 2a trial, the primary end points of changes in serum ALT and liver stiffness were not met at either dose of epeleuton at 16 weeks. Although numerical decreases were observed in all treatment groups, changes from baseline were significant only in the placebo group that had notably higher median ALT and liver stiffness levels at baseline compared with the epeleuton treatment groups, possibly indicating a regression to the mean effect.

Epeleuton 2 g/day significantly decreased hepatic fat from baseline, although the between-group comparison between epeleuton 2 g/day and placebo was not significant at week 16. These results are consistent with other short-duration n-3 fatty acid studies in patients with NAFLD.[31,32] In a phase 2 trial conducted to investigate the effect of dapaglifozin monotherapy, n-3 carboxylic acid (EPA and docosahexanoic acid) monotherapy and combination treatment with dapaglifozin and n-3 carboxylic acids on hepatic fat in patients with NAFLD and type 2 diabetes mellitus, both monotherapy groups had significant decreases in hepatic fat from baseline after 12 weeks of treatment, but no significant change occurred in the placebo group. However, only the combination treatment reduced hepatic fat significantly compared with placebo. Notably, n-3 carboxylic acids did not significantly decrease the levels of hepatocellular injury biomarkers including serum ALT despite the effects on hepatic fat.[31] Both the significant decrease of hepatic fat from baseline and the lack of effect on ALT with n-3 carboxylic acids mirror the results of the present trial with epeleuton, though, given baseline differences, further studies are needed to validate such findings.

We hypothesized that epeleuton would have beneficial effects in patients with NAFLD because of improvements in liver histology, hepatic fat content, and inflammation observed in preclinical studies and the reported effects of n-3 fatty acids on fatty acid oxidation and hepatic fat.[25] Although the primary end points were not met in the present trial, changes in hepatic fat indicate a potential utility for epeleuton in the treatment of NAFLD that requires further investigation.

Future studies may need to consider longer treatment durations to establish the full effect of epeleuton on hepatic steatosis and combinatorial approaches with complementary therapies to address the multiplicity of pathways responsible for the development of fatty liver injury.

Furthermore, epeleuton decreased triglycerides, VLDL-C, RLP-C, total cholesterol, and non–HDL-C in a dose-dependent manner, although increases were seen in the placebo group. Additionally, analyses of subgroups with elevated triglycerides at baseline, ≥150 mg/dL, and ≥200 mg/dL demonstrated greater reductions at both doses of epeleuton, suggesting that in a prospectively selected hypertriglyceridemic population, further reductions may be achieved.

The observed reductions in triglycerides with an EPA derivative, while post hoc and hypothesis generating, are particularly relevant after the REDUCE-IT trial that demonstrated treatment of patients with hypertriglyceridemia on optimized statins with icosapent ethyl resulted in significant reductions in major adverse cardiovascular outcomes. As a result, the REDUCE-IT results have established a new paradigm for residual cardiovascular risk reduction.[5,33] Furthermore, despite the lower daily dose of epeleuton, the reductions of triglycerides observed in the present trial are comparable to those seen in REDUCE-IT and ANCHOR (Effect of AMR101 [Ethyl Icosapentate] on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥200 and <500 mg/dL), a phase III trial of icosapent ethyl in patients with high triglyceride levels.[5,34] However, it should be acknowledged that differences in trial populations limit the scope of such comparisons.

Notably, the therapeutic effects of epeleuton on multiple lipids were observed without an increase in LDL-C. This is consistent with results from studies with other EPA-axis n-3 fatty acid treatments.[5,11,34] Definitive differences in cardiovascular outcomes between EPA axis treatments and combination EPA/docosahexaenoic acid treatments will be clarified following the results of the STRENGTH (Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia) trial, an event-driven trial of n-3 carboxylic acids, in statin-treated patients with high triglyceride and low HDL-C levels.[35] Notably, the STRENGTH trial has been discontinued following the recommendation of an independent data monitoring committee because of a low likelihood of demonstrating a benefit to patients.[36]

Although other studies with n-3 fatty acids including icosapent ethyl and other EPA preparations have demonstrated a triglyceride-lowering effect, this has not been associated with an improvement of glycemic control or insulin resistance.[34,37] Instead, it had been speculated that non-EPA n-3 fatty acids may increase HbA_{1c} levels and predispose to the development of diabetes mellitus.[38] In the present trial, epeleuton 2 g/day significantly decreased, rather than increased, HbA_{1c} at week 16 despite a relatively low mean baseline HbA_{1c} (6.3%). Analysis of subgroups by baseline HbA_{1c} levels indicated that patients with higher HbA_{1c} at baseline exhibited greater improvements. In patients with HbA_{1c} >6.5% at baseline, epeleuton significantly decreased HbA_{1c} by 1.13%. The HbA_{1c}-lowering effects seen in this trial, while post hoc and hypothesis generating, indicate epeleuton's potential as a novel antihyperglycemic agent for patients with type 2 diabetes mellitus. Importantly, the results in the subgroup analyses, although in a small sample, are comparable to those seen after treatment with most established antihyperglycemics for longer durations of 24 weeks or more.[39,40]

Epeleuton's effects on hyperglycemia and insulin resistance are also evident in the broadly consistent decreases of multiple parameters including fasting plasma glucose, insulin, and free fatty acids. In this trial, treatment with epeleuton 2 g/day produced significant decreases of HOMA-IR, which quantifies insulin resistance and beta cell function and correlates with estimates using euglycemic clamp methods.[27]

One of the potential explanations for increased risk in patients with high triglycerides is the presence of a proinflammatory state.[41] In fact, it has been speculated that the effects of icosapent ethyl on rates of ischemic events in the REDUCE-IT trial are not fully explained by its triglyceride-lowering effect.[42] It is postulated that an anti-inflammatory effect may have contributed to the magnitude of reduction seen in REDUCE-IT. In the present analysis, epeleuton 2 g/day did not decrease hsCRP but significantly decreased the circulating levels of an array of chemokines, adhesion molecules, tumor necrosis factor receptor superfamily members, and other markers of endothelial dysfunction, cardiovascular, and diabetes mellitus risk. Notably, in phase 3 studies of icosapent ethyl, reductions of hsCRP compared with baseline levels were observed only at the higher 4 g/day dose and not at the 2 g/day dose, which may suggest that similarly a higher dose of epeleuton is required to decrease hsCRP.[34,43] The positive data at the 2 g/day dose and the lack of effect of the lower dose of epeleuton on most inflammatory markers provide mechanistic indications that epeleuton may exert a meaningful systemic and/or tissue-level anti-inflammatory effect when administered above a certain dose threshold. These findings also suggest there is merit in examining a dose of 4 g/day in the future.

In summary, the present work builds on the accumulating evidence that multiple strategies may delay the progression of atherosclerosis and reduce the incidence of ischemic events. Treatment of

hypertriglyceridemia, hyperglycemia, and inflammation have been individually shown to effectively reduce cardiovascular risk and the rate of ischemic events. Epeleuton is a synthetic EPA-derived second-generation n-3 fatty acid with a therapeutic profile distinct from other n-3 fatty acids. The results of this trial, while post hoc and exploratory, have identified epeleuton's unique potential to address synergistically multiple axes of cardiovascular risk and several aspects of the metabolic syndrome.

Limitations

The present results are partly based on post hoc analyses, which include subgroups. Although comparisons were made between randomized groups, minimizing the risk of residual confounding, it cannot be fully excluded. Of note, LDL cholesterol levels were not optimized at baseline, and most patients were not on a statin. Additionally, baseline ALT and liver stiffness levels were higher in the placebo group, and baseline triglyceride levels were higher in the epeleuton 2 g/day group. The reported positive post hoc results indicate meaningful therapeutic potential, but they are hypothesis generating and must be reproduced prospectively in patients with hypertriglyceridemia and type 2 diabetes mellitus.

CONCLUSIONS

Epeleuton was well tolerated, with a safety profile not different from placebo, and although the primary end-points of serum ALT and liver stiffness were not met, its administration was associated with significant dose-dependent decreases of triglycerides, total cholesterol, and multiple atherogenic lipids without raising LDL-C. Additionally, epeleuton meaningfully decreased HbA1c and fasting plasma glucose, and improved insulin resistance and systemic levels of inflammation and endothelial dysfunction markers. These data suggest that epeleuton may have important therapeutic potential for cardiovascular risk reduction by simultaneously targeting hypertriglyceridemia, hyperglycemia, and inflammation. Further studies will be necessary to confirm these hypothesis-generating findings and to investigate the full therapeutic effects of epeleuton for the treatment of NAFLD, hyperglycemia and diabetes mellitus, dyslipidemia, and prevention of ischemic events.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S8
Figures S1–S10

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SUPPLEMENTAL MATERIAL

Table S1. Inclusion and exclusion criteria.

Inclusion Criteria
1. Patients diagnosed with NAFLD by the presence of hepatic steatosis on imaging or histology in the absence of any secondary causes.
2. Patients with an ALT ≥ 1.5 ULN and < 5 ULN on two occasions 7 or more days apart during screening.
3. Patients with historical liver biopsy showing NASH and/or ≥ F1 fibrosis OR NFS ≥ -1.455 OR FIB-4 ≥ 1.3 OR Fibroscan ≥8kPa within 3 months of screening.
4. Patients with a body mass index (BMI) between 25.0 and 40.0 kg/m² inclusive. Patients with a history of controlled obesity or controlled diabetes are allowed on the study.
5. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator.
6. Patients aged between 18 and 75 years inclusive.
7. Female patients and male patients with female partners of child bearing potential must use adequate contraception or have a sterilized partner for the duration of the study. Adequate contraception is defined as: systemic hormonal contraceptives, intrauterine device or barrier method of contraception; in conjunction with spermicide; or agree to sexual abstinence, defined as a patient refraining from heterosexual intercourse during the entire period of risk associated with the study treatments and in line with their preferred and usual lifestyle. Hormonal contraceptives must be on a stable dose for at least one month before baseline
8. Patients who are able to communicate well with the Investigator, to understand and comply with the requirements of the study, and understand and sign the written informed consent.
Exclusion criteria
1. Patients with an unstable metabolic condition such as weight change > 5% in the 3 months prior to inclusion.
2. Patients with medical/surgical history of gastric bypass surgery, orthotopic liver transplant (OLT) or listed for OLT.
3. Patients with uncontrolled diabetes mellitus type 2, i.e. HbA1c ≥ 9% (75mmol/mol) at the time of screening.
4. Patients with decompensated or severe liver disease as evidenced by one or more of the following: confirmed cirrhosis or suspicion of cirrhosis, esophageal varices, ascites, suspicion of portal hypertension, hospitalization for liver disease within 60 days of screening, bilirubin ≥ 2 x ULN, or ALT or AST ≥ 5 x ULN. Patient's with Gilbert's syndrome are eligible if the conjugated bilirubin is ≤1.5 x ULN.
5. Patients with inflammatory bowel disease that is either active or requiring medical therapy.
6. Patients with diagnosed or suspected autoimmune diseases such as systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA).

7. Patients with a history of or active non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas).

8. Patients with significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal insufficiency, serious psychiatric disease, respiratory or hypertensive disease, as well as diabetes and arthritis that, in the opinion of the Investigator, would preclude the patient from participating in and completing the study.

9. Patients requiring anti-diabetic treatment (including insulin sensitizing agents), and/or lipid lowering treatment, and who are not on a stable dose for at least 3 months prior to screening should be excluded. If patients are insulin dependent this treatment should have commenced at least 3 months prior to screening, however changes in dose are permitted.

10. Patients with known hypersensitivity to any ingredients of the study treatment.

11. Patients with a positive test for human immunodeficiency virus (HIV) antibodies, Hepatitis B surface antigen or Hepatitis C antibodies at screening.

12. Patients with liver disease of other aetiologies such as drug-induced, autoimmune hepatitis, PBC, PSC, haemochromatosis, A1AT deficiency or Wilson's disease.

13. Patients with a significant history of drug/solvent abuse, in the opinion of the investigator.

14. Patients with a history of alcohol abuse in the opinion of the Investigator, or who currently drinks in excess of 21 units per week (males) or 14 units per week (females), whereby a unit consists of 10ml or 8mg of pure alcohol.

15. Patients who have used dietary supplements rich in omega-3 or omega-6 fatty acids in the 4 weeks prior to baseline.

16. Patients who have participated in any other clinical study with an investigational drug within 3 months before the first day of administration of study treatment.

17. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in inclusion criterion 7) during the trial.

18. Patients, in the opinion of the Investigator, not suitable to participate in the study.

NAFLD indicates non-alcoholic fatty liver disease; ALT, alanine aminotransferase; ULN, upper limit of normal; NASH, non-alcoholic steatohepatitis; NFS, non-alcoholic fatty liver disease fibrosis score; FIB-4, fibrosis-4 score; F1 fibrosis, mild liver fibrosis (portal fibrosis without septa); BMI, body mass index; OLT, orthotopic liver transplant; HbA1C, hemoglobin A1C; AST, aspartate aminotransferase; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; HIV, human immunodeficiency virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; A1AT, alpha-1 antitrypsin.

Table S2. Analytes and bioanalytical laboratories.

Analytes	Bioanalytical laboratories
ALT, Triglycerides, Total cholesterol, HDL-C, LDL-C, VLDL-C, HbA1c, plasma glucose, free fatty acids, plasma insulin, hsCRP	ICON Laboratory Services, Inc., South County Business Park, Carmanhall and Leopardstown, Dublin 18
High throughput serum proteomics OLINK cardiovascular II, cardiovascular III, cardio-metabolic and immuno-oncology panels (92 biomarkers each)	OLINK Proteomics, Uppsala Science Park, SE-751 83 Uppsala, Sweden
Pharmacokinetics (Trough plasma total and unesterified 15(S)-HEPE)	Charles River Laboratories, Elphinstone, Tranent EH33 2NE, United Kingdom

*Non-HDL-C, RLP-C, HOMA-IR and Adipo-IR are calculated parameters. ALT indicates alanine aminotransferase; Non-HDL-C, non-high-density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; RLP-C, remnant-lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol, HbA1c, hemoglobin A1C; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance, Adipo-IR, adipose tissue insulin resistance and 15(S)-HEPE, 15-hydroxy eicosapentaenoic acid.

Table S3. Changes from baseline in ALT and liver stiffness in sub-groups with BMI >30 and BMI <30.

		Epeleuton						Placebo	
		Epeleuton 2g/day			Epeleuton 1g/day				
		Baseline Value Mean (SD)	Change from Baseline Mean (SD)	p-value (vs placebo)	Baseline Value Mean (SD)	Change from Baseline Mean (SD)	p-value (vs placebo)	Baseline Value Mean (SD)	Change from Baseline Mean (SD)
ALT, U/L	**mITT**	93.3 (47.6)	-15.1 (51.5) n = 28 **p = 0.0737*	0.7309	82.7 (33.8)	-5.2 (97.0) n = 30 **p = 0.7347*	0.5946	98.1 (35.0)	-27.6 (39.8) n = 28 ****p = 0.0008***
	Sub-group BMI >30	83.1 (45.9)	-11.3 (54.3) n = 19 **p = 0.378*	0.3998	77.8 (32.2)	4.0 (111.5) n = 21 **p = 0.871*	0.1270	100.3 (38.0)	-30.9 (39.0) n = 23 ****p = 0.001***
	Sub-group BMI <30	106.8 (50.7)	-24.7 (41.4) n = 12 **p = 0.0636*	0.5640	91.9 (36.5)	-24.2 (44.8) n = 11 **p = 0.1038*	0.5864	91.0 (38.0)	-13.0 (38) n = 7 **p = 0.4003*
Liver stiffness, kPa	**mITT**	9.0 (6.7)	-0.7 (2.4) n = 30 **p = 0.1165*	**0.0058**	8.5 (3.5)	-1.3 (2.4) n = 31 ****p = 0.0038***	0.0763	9.1 (4.1)	-2.4 (2.9) n = 28 ****p = 0.0003***
	Sub-group BMI >30	10.1 (8.3)	-0.5 (2.9) n = 19 **p = 0.497*	**0.0365**	9.2 (3.4)	-1.6 (2.6) n = 21 ****p = 0.0105***	0.3349	9.3 (4.5)	-2.4 (3.1) n = 22 ****p = 0.0014***
	Sub-group BMI <30	7.2 (2.5)	-1.1 (1.4) n = 12 ****p = 0.0253***	0.4014	7.2 (3.6)	-0.8 (1.9) n = 10 **p = 0.2076*	0.2866	8.4 (2.3)	-1.9 (2.5) n = 6 **p = 0.124*

* indicates p-value of within-group change from baseline. ALT indicates alanine aminotransferase; SD, standard deviation; BMI, body mass index and mITT, modified intention-to-treat.

Table S4. Median percentage change in triglycerides in the mITT population and sub-groups excluding outliers and with elevated triglycerides at baseline.

	Epeleuton						Placebo		Between-group differences		
	Epeleuton 2g/day			Epeleuton 1g/day							
	Baseline Value (mg/dL)	Percent change from Baseline	p-value v placebo	Baseline Value (mg/dL)	Percent change from Baseline	p-value v placebo	Baseline Value (mg/dL)	Percent change from Baseline	Epeleuton 2g/day vs Placebo (%)	Epeleuton 1g/day vs Placebo (%)	Epeleuton 2g/day vs 1g/day (%)
Triglycerides, mg/dL mITT	242.0 (155.0) n = 31	-13.9 (48.7) *p = 0.017	0.0001	146.0 (122.3) n = 32	-4.6 (54.2) *p = 0.94	0.0163	150.0 (94.3) n = 30	24.1 (47.9) *p = 0.008	-40.2 (-60.1, -21.5)	-26.7 (-46.3, -7.1)	-13.9 (-34.6, 4.0)
Triglycerides, mg/dL Excluding outliers	242.0 (155.0) n = 31	-13.9 (48.7) *p = 0.017	0.0002	146.0 (122.3) n = 32	-4.6 (54.2) *p = 0.94	0.0257	150.0 (76.0) n = 29	22.7 (52.2) *p = 0.002	-37.9 (-56.5, -19.6)	-24.2 (-43.3, -3.0)	-13.9 (-34.6, 4.0)
Triglycerides, mg/dL Baseline trigycerides >150 mg/dL	270.0 (131.0) n = 23	-22.0 (52.1) *p = 0.005	0.011	250.0 (114.5) n = 15	-20.3 (51.0) *p = 0.11	0.052	210.5 (52.0) n = 14	13.9 (51.7) *p = 0.17	-36.9 (-64.2, -10.5)	-29.6 (-60.3, 1.1)	-6.4 (-30.3, 18.1)
Triglycerides, mg/dL Baseline trigycerides >200 mg/dL	279.0 (107.8) n = 18	-25.1 (54.7) *p = 0.03	0.2787	299.0 (82.0) n = 9	-20.6 (37.1) *p = 0.13	0.4705	239.0 (53.0) n = 8	-5.0 (64.8) *p = 0.95	-23.2 (-55.0, 16.5)	-16.0 (-60.5, 17.1)	-5.5 (-38.3, 27.7)

***** indicates p-value of within-group change from baseline**.** Baseline values and percent changes from baseline are presented as median (interquartile ranges). Median differences between treatment groups and 95% confidence intervals were estimated with the Hodges-Lehmann method. P-values are from the Wilcoxon rank-sum test. mITT indicates modified intention-to-treat.

Table S5. Change from baseline to week 16 in blood pressure and weight (safety analysis set).

	Epeleuton						Placebo (n = 31)	
	Epeleuton 2g/day (n = 33)			Epeleuton 1g/day (n = 32)				
	Baseline Value Mean (SD)	Change from Baseline Mean (SD)	p-value v placebo	Baseline Value Mean (SD)	Change from Baseline Mean (SD)	p-value v placebo	Baseline Value Mean (SD)	Change from Baseline Mean (SD)
Systolic BP, mmHg	127.3 (12.3)	-1.4 (8.9)	0.2510	127.8 (10.6)	0.2 (8.7)	0.1002	129.3 (15.4)	-5.1 (15.1)
Diastolic BP, mmHg	78.8 (9.6)	-0.9 (7.9)	0.6821	77.9 (7.3)	1.0 (8.2)	0.5821	77.9 (6.9)	-0.1 (7.0)
Weight, kg	94.5 (17.3)	-2.2 (3.7)	0.7801	98.1 (19.1)	-1.3 (4.8)	0.6169	100.5 (16.3)	-1.9 (-3.6)

BP indicates blood pressure and SD, standard deviation.

Table S6. Change in the expression of serum proteomic biomarkers at week 16 – Epeleuton 2g/day group

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00588_TLT-2	0.359981935	0.065112137	0.001262056
OID01269_SAA4	0.670703548	0.124284068	0.001262056
OID01275_PLTP	0.274876452	0.052291178	0.001262056
OID00593_TR	0.440689677	0.085555679	0.00128194
OID01252_ST6GAL1	0.517553548	0.104786217	0.001881884
OID00609_PI3	0.331056452	0.069533979	0.002379072
OID00591_PAI	0.53248	0.113369577	0.002379072
OID01224_TIMP1	0.421118387	0.089738126	0.002379072
OID01297_LILRB1	0.34294	0.073784319	0.002403429
OID00654_CCL16	0.322883548	0.071694104	0.00326062
OID00576_MCP-1	0.331639032	0.075229534	0.00359268
OID01266_DPP4	0.365338387	0.082935037	0.00359268
OID00394_TNFRSF11A	0.297192393	0.067844924	0.003693541
OID00440_CCL3	0.393149626	0.091834935	0.004031497
OID01230_ICAM1	0.352782258	0.083171087	0.004031497
OID00460_hOSCAR	0.143438103	0.033444927	0.004031497
OID01294_AOC3	0.311744516	0.073806027	0.004031497
OID00408_SCF	0.282204047	0.066811514	0.004031497
OID00435_SORT1	0.244954004	0.058566197	0.004031497
OID00457_ACE2	0.351636098	0.084162157	0.004031497
OID00430_AMBP	0.14289171	0.034247936	0.004031497
OID00464_CA5A	0.652995136	0.157956101	0.004246167
OID01257_VCAM1	0.323402258	0.078598692	0.004246167
OID00567_TNF-R2	0.267878065	0.066360591	0.004816242
OID00400_IL1RL2	0.266332472	0.066004629	0.004816242
OID01253_IL7R	0.415291613	0.10348087	0.004816242
OID00615_FAS	0.260293548	0.064879557	0.004816242
OID00572_ALCAM	0.287693871	0.07209572	0.004832355
OID00459_CTSL1	0.243419852	0.061258739	0.004832355
OID00398_TIE2	0.194010048	0.04872056	0.004832355
OID00563_TNFRSF14	0.286927742	0.072599352	0.004832355
OID01307_LYVE1	0.339177742	0.085877366	0.004832355
OID00589_FABP4	0.34398	0.087365055	0.004848185
OID00565_ITGB2	0.404344516	0.102984628	0.004851263
OID01236_PRSS2	0.365559355	0.093494377	0.004930021
OID01273_NOTCH1	0.278356129	0.071484463	0.005010076
OID01249_SELL	0.31342129	0.081172191	0.00526538

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00428_TM	0.204390864	0.052914205	0.00526538
OID00605_CHIT1	0.379314194	0.099904085	0.005935534
OID01229_SERPINA5	0.472019355	0.124408589	0.005935534
OID00569_EPHB4	0.234336452	0.061938116	0.005963395
OID01233_C2	0.360506452	0.095689514	0.006081274
OID01247_NCAM1	0.285782581	0.076086956	0.006129178
OID01291_TGFBI	0.381297742	0.102002938	0.006172957
OID00612_AXL	0.257869032	0.069008483	0.006172957
OID00583_LTBR	0.246693548	0.066374178	0.006193212
OID00611_AP-N	0.209735161	0.05660671	0.006193212
OID01300_OSMR	0.152352581	0.041129917	0.006193212
OID01246_CCL5	0.647337097	0.174961327	0.006193212
OID00649_TNF-R1	0.231846452	0.062712703	0.006193212
OID01258_CR2	0.326834194	0.088689848	0.006270503
OID00581_BLM hydrolase	0.333539355	0.090886257	0.006410993
OID00638_IGFBP-7	0.303984516	0.083126293	0.006515426
OID00575_CSTB	0.52795	0.144979764	0.006572456
OID00622_CTSD	0.258496774	0.07108503	0.006572456
OID01289_PCOLCE	0.335266452	0.09227351	0.006572456
OID01255_IGFBP3	0.336529032	0.092865221	0.006626543
OID01238_MET	0.220988065	0.06467693	0.007129849
OID00396_TRAIL-R2	0.23344174	0.065108898	0.007521235
OID00627_IL-1RT2	0.226824839	0.064368786	0.008244858
OID01270_TIE1	0.214983871	0.061126187	0.008258751
OID01217_NRP1	0.146735806	0.041886399	0.008433487
OID01225_CST3	0.371696774	0.10644187	0.008551774
OID01256_PAM	0.343070968	0.098664954	0.0087028
OID01218_PLXNB2	0.254206452	0.073178274	0.0087028
OID01305_FETUB	0.341472903	0.098747801	0.00891216
OID01295_VASN	0.222114516	0.064314774	0.00891216
OID00640_IL-18BP	0.233189032	0.067779518	0.00902651
OID00628_SHPS-1	0.181593548	0.052823473	0.00902651
OID00404_CXCL1	0.675621114	0.197225658	0.009285618
OID01284_PTPRS	0.214746452	0.062970382	0.009437477
OID00410_FGF-21	0.588281576	0.172681833	0.009497637
OID00389_IL-1ra	0.487715001	0.143630973	0.009571615
OID01232_SERPINA7	0.295994194	0.087378811	0.009619749
OID01263_CES1	0.49632	0.148125872	0.010463043
OID01254_ENG	0.257549677	0.077169055	0.010691276
OID01240_IGLC2	0.305335484	0.091860257	0.010778012

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00461_TNFRSF13B	0.191221761	0.057034478	0.010778012
OID01298_TIMD4	0.283011935	0.085442439	0.010778012
OID00439_CCL17	0.418362126	0.126190372	0.010778012
OID01231_REG1A	0.339298065	0.102574122	0.010778012
OID01303_MEGF9	0.295613226	0.08942918	0.010778012
OID01239_F7	0.352515484	0.10705442	0.011009332
OID01264_IGFBP6	0.281326774	0.086194467	0.011737655
OID01260_TNXB	0.181384839	0.055977789	0.012336482
OID00645_RARRES2	0.168700323	0.052257564	0.01258256
OID00391_TNFRSF10A	0.199250307	0.061420316	0.012750792
OID01267_ICAM3	0.268346452	0.083752009	0.012750792
OID01227_F11	0.240667742	0.075116725	0.012750792
OID00595_GDF-15	0.365782903	0.114238618	0.012750792
OID01287_SPARCL1	0.215642258	0.067357965	0.012750792
OID01292_CCL14	0.307789032	0.09674817	0.013287635
OID00599_SPON1	0.193950645	0.06164324	0.014194799
OID00795_MCP-2	0.339158736	0.107239645	0.014194799
OID01220_LILRB5	0.261383871	0.083152833	0.014194799
OID01244_FCGR2A	0.298181613	0.095526758	0.014865472
OID01288_LTBP2	0.245926452	0.079128735	0.015232799
OID00582_PLC	0.196995484	0.063552136	0.015259923
OID00577_CD163	0.290814839	0.09383269	0.015259923
OID00570_IL2-RA	0.189056452	0.061336419	0.015780756
OID00586_CNTN1	0.274970968	0.089324892	0.015783919
OID01276_CCL18	0.351081613	0.11437898	0.015987818
OID00617_TNFSF13B	0.21557	0.070714272	0.016704821
OID01241_KIT	0.212447742	0.070316491	0.017496081
OID00384_PGF	0.218411824	0.072372681	0.017496081
OID00412_RAGE	0.198515984	0.065790159	0.017496081
OID00626_Gal-4	0.268959355	0.089300887	0.017496081
OID00429_VSIG2	0.186835259	0.06192845	0.017496081
OID00621_OPN	0.236886129	0.078850076	0.017663772
OID00620_U-PAR	0.256761935	0.08668674	0.019479699
OID00785_LAP TGF-beta-1	0.240168914	0.081325529	0.020172154
OID00608_PSP-D	0.218430323	0.074349524	0.020326749
OID01272_PRCP	0.253984194	0.087008696	0.021121167
OID00643_CTSZ	0.225562258	0.0779427	0.022220164
OID01259_TCN2	0.216679677	0.074929651	0.022220164
OID00571_OPG	0.245468065	0.085049483	0.022338359
OID00801_CXCL5	0.557589463	0.19291279	0.022646119

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00445_Dkk-1	0.374826344	0.130251056	0.022668554
OID00592_CCL24	0.239889032	0.083609972	0.022668554
OID00639_CD93	0.212893871	0.074265003	0.022668554
OID00564_LDL receptor	0.33041129	0.115753218	0.02313152
OID00601_CXCL16	0.203412258	0.071368376	0.02313152
OID00587_CDH5	0.266906129	0.093760312	0.02313152
OID00629_CCL15	0.187909355	0.066041247	0.02313152
OID00466_CD4	0.180756267	0.063522522	0.024763229
OID00598_DLK-1	0.309155806	0.110115246	0.024763229
OID00383_SLAMF7	0.354690946	0.126236845	0.024763229
OID01226_ANG	0.258613548	0.09220023	0.024763229
OID00390_IL6	0.254965218	0.090924198	0.025148086
OID00821_CCL17	0.34852232	0.124528606	0.025250885
OID00579_GRN	0.179808387	0.064558371	0.025250885
OID00786_CXCL1	0.565118243	0.202480016	0.025250885
OID00646_ICAM-2	0.197754839	0.071146008	0.025365264
OID00444_DCN	0.148833694	0.053926954	0.026006978
OID00449_HB-EGF	0.448232858	0.162189928	0.026006978
OID00632_CPB1	0.281275161	0.102011009	0.026006978
OID01274_COMP	0.30057129	0.109010397	0.026006978
OID00636_SCGB3A2	0.201600968	0.073315855	0.026296967
OID00830_CXCL13	0.266492997	0.096733049	0.026923687
OID00468_VEGFD	0.133320488	0.048704787	0.026923687
OID00442_IgG Fc receptor II-b	0.166729372	0.060936401	0.026923687
OID01222_SOD1	0.561411613	0.212722295	0.027204263
OID01228_PROC	0.316255806	0.116274328	0.027292191
OID00584_Notch 3	0.287632903	0.106030241	0.027328834
OID00616_MB	0.212380323	0.078318843	0.027328834
OID00631_uPA	0.183345806	0.067635028	0.027328834
OID00761_IL7	0.333427296	0.12297273	0.027930937
OID01245_CDH1	0.259451613	0.096764971	0.028939094
OID01290_FCN2	0.274259677	0.102383059	0.028939094
OID00832_VEGFA	0.244530632	0.091684504	0.029282865
OID00578_Gal-3	0.256433226	0.096302462	0.029282865
OID00397_PRSS27	0.196227409	0.073499865	0.029282865
OID00463_LEP	0.253968597	0.095175861	0.029282865
OID00573_TFF3	0.157144516	0.059081051	0.029282865
OID00470_HAOX1	0.600021116	0.225061419	0.029282865
OID00596_SELE	0.257854194	0.098348739	0.031691649
OID00566_IL-17RA	0.219774839	0.08452387	0.03296406

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00637_EGFR	0.163594194	0.062920849	0.03296406
OID01219_FCGR3B	0.228976129	0.088366841	0.033268087
OID00803_HGF	0.272250991	0.10478027	0.033268087
OID01265_TNC	0.246414516	0.095602574	0.034127834
OID01268_THBS4	0.366089032	0.142687114	0.034879791
OID01296_LILRB2	0.24948129	0.097643272	0.035549783
OID01223_CA1	0.615943871	0.249005212	0.036043307
OID00841_CD83	0.208606813	0.081680963	0.036043307
OID00828_ICOSLG	0.312941103	0.120938297	0.036043307
OID00426_KIM1	0.395906586	0.157437453	0.038325791
OID01302_CFHR5	0.25579129	0.101899821	0.038325791
OID00842_IL12	0.276824177	0.11053046	0.039954346
OID00452_THPO	0.167891349	0.067500766	0.040108608
OID00409_IL18	0.266801643	0.108234443	0.042019771
OID00799_PD-L1	0.214518073	0.08692847	0.042164581
OID01216_CHL1	0.207999355	0.084676478	0.042192168
OID00447_PRSS8	0.137175964	0.055966768	0.043202386
OID00590_TFPI	0.182272258	0.074787835	0.043605909
OID01285_MFAP5	0.220938387	0.09098739	0.044264026
OID00594_TNFRSF10C	0.159773871	0.066263303	0.045773844
OID01286_GAS6	0.256347419	0.106668494	0.046358406
OID01283_PLA2G7	0.203814839	0.084937262	0.046484032
OID01280_REG3A	0.086106774	0.03611923	0.047909688
OID00824_CXCL12	0.105634349	0.044586377	0.049515608
OID01293_QPCT	0.20845129	0.090412766	0.049527636
OID00602_IL-6RA	0.156937097	0.066853926	0.051206666
OID01250_NID1	0.225517419	0.096608977	0.052460662
OID00623_PGLYRP1	0.308000323	0.132076992	0.052460662
OID00458_PD-L2	0.136346008	0.05834796	0.052567349
OID00433_XCL1	0.252960251	0.110205035	0.056491897
OID00614_MMP-2	0.169786129	0.074194654	0.056942516
OID01248_CD59	0.207556129	0.093782563	0.059534173
OID01282_FAP	0.172878065	0.076716408	0.060907157
OID00574_SELP	0.329974839	0.146989048	0.06145126
OID00405_LOX-1	0.475353517	0.211715503	0.06145126
OID05026_GP6	0.368930323	0.164819125	0.061784626
OID01281_EFEMP1	0.213708387	0.095506681	0.061784626
OID00648_PDGF subunit A	0.357155806	0.159877932	0.061973135
OID00815_ARG1	0.430028724	0.197696908	0.06315174
OID00399_TF	0.136791837	0.062562149	0.068200709

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00753_TNFRSF9	0.174204212	0.079838785	0.069474188
OID00650_IGFBP-2	0.157280968	0.072391869	0.069480822
OID00462_TGM2	0.32342243	0.150488913	0.073193795
OID00568_MMP-9	0.346425161	0.16324927	0.076761145
OID00756_CD40-L	0.616385033	0.290843042	0.076959704
OID00420_CD84	0.211190435	0.10005221	0.077848763
OID00634_ST2	0.150903871	0.073027045	0.085200184
OID00425_MERTK	0.160493481	0.077966433	0.086753861
OID00450_GDF-2	0.201788874	0.098363058	0.087953203
OID00827_CASP-8	0.715839333	0.359559895	0.090842598
OID00755_MCP-3	0.23783271	0.117114157	0.090842598
OID01235_CA3	0.312035484	0.154397373	0.09154114
OID00415_FGF-23	0.212163065	0.10521108	0.091903404
OID00767_CXCL11	0.306087323	0.151655017	0.091903404
OID00768_MCP-4	0.275782759	0.136521214	0.091903404
OID01221_APOM	0.205996774	0.102516189	0.092031597
OID00791_PDCD1	0.148789621	0.074135016	0.093407531
OID00754_TIE2	0.14816055	0.074145968	0.093407531
OID00604_IGFBP-1	0.265002581	0.132879694	0.093664913
OID00796_CCL4	0.276642188	0.138764257	0.093902205
OID00624_CPA1	0.202831613	0.102019157	0.093999953
OID01237_UMOD	0.098516129	0.050029698	0.097343115
OID00423_REN	0.150064164	0.07643813	0.098846037
OID00418_FS	0.171130584	0.087228282	0.098846037
OID00816_NCR1	0.169461612	0.086895467	0.100962657
OID00465_HSP 27	0.296162692	0.152197761	0.100962657
OID00388_SRC	0.553211326	0.286576444	0.103617052
OID01278_LCN2	0.29407	0.158601451	0.111996987
OID00469_PARP-1	0.835621269	0.452055297	0.112971697
OID00813_CCL3	0.210157995	0.113179777	0.11904954
OID00838_TNF	0.17685395	0.095622018	0.120796299
OID00585_TIMP4	0.133085806	0.072392068	0.121491079
OID00387_IL-4RA	0.149023986	0.081755976	0.125211764
OID01271_COL18A1	0.194610323	0.1084035	0.131222902
OID00789_TWEAK	0.169330315	0.094460683	0.131810352
OID00453_MARCO	0.175005646	0.097828276	0.131810352
OID00765_MCP-1	0.214058635	0.119843323	0.131810352
OID01251_CD46	0.260680645	0.148867015	0.132910741
OID00401_PDGF subunit B	0.261065627	0.146803501	0.132993966
OID00422_SERPINA12	0.210571361	0.118799599	0.134066572

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00758_CD244	0.1912291	0.108637622	0.136401361
OID00793_CD28	0.107025705	0.060772807	0.136401361
OID00831_PD-L2	0.122241701	0.069641324	0.138926766
OID00406_Gal-9	0.12494343	0.071897789	0.140831208
OID00764_ADGRG1	0.165092448	0.09511041	0.142021923
OID00800_CD27	0.128674643	0.074390648	0.142579024
OID00843_CSF-1	0.105145432	0.060978693	0.142579024
OID01306_ANGPTL3	0.198357419	0.117410382	0.15196218
OID00808_CD70	0.16128109	0.095338837	0.152660511
OID00635_t-PA	0.211474516	0.125881509	0.153438679
OID00432_HO-1	0.112395249	0.066927541	0.153438679
OID01234_GP1BA	0.297439032	0.178062911	0.155040611
OID00402_IL-27	0.092704855	0.055727161	0.156945363
OID00630_CASP-3	0.555828065	0.342379335	0.160647558
OID00806_CX3CL1	0.14892547	0.090948571	0.163585175
OID00597_AZU1	0.690539355	0.422716272	0.163585175
OID00759_EGF	0.475197358	0.2920619	0.165365399
OID00600_MPO	0.274569677	0.172599177	0.168475491
OID00613_IL-1RT1	0.140924839	0.087718278	0.169435799
OID00417_GH	-0.483452741	0.300692483	0.169435799
OID00603_RETN	0.311310645	0.194054521	0.169435799
OID00382_CD40-L	0.501814076	0.313237553	0.169435799
OID00618_PRTN3	0.489074194	0.310393197	0.170120021
OID00826_LAMP3	0.173437393	0.108581791	0.170684371
OID00446_LPL	-0.150906082	0.095147076	0.172650915
OID00807_CXCL10	0.218846764	0.138790959	0.176360217
OID00456_MMP12	0.136517511	0.087428719	0.17941192
OID00443_ITGB1BP2	0.585588355	0.381414095	0.179876383
OID00392_STK4	0.578346593	0.371827417	0.179876383
OID00606_TR-AP	0.098203548	0.063367501	0.180067117
OID00781_CD40	0.169041616	0.108770153	0.180067117
OID00835_IL12RB1	0.118354029	0.076387239	0.180067117
OID00819_TNFRSF4	0.129265563	0.084105202	0.184128417
OID00762_PGF	0.139127628	0.090857083	0.18435702
OID01301_C1QTNF1	0.234535484	0.154527901	0.188342052
OID00436_CEACAM8	0.512183763	0.342373576	0.188468886
OID00782_IL18	0.202409718	0.133485519	0.188526792
OID00652_PECAM-1	0.200832903	0.133489111	0.190793708
OID00777_NOS3	0.115774582	0.078153668	0.198476908
OID00763_IL6	0.163193565	0.110544882	0.200349529

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00633_CHI3L1	0.241047419	0.164436154	0.201758219
OID00792_FASLG	0.138222334	0.094114118	0.201758219
OID00451_FABP2	0.167127906	0.114765968	0.204524064
OID00820_MIC-A/B	0.232183189	0.159609567	0.205104274
OID00794_CCL19	0.209261442	0.145888163	0.211677496
OID00419_GLO1	0.296505785	0.213453224	0.220872565
OID00431_PRELP	0.062528194	0.046246908	0.241375334
OID00784_VEGFC	0.183473321	0.135847271	0.241725578
OID01262_GNLY	0.228847419	0.172934051	0.244735011
OID00625_JAM-A	0.28289	0.211543931	0.244735011
OID00641_COL1A1	0.108381613	0.082319879	0.252243673
OID00776_CD4	0.092162395	0.070036032	0.252243673
OID01243_MBL2	0.172016452	0.131775424	0.255532549
OID00811_CCL23	0.139924391	0.107465623	0.256432058
OID00837_CCL20	0.32879369	0.256114592	0.265445532
OID00797_IL-35	0.197743873	0.15640675	0.271033901
OID00825_IFN-gamma	0.048847092	0.040488598	0.29097405
OID00385_ADAM-TS13	0.049072348	0.04126751	0.304030265
OID01277_DEFA1	0.431713871	0.369721209	0.30758982
OID00779_Gal-9	0.092644825	0.079306831	0.311860256
OID00438_PSGL-1	0.042489904	0.03652202	0.313308047
OID00647_KLK6	0.087700968	0.076288561	0.318895662
OID00752_IL8	0.340757213	0.299186101	0.32302996
OID00798_Gal-1	0.069056713	0.061575382	0.325966653
OID00766_CRTAM	0.13209834	0.116720614	0.326158256
OID00448_AGRP	0.101087017	0.089756312	0.326417154
OID00386_BOC	0.079943667	0.072316425	0.330833085
OID00790_PDGF subunit B	0.137574072	0.124153986	0.333827982
OID00395_PAR-1	0.115852748	0.105536131	0.338053337
OID01261_CA4	0.143265161	0.131170738	0.339422313
OID00805_HO-1	0.094744384	0.088489988	0.350543744
OID00434_IL16	0.255886333	0.241991169	0.350718962
OID00783_GZMH	0.630053184	0.624834207	0.376787927
OID00424_DECR1	0.391644882	0.39238559	0.381214746
OID00414_CTRC	0.085778411	0.085476251	0.381660836
OID00413_SOD2	0.027599018	0.027640108	0.382957382
OID00810_TNFRSF12A	0.098203713	0.099404096	0.383498274
OID00787_TNFSF14	0.231136034	0.235314997	0.384413807
OID00380_ANG-1	0.18911714	0.191069188	0.384413807
OID01279_TGFBR3	0.127857097	0.130281812	0.386996277

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00817_DCN	0.07174812	0.073184338	0.386996277
OID00769_TRAIL	0.071224401	0.072738026	0.386996277
OID00403_IL-17D	0.05473885	0.056312719	0.389495423
OID00437_PTX3	0.147021299	0.152549188	0.392827883
OID00788_IL33	0.052839321	0.055068301	0.393961136
OID00840_GZMB	0.482109092	0.508764772	0.395565516
OID00393_IDUA	-0.122096063	0.128475219	0.396522441
OID00775_ADA	0.13651223	0.14496465	0.396522441
OID00454_GT	0.099378144	0.109384273	0.417215923
OID00421_PAPPA	0.102431003	0.112860006	0.417215923
OID00132_MEPE	0.078620968	0.086767466	0.417215923
OID00651_vWF	0.211517419	0.235429988	0.420439142
OID00619_PCSK9	0.113284194	0.130427793	0.43687551
OID00642_PON3	0.084384194	0.098622185	0.443342358
OID00812_CD5	0.158221115	0.190461382	0.453879134
OID00778_IL2	-0.076674389	0.093381111	0.461758623
OID01304_CRTAC1	0.104294839	0.127360119	0.461758623
OID00822_ANGPT2	-0.117735667	0.145924345	0.467734437
OID01242_ITGAM	0.139643871	0.183130996	0.494504443
OID00829_MMP12	0.077741849	0.104294226	0.504318478
OID00770_FGF2	0.117212793	0.165049312	0.523036244
OID00834_IL-21	0.05006223	0.073426836	0.540639577
OID00760_ANG-1	0.131353703	0.194420304	0.546150447
OID00771_CXCL9	0.096851002	0.147181475	0.55706771
OID00809_IL10	0.075103019	0.114983608	0.55706771
OID00774_IFN-beta	-0.058571897	0.090047262	0.55706771
OID00804_GZMA	0.163120529	0.252480016	0.55706771
OID00780_VEGFR-2	0.046355002	0.074111833	0.570364293
OID00833_IL4	0.07348651	0.117788931	0.570364293
OID00772_CD8A	-0.070714993	0.11340347	0.570364293
OID00467_NEMO	0.190709011	0.31283229	0.575663374
OID01299_CNDP1	0.11038129	0.181203118	0.576630293
OID00823_PTN	0.144157287	0.241572195	0.581397843
OID00818_TNFRSF21	0.038091574	0.066971578	0.601384329
OID00644_MMP-3	0.032370323	0.06888213	0.670856251
OID00839_KLRD1	0.048318402	0.108035772	0.685957019
OID00773_CAIX	-0.053153442	0.134463109	0.722895092
OID00757_IL-1 alpha	-0.054084841	0.144570692	0.737028869
OID00814_MMP7	-0.06653047	0.181668092	0.740963727
OID00441_MMP7	-0.053640318	0.162456429	0.766434539

Epeleuton 2g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00379_BMP-6	-0.064117457	0.227747445	0.802475627
OID00610_Ep-CAM	0.033975806	0.168012201	0.862149442
OID00407_GIF	0.017635003	0.128589748	0.909570131
OID00381_ADM	0.019217838	0.140607383	0.909570131
OID00836_IL13	-0.017515243	0.133121448	0.911028363
OID00411_PIgR	0.002790656	0.027841446	0.931612719
OID00131_NT-proBNP	0.020771935	0.209468277	0.931612719
OID00427_THBS2	0.003442981	0.035802748	0.931612719
OID00416_SPON2	-0.006643769	0.074774124	0.934855051
OID00802_IL5	-0.00835897	0.148813133	0.958200749
OID00455_BNP	-0.004379936	0.111693014	0.968972997

npx denotes normalised protein expression. **TLT-2** indicates trem-like transcript 2 protein; **SAA4**, serum amyloid A4; **PLTP**, phospholipid transfer protein; **TR**, transferrin receptor 1; **ST6GAL1**, beta-galactoside alpha-2,6-sialyltransferase 1; **PI3**, elafin; **PAI**, plasminogen activator inhibitor; **TIMP**, tissue inhibitor of metalloproteinases; **LILRB**, leukocyte immunoglobulin-like receptor subfamily B member; **CCL**, chemokine (C-C motif) ligand; **MCP**, monocyte chemoattractant protein; **DPP4**, dipeptidyl peptidase 4; **TNFRSF**, tumor necrosis factor receptor superfamily member; **ICAM**, intercellular adhesion molecule; **hOSCAR**, osteoclast-associated immunoglobulin-like receptor; **AOC3**, amine oxidase copper containing 3 / vascular adhesion protein 1; **SCF**, stem cell factor; **SORT1**, sortilin; **ACE2**, angiotensin-converting enzyme 2; **AMBP**; alpha-1-microglobulin/bikunin precursor; **CA5A**, carbonic anhydrase 5A, mitochondrial; **VCAM-1**, vascular cell adhesion molecule 1; **TNF-R**, tumor necrosis factor receptor; **IL1RL2**, interleukin-1 receptor-like 2; **IL7R**, interleukin-7 receptor subunit alpha; **FAS**, tumor necrosis factor receptor superfamily member 6; **ALCAM**, activated leukocyte cell adhesion molecule; **CTSL1**, cathepsin L1; **TIE2**, angiopoietin-1 receptor; **TIE1**, tyrosine-protein kinase receptor Tie-1; **LYVE1**, Lymphatic vessel endothelial hyaluronic acid receptor 1; **FABP**, fatty acid binding protein; **ITGB2**, integrin beta-2; **PRSS2**, trypsin-2; **PRSS8**, prostasin; **PRSS27**, serine protease 27; **NOTCH**, neurogenic locus notch homolog protein; **SELL**, L-selectin; **TM**, thrombomodulin, **CHIT**, chitotriosidase-1; **SERPINA5**, plasma serine protease inhibitor; **SERPINA7**, thyroxine-binding globulin; **SERPINA12**, visceral adipose tissue-derived serine protease inhibitor; **EPHB4**, ephrin type-B receptor 4; **C2**, complement C2; **NCAM1**, neural cell adhesion molecule 1; **TGFBI**, transforming growth factor-beta-induced protein ig-h3; **AXL**, tyrosine-protein kinase receptor UFO; **LTBR**, lymphotoxin beta receptor; **AP-N**, aminopeptidase N; **OSMR**, oncostatin-M-specific

receptor subunit beta; **CR2**, complement receptor type 2; **BLM hydrolase**, bleomycin hydrolase; **IGFBP**, insulin-like growth factor-binding protein; **CSTB**, cystatin B; **CTSD**, cathepsin D; **PCOLCE**, procollagen C-endopeptidase enhancer 1; **MET**, hepatocyte growth factor receptor; **TRAIL-R2**, tumor necrosis factor related apoptosis-inducing ligand receptor 2; **IL-1RT2**, interleukin-1 receptor type 2; **IL-1RT1**, interleukin-1 receptor type 1; **NRP1**, neuropilin-1; **CST3**, cystatin-C; **PAM**, peptidyl-glycine alpha-amidating monooxygenase; **PLXNB2**, plexin-B2; **FETUB**, fetuin-B; **VASN**, vasorin; **IL-18BP**, interleukin-18-binding protein; **SHPS1**, tyrosine-protein phosphatase non-receptor type substrate 1; **CXCL**, chemokine (C-X-C motif) ligand; **PTPRS**, receptor-type tyrosine-protein phosphatase S; **FGF**, fibroblast growth factor; **IL-1ra**, interleukin-1 receptor antagonist protein; **CES1**, liver carboxylesterase 1; **ENG**, endoglin; **IGLC2**, Ig lambda-2 chain C regions; **TIMD4**, T-cell immunoglobulin and mucin domain-containing protein 4; **REG1A**, lithostathine-1-alpha; **REG3A**, regenerating islet-derived protein 3-alpha; **MEGF9**, multiple epidermal growth factor-like domains protein 9; **F7**, coagulation factor VII; **TNXB**, tenascin-X; **RARRES2**, retinoic acid receptor responder protein 2; **F11**, coagulation factor XI; **GDF-15**, growth differentiation factor 15; **GDF-2**, growth differentiation factor 2; **SPARCL1**, SPARC-like protein 1; **SPON1**, spondin-1; **SPON2**, spondin-2; **FCGR2A**, low affinity immunoglobulin gamma Fc region receptor II-a; **FCGR3B**, low affinity immunoglobulin gamma Fc region receptor III-B; **LTBP2**, latent-transforming growth factor beta-binding protein 2; **PLC**, perlecan; **CD163**, scavenger receptor cysteine-rich type 1 protein M130; **IL2-RA**, interleukin-2 receptor subunit alpha; **CNTN1**, contactin-1; **TNFSF**, tumor necrosis factor ligand superfamily member; **KIT**, mast/stem cell growth factor receptor Kit; **PGF**, placenta growth factor; **RAGE**, receptor for advanced glycosylation end products; **Gal-4**, galectin-4; **VSIG2**, V-set and immunoglobulin domain-containing protein 2; **OPN**, osteopontin; **U-PAR**, urokinase plasminogen activator surface receptor; **LAP TGF-beta-1**, latency-associated peptide transforming growth factor beta-1; **PSP-D**, pulmonary surfactant-associated protein D; **PRCP**, lysosomal Pro-X carboxypeptidase; **CTSZ**, cathepsin Z; **TCN2**, transcobalamin-2; **OPG**, osteoprotegrin; **Dkk-1**, Dickkopf-related protein 1; **CD93**, complement component C1q receptor; **LDL receptor**, low-density lipoprotein receptor; **CDH5**, cadherin-5; **CD4**, T-cell surface glycoprotein CD4; **DLK-1**, protein delta homolog 1; **SLAMF7**, SLAM family member 7; **ANG**, angiogenin; **IL6**, interleukin-6; **GRN**, granulins; **DCN**, decorin; **HB-EGF**, proheparin-binding EGF-like growth factor; **CPB1**, carboxypeptidase B; **COMP**, cartilage oligomeric matrix protein; **SCGB3A2**, secretoglobin family 3A member 2; **VEGFD**, vascular endothelial growth factor D; **IgG Fc receptor II-b**, low affinity immunoglobulin gamma Fc region receptor II-b; **SOD1**, superoxide dismutase [Cu-Zn]; **PROC**, vitamin K-dependent protein C; **MB**, myoglobin; **uPA**, urokinase-type plasminogen activator; **IL7**, interleukin-7; **CDH1**, cadherin-1; **FCN2**, ficolin-2; **VEGFA**, vascular endothelial growth factor A; **Gal-3**, galectin-3; **LEP**, leptin; **TFF3**, trefoil factor 3; **HAOX1**,

hydroxyacid oxidase 1; **SELE**, e-selectin; **IL-17RA**, interleukin-17 receptor A; **EGFR**, epidermal growth factor receptor; **HGF**, hepatocyte growth factor; **TNC**, tenascin; **THBS4**, thrombospondin-4; **CA**, carbonic anhydrase 1; **CD83**, CD83 antigen; **ICOSLG**, ICOS ligand; **KIM1**, kidney injury molecule 1; **CFHR5**, complement factor H-related protein 5; **IL12**, interleukin-12; **THPO**, thrombopoietin; **IL18**, interleukin-18; **PD-L1**, programmed cell death 1 ligand 1; **CHL1**, neural cell adhesion molecule L1-like protein; **TFPI**, tissue factor pathway inhibitor; **MFAP5**, microfibrillar-associated protein 5; **GAS6**, growth arrest-specific protein 6; **PLA2G7**, platelet-activating factor acetylhydrolase; **QPCT**, glutaminyl-peptide cyclotransferase; **IL-6RA**, interleukin-6 receptor subunit alpha; **NID1**, nidogen-1; **PGLYRP1**, peptidoglycan recognition protein 1; **PD-L2**, programmed cell death 1 ligand 2; **XCL1**, lymphotactin; **MMP**, matrix metalloproteinase; **CD59**, CD59 glycoprotein; **FAP**, prolyl endopeptidase FAP; **SELP**, p-selectin; **LOX-1**, lectin-like oxidized LDL receptor 1; **GP6**, platelet glycoprotein VI; **EFEMP1**, EGF-containing fibulin-like extracellular matrix protein 1; **PDGF subunit A**, platelet-derived growth factor subunit A; **ARG1**, arginase-1; **TF**, tissue factor; **TGM2**, protein-glutamine gamma-glutamyltransferase 2; **CD40-L**, CD40 ligand; **CD84**, SLAM family member 5; **ST2**, ST2 protein; **MERTK**, tyrosine-protein kinase Mer; **CASP-8**, caspase-8; **CA3**, carbonic anhydrase 3; **APOM**, apolipoprotein M; **PDCD1**, programmed cell death protein 1; **CPA1**, carboxypeptidase A1; **UMOD**, uromodulin; **REN**, renin; **FS**, follistatin; **NCR1**, natural cytotoxicity triggering receptor 1; **HSP 27**, heat shock 27 kDa protein; **SRC**, proto-oncogene tyrosine-protein kinase Src; **LCN2**, neutrophil gelatinase-associated lipocalin; **PARP-1**, poly [ADP-ribose] polymerase 1; **TNF**, tumor necrosis factor; **IL-4RA**, interleukin-4 receptor subunit alpha; **COL18A1**, collagen alpha-1(XVIII) chain; **TWEAK**, tumor necrosis factor (Ligand) superfamily, member 12; **MARCO**, Macrophage receptor MARCO; **CD46**, membrane cofactor protein; **PDGF subunit B**, platelet-derived growth factor subunit B; **CD244**, natural killer cell receptor 2B4; **CD28**, T-cell-specific surface glycoprotein CD28; **Gal-9**, galectin-9; **ADGRG1**, adhesion G-protein coupled receptor G1; **CD27**, CD27 antigen; **CSF-1**, macrophage colony-stimulating factor 1; **ANGPTL3**, angiopoietin-related protein 3; **CD70**, CD70 antigen; **t-PA**, tissue-type plasminogen activator; **HO-1**, heme oxygenase 1; **GP1BA**, platelet glycoprotein Ib alpha chain; **IL-27**, interleukin-27; **CASP-3**, caspase-3; **CX3CL1**, fractalkine; **AZU1**, azurocidin; **EGF**, pro-epidermal growth factor; **MPO**, myeloperoxidase; **GH**, growth hormone; **RETN**, resistin; **PRTN3**, myeloblastin; **LAMP3**, lysosome-associated membrane glycoprotein 3; **LPL**, lipoprotein lipase; **ITGB1BP2**, melusin; **STK4**, serine/threonine-protein kinase 4; **TR-AP**, tartrate-resistant acid phosphatase type 5; **CD40**, CD40 ligand receptor; **IL12RB1**, interleukin-12 receptor subunit beta-1; **C1QTNF1**, complement C1q tumor necrosis factor-related protein 1; **CEACAM8**, carcinoembryonic antigenrelated cell adhesion molecule 8; **PECAM-1**, platelet endothelial cell adhesion molecule; **NOS3**, nitric oxide synthase, endothelial; **CHI3L1**, chitinase-3-like protein 1; **FASLG**, tyrosine-protein kinase Fgr; **MIC-A/B**, MHC

class I polypeptide-related sequence A/B; **GLO1**, lactoylglutathione lyase; **PRELP**, prolargin; **VEGFC**, vascular endothelial growth factor c; **GNLY**, granulysin; **JAM-A**, junctional adhesion molecule A; **COL1A1**, collagen alpha-1(I) chain; **MBL2**, mannose-binding protein C; **IL-35**, interleukin-35; **IFN-gamma**, interferon gamma; **ADAM-TS13**, A disintegrin and metalloproteinase with thrombospondin motifs 13; **DEFA1**, neutrophil defensin 1; **PSGL-1**, p-selectin glycoprotein ligand 1; **KLK6**, kallikrein-6; **IL-8**, interleukin-8; **Gal-1**, galectin-1; **CRTAM**, cytotoxic and regulatory T-cell molecule; **AGRP**, agouti-related protein; **BOC**, brother of CDO; **PAR-1**; proteinase-activated receptor 1; **CA4**, carbonic anhydrase 4; **IL16**, pro-interleukin-16; **GZMH**, granzyme H; **DECR1**, 2,4-dienoyl-CoA reductase, mitochondrial; **CTRC**, chymotrypsin C; **SOD2**, superoxide dismutase [Mn], mitochondrial; **ANG-1**, angiopoietin-1; **TGFBR3**, transforming growth factor beta receptor type 3; **TRAIL**, TNF-related apoptosis-inducing ligand; **IL-17D**, interleukin-17D; **PTX3**, pentraxin-related protein PTX3; **IL33**, interleukin-33; **GZMB**, granzyme B; **IDUA**, alpha-L-iduronidase; **ADA**, adenosine deaminase; **GT**, gastrotropin; **PAPPA**, pappalysin-1; **MEPE**, matrix extracellular phosphoglycoprotein; **vWF**, von Willebrand factor; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **PON3**, paraoxonase; **CD5**, T-cell surface glycoprotein CD5; **IL2**, interleukin-2; **CRTAC1**, cartilage acidic protein 1; **ANGPT2**, angiopoietin-2; **ITGAM**, integrin alpha-M; **IL-21**, interleukin-21; **IL10**, interleukin-10; **IFN-beta**, interferon beta; **GZMA**, granzyme A; **VEGFR-2**, vascular endothelial growth factor receptor 2; **IL4**, interleukin-4; **CD8A**, T-cell surface glycoprotein CD8 alpha chain; **NEMO**, NF-kappa-B essential modulator; **CNDP1**, Beta-Ala-His dipeptidase; **PTN**, pleiotrophin; **KLRD1**, natural killer cells antigen CD94; **CAIX**, carbonic anhydrase IX; **IL-1 alpha**, interleukin-1 alpha; **BMP-6**, bone morphogenetic protein 6; **Ep-CAM**, epithelial cell adhesion molecule; **GIF**, gastric intrinsic factor; **ADM**, adrenomedullin; **IL13**, interleukin-13; **PlgR**, polymeric immunoglobulin receptor; **NT-proBNP**, N-terminal prohormone brain natriuretic peptide; **THBS2**, thrombospondin-2; **IL5**, interleukin-5; **BNP**, brain natriuretic peptide.

Table S7. Change in the expression of serum proteomic biomarkers at week 16 – Epeleuton 1g/day group

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00593_TR	0.301989667	0.068657614	0.046538965
OID00755_MCP-3	0.368241808	0.112256794	0.436709935
OID00778_IL2	0.231906245	0.073117156	0.436709935
OID00825_IFN-gamma	0.137373959	0.044841534	0.439497842
OID00408_SCF	0.152430541	0.054198204	0.458101854
OID00418_FS	0.194803848	0.070655907	0.458101854
OID00765_MCP-1	0.231138689	0.085324268	0.458101854
OID00389_IL-1ra	0.239029057	0.089612442	0.458101854
OID00394_TNFRSF11A	0.146191668	0.055646226	0.458101854
OID01269_SAA4	0.31383	0.120412373	0.458101854
OID00754_TIE2	0.117385305	0.045822297	0.458101854
OID00779_Gal-9	0.128787452	0.050599361	0.458101854
OID01252_ST6GAL1	0.219905667	0.087267206	0.458101854
OID00565_ITGB2	0.210782	0.084617992	0.458101854
OID00794_CCL19	0.251192432	0.100650068	0.458101854
OID00808_CD70	0.157715916	0.065294731	0.516724234
OID00589_FABP4	0.232197	0.100965901	0.619039358
OID00807_CXCL10	0.269013511	0.119978729	0.632650374
OID00813_CCL3	0.1886057	0.084678177	0.632650374
OID00805_HO-1	0.130809468	0.059580577	0.632650374
OID01224_TIMP1	0.153772667	0.070583959	0.632650374
OID00771_CXCL9	0.208496069	0.096343622	0.632650374
OID00795_MCP-2	0.203815384	0.094767679	0.632650374
OID00440_CCL3	0.186231763	0.087088299	0.632650374
OID00406_Gal-9	0.091624264	0.045141513	0.688837315
OID00824_CXCL12	0.130438358	0.06441211	0.688837315
OID01253_IL7R	0.200739333	0.099941085	0.688837315
OID00423_REN	0.217790049	0.109912513	0.688837315
OID01257_VCAM1	0.116132333	0.059038632	0.688837315
OID00796_CCL4	0.173569189	0.088233299	0.688837315
OID00774_IFN-beta	0.094373723	0.047887385	0.688837315
OID00606_TR-AP	-0.155138	0.080215556	0.688837315
OID00382_CD40-L	0.536493952	0.277637708	0.688837315
OID00391_TNFRSF10A	0.08473968	0.043932621	0.688837315
OID01286_GAS6	0.118239	0.062518876	0.688837315
OID00457_ACE2	0.137217805	0.072382286	0.688837315
OID00576_MCP-1	0.168547667	0.089612726	0.688837315

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00817_DCN	0.068293136	0.036729242	0.688837315
OID00432_HO-1	0.10863558	0.05930909	0.688837315
OID00591_PAI	0.257785667	0.141541139	0.688837315
OID00841_CD83	0.07908627	0.043591142	0.688837315
OID00756_CD40-L	0.551320312	0.306318169	0.688837315
OID00636_SCGB3A2	0.100788667	0.056305244	0.688837315
OID00632_CPB1	0.198780667	0.111328931	0.688837315
OID00828_ICOSLG	0.14284173	0.080429781	0.688837315
OID00818_TNFRSF21	0.062768959	0.035403987	0.688837315
OID00843_CSF-1	0.066642614	0.037722141	0.688837315
OID00567_TNF-R2	0.114899333	0.066217635	0.712794918
OID01296_LILRB2	0.100041333	0.058096771	0.71625378
OID00460_hOSCAR	0.043254861	0.025523277	0.724574097
OID00468_VEGFD	0.07307599	0.043436469	0.724574097
OID00452_THPO	0.125504477	0.074725637	0.724574097
OID00767_CXCL11	0.226460357	0.135437475	0.724574097
OID01250_NID1	0.130034333	0.078438141	0.724574097
OID00768_MCP-4	0.226094223	0.136381012	0.724574097
OID00834_IL-21	0.095933898	0.059510469	0.774446267
OID00758_CD244	0.114992391	0.072810625	0.808872666
OID00446_LPL	-0.116901493	0.074719339	0.816416864
OID00822_ANGPT2	0.091344994	0.058932015	0.816416864
OID01244_FCGR2A	0.095255667	0.061700489	0.816416864
OID00624_CPA1	0.198006333	0.129189061	0.819257259
OID00413_SOD2	0.02532822	0.016677648	0.819257259
OID00439_CCL17	0.25927785	0.170885968	0.819257259
OID00821_CCL17	0.249948151	0.167607509	0.837778399
OID00604_IGFBP-1	0.233236333	0.159080945	0.837778399
OID00579_GRN	0.087367333	0.059667448	0.837778399
OID01288_LTBP2	0.115446667	0.07891664	0.837778399
OID01270_TIE1	0.060302	0.041384505	0.837778399
OID00414_CTRC	0.12321794	0.085411975	0.837778399
OID01229_SERPINA5	0.154502	0.107518507	0.837778399
OID00435_SORT1	0.098029202	0.06859119	0.837778399
OID00622_CTSD	0.092066333	0.064855157	0.837778399
OID00775_ADA	-0.153854781	0.10850037	0.837778399
OID00398_TIE2	0.06295158	0.04462634	0.837778399
OID01265_TNC	0.104188	0.074235902	0.837778399
OID00581_BLM hydrolase	0.084663	0.061323133	0.859962608
OID01237_UMOD	0.071092667	0.051789508	0.860326411

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID01256_PAM	0.092228667	0.069366099	0.872207027
OID00444_DCN	0.047553026	0.035771928	0.872207027
OID00430_AMBP	0.032981516	0.024916075	0.872207027
OID01240_IGLC2	0.084382	0.064181635	0.872207027
OID00810_TNFRSF12A	0.097670051	0.075235887	0.872207027
OID00644_MMP-3	0.121933333	0.094359606	0.872207027
OID00633_CHI3L1	0.126133333	0.097644835	0.872207027
OID01218_PLXNB2	0.065945333	0.051201116	0.872207027
OID00648_PDGF subunit A	0.258923	0.201568865	0.872207027
OID00631_uPA	0.090536667	0.070595199	0.872207027
OID01297_LILRB1	0.065199	0.050893994	0.872207027
OID00454_GT	0.142055005	0.111932274	0.872207027
OID01236_PRSS2	0.074123333	0.059090173	0.872207027
OID00643_CTSZ	0.075396667	0.060255972	0.872207027
OID00784_VEGFC	0.224032224	0.178960814	0.872207027
OID00789_TWEAK	0.097887276	0.078201585	0.872207027
OID00400_IL1RL2	0.072829163	0.058384946	0.872207027
OID00792_FASLG	0.076656784	0.061902715	0.875351885
OID00839_KLRD1	0.088940582	0.07278496	0.887140515
OID00417_GH	0.375188726	0.309486932	0.887140515
OID00835_IL12RB1	0.063291061	0.052308393	0.887140515
OID00574_SELP	0.117773	0.098031378	0.888413601
OID00797_IL-35	0.159146997	0.13316363	0.889240083
OID01234_GP1BA	0.101344333	0.087613088	0.901686352
OID00829_MMP12	0.069100838	0.059995623	0.901686352
OID00571_OPG	0.070236	0.061152035	0.901686352
OID01292_CCL14	0.094667	0.082900548	0.901686352
OID00416_SPON2	0.03125141	0.027861996	0.901686352
OID00781_CD40	0.089021237	0.079564411	0.901686352
OID00836_IL13	-0.154798895	0.138499092	0.901686352
OID00762_PGF	0.057185691	0.051561484	0.901686352
OID00445_Dkk-1	0.168098007	0.152811954	0.901686352
OID01239_F7	0.088066	0.080613709	0.901686352
OID00638_IGFBP-7	0.085321667	0.078375023	0.901686352
OID01291_TGFBI	0.084564667	0.079368929	0.901686352
OID01305_FETUB	0.093966667	0.088406169	0.901686352
OID01266_DPP4	0.074086667	0.069929495	0.901686352
OID00592_CCL24	0.094170333	0.088934894	0.901686352
OID00788_IL33	0.042864476	0.04044977	0.901686352
OID00626_Gal-4	-0.065301667	0.061719102	0.901686352

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00403_IL-17D	-0.044685602	0.042294006	0.901686352
OID00612_AXL	0.068313	0.06511641	0.901686352
OID00386_BOC	0.054470342	0.051920467	0.901686352
OID01251_CD46	0.068904667	0.066059795	0.901686352
OID00759_EGF	0.359672453	0.345703352	0.901686352
OID00640_IL-18BP	0.060553667	0.05859697	0.901686352
OID00763_IL6	0.128375037	0.126177115	0.901686352
OID00641_COL1A1	0.066778667	0.065742018	0.901686352
OID00772_CD8A	0.087534392	0.086524887	0.901686352
OID00572_ALCAM	0.061857	0.062424542	0.901686352
OID01264_IGFBP6	0.062886667	0.06347492	0.901686352
OID01268_THBS4	0.090824667	0.0922102	0.901686352
OID01300_OSMR	0.037059	0.037670472	0.901686352
OID00422_SERPINA12	-0.105071017	0.106672258	0.901686352
OID00459_CTSL1	0.056935931	0.058305235	0.901686352
OID00449_HB-EGF	0.205816167	0.211806716	0.901686352
OID00799_PD-L1	0.053427388	0.055357731	0.901686352
OID00611_AP-N	0.057108333	0.059266485	0.901686352
OID01301_C1QTNF1	0.163686	0.171936341	0.901686352
OID00830_CXCL13	0.080953851	0.086326213	0.901686352
OID00651_vWF	0.196428667	0.209902087	0.901686352
OID00838_TNF	-0.191956986	0.204993718	0.901686352
OID00568_MMP-9	-0.127722	0.137025783	0.901686352
OID01274_COMP	0.074695	0.080368044	0.901686352
OID00397_PRSS27	0.063493539	0.06857853	0.901686352
OID00842_IL12	0.059200874	0.064214351	0.901686352
OID01259_TCN2	0.050044333	0.054377556	0.901686352
OID00563_TNFRSF14	0.063557	0.069362908	0.901686352
OID00761_IL7	0.167012446	0.182171854	0.901686352
OID00393_IDUA	-0.104334361	0.113914437	0.901686352
OID00620_U-PAR	0.055464667	0.060683152	0.901686352
OID00608_PSP-D	-0.080075333	0.087613433	0.901686352
OID00757_IL-1 alpha	0.118876562	0.131615005	0.901686352
OID01276_CCL18	0.072798	0.081073322	0.901686352
OID00384_PGF	0.040609894	0.045172007	0.901686352
OID01299_CNDP1	0.125427667	0.141113898	0.901686352
OID00760_ANG-1	0.18534487	0.208457976	0.901686352
OID00642_PON3	-0.107021667	0.121532426	0.901686352
OID00800_CD27	0.042160862	0.047981306	0.901686352
OID00802_IL5	-0.132821101	0.153632853	0.901686352

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00764_ADGRG1	0.059127162	0.068961079	0.901686352
OID00577_CD163	0.055887333	0.065432159	0.901686352
OID00833_IL4	-0.069203042	0.080967835	0.901686352
OID00793_CD28	0.037282095	0.043965738	0.901686352
OID01233_C2	0.061611	0.072924216	0.901686352
OID00131_NT-proBNP	-0.138076	0.165039685	0.901686352
OID00635_t-PA	0.144517667	0.173878976	0.901686352
OID00780_VEGFR-2	0.0353631	0.04251699	0.901686352
OID01262_GNLY	0.109701333	0.133287762	0.901686352
OID01258_CR2	0.062197	0.075640993	0.901686352
OID00601_CXCL16	0.051005667	0.062260089	0.901686352
OID01273_NOTCH1	0.050941333	0.062410653	0.901686352
OID00456_MMP12	0.047661913	0.058980015	0.901686352
OID01263_CES1	0.087399667	0.108701215	0.901686352
OID00628_SHPS-1	0.051159667	0.063759543	0.901686352
OID00461_TNFRSF13B	0.044669455	0.055665694	0.901686352
OID00385_ADAM-TS13	0.034930853	0.043670311	0.901686352
OID01267_ICAM3	0.054681	0.068438868	0.901686352
OID01245_CDH1	0.05263	0.06596671	0.901686352
OID00616_MB	0.145258	0.183138772	0.901698969
OID00790_PDGF subunit B	0.117303936	0.15148168	0.901698969
OID00585_TIMP4	-0.049643333	0.064311697	0.901698969
OID00752_IL8	0.136999173	0.177445711	0.901698969
OID00436_CEACAM8	-0.193864878	0.25191672	0.901698969
OID01230_ICAM1	0.053413	0.070224203	0.901698969
OID00379_BMP-6	-0.097039869	0.127835948	0.901698969
OID01272_PRCP	-0.048068667	0.064731767	0.901698969
OID00594_TNFRSF10C	-0.054091	0.073563303	0.901698969
OID01232_SERPINA7	0.050542667	0.069361333	0.901698969
OID01295_VASN	0.041825333	0.057646196	0.901698969
OID00803_HGF	0.061082154	0.084172693	0.901698969
OID00401_PDGF subunit B	0.127586901	0.177038765	0.901698969
OID00443_ITGB1BP2	0.189302728	0.263209915	0.901698969
OID00447_PRSS8	0.038579912	0.053883773	0.901698969
OID01249_SELL	0.051024667	0.071355331	0.901698969
OID00782_IL18	0.055516624	0.077885016	0.901698969
OID01247_NCAM1	0.048134333	0.067734095	0.901698969
OID00595_GDF-15	0.049799667	0.071150641	0.901698969
OID00603_RETN	-0.078166	0.111827722	0.901698969
OID01221_APOM	-0.051680667	0.074238635	0.901698969

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID01225_CST3	0.052377	0.07569296	0.901698969
OID00431_PRELP	0.029125963	0.042204444	0.901698969
OID00387_IL-4RA	0.043846366	0.064140258	0.901698969
OID01242_ITGAM	0.082792667	0.124418189	0.901698969
OID00409_IL18	0.04850638	0.073073374	0.901698969
OID00383_SLAMF7	0.041222855	0.062273063	0.901698969
OID00441_MMP7	-0.168325263	0.254230623	0.901698969
OID00429_VSIG2	0.041176083	0.062829675	0.901698969
OID00380_ANG-1	0.118935842	0.183570474	0.901698969
OID00637_EGFR	0.042498667	0.065840297	0.901698969
OID01289_PCOLCE	0.047700667	0.07397888	0.901698969
OID00462_TGM2	-0.124017586	0.194990495	0.901698969
OID00467_NEMO	-0.145393783	0.227324778	0.901698969
OID01275_PLTP	0.046043333	0.072347682	0.901698969
OID01219_FCGR3B	0.045503	0.071671296	0.901698969
OID00827_CASP-8	0.159031786	0.253021783	0.901698969
OID00798_Gal-1	0.027222249	0.043069212	0.901698969
OID00811_CCL23	0.045630912	0.072341003	0.901698969
OID00388_SRC	0.191459387	0.305914794	0.901698969
OID00809_IL10	0.07743529	0.124047339	0.901698969
OID00831_PD-L2	0.025820676	0.041360891	0.901698969
OID00617_TNFSF13B	0.038300667	0.061555904	0.901698969
OID00564_LDL receptor	0.059157	0.095677911	0.901698969
OID00451_FABP2	-0.083212053	0.137113481	0.901698969
OID00590_TFPI	0.048295333	0.079763888	0.901698969
OID00390_IL6	0.073721414	0.121877255	0.901698969
OID00623_PGLYRP1	-0.052564333	0.087571704	0.901698969
OID00437_PTX3	0.066128445	0.110208655	0.901698969
OID00442_IgG Fc receptor II-b	-0.031925484	0.053509147	0.901698969
OID00634_ST2	0.046163333	0.077788085	0.901698969
OID00605_CHIT1	0.040043667	0.067998056	0.901698969
OID00428_TM	0.03108958	0.052852278	0.901698969
OID00395_PAR-1	-0.08063394	0.138729353	0.904668253
OID00410_FGF-21	0.099037386	0.172931002	0.904840956
OID01217_NRP1	0.018124	0.03189561	0.904840956
OID00649_TNF-R1	0.039074	0.068864519	0.904840956
OID00427_THBS2	0.013504936	0.023824911	0.904840956
OID00405_LOX-1	-0.111504635	0.199022141	0.907434286
OID00652_PECAM-1	0.052043333	0.094381958	0.912882328
OID00465_HSP 27	0.084422192	0.155105877	0.914641526

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00621_OPN	0.045359333	0.085045652	0.914641526
OID01279_TGFBR3	0.052243667	0.098398947	0.914641526
OID01227_F11	0.035695333	0.067454963	0.914641526
OID00448_AGRP	0.044724714	0.084618678	0.914641526
OID00826_LAMP3	0.042106916	0.07972217	0.914641526
OID00464_CA5A	0.070447588	0.137825657	0.925356703
OID00434_IL16	-0.097147058	0.190451278	0.925356703
OID00816_NCR1	0.026666695	0.053052605	0.925356703
OID01220_LILRB5	0.033979333	0.06836695	0.925356703
OID00627_IL-1RT2	0.032614667	0.065776093	0.925356703
OID00819_TNFRSF4	0.025713398	0.052597764	0.925356703
OID01307_LYVE1	0.031171	0.064270075	0.925356703
OID01231_REG1A	0.052909	0.109175906	0.925356703
OID00619_PCSK9	0.036514333	0.076147803	0.925356703
OID00647_KLK6	-0.031674667	0.066273762	0.925356703
OID01293_QPCT	-0.02834	0.059300647	0.925356703
OID00614_MMP-2	0.040997667	0.087863518	0.933143746
OID01306_ANGPTL3	-0.045267	0.098715802	0.933143746
OID00598_DLK-1	-0.032175	0.070507623	0.933143746
OID00773_CAIX	0.040838961	0.090166186	0.933143746
OID00575_CSTB	0.044969667	0.099771175	0.933143746
OID01222_SOD1	-0.073706667	0.164204625	0.933143746
OID01298_TIMD4	-0.031449	0.071599384	0.936115788
OID00455_BNP	-0.035416011	0.080672308	0.936115788
OID00613_IL-1RT1	-0.031855667	0.075675167	0.938071219
OID01290_FCN2	0.040301667	0.095753579	0.938071219
OID01254_ENG	0.027559333	0.066272893	0.938071219
OID00615_FAS	0.030279	0.073184108	0.938071219
OID00766_CRTAM	0.028231634	0.06856821	0.938071219
OID00629_CCL15	0.026402	0.064340193	0.938071219
OID00602_IL-6RA	0.023560333	0.058153677	0.938071219
OID00785_LAP TGF-beta-1	0.029935838	0.073905646	0.938071219
OID00381_ADM	-0.036396294	0.091366674	0.938071219
OID00573_TFF3	-0.025067	0.063557861	0.938071219
OID01271_COL18A1	0.036599	0.092908005	0.938071219
OID01302_CFHR5	0.033646667	0.086395685	0.938071219
OID00433_XCL1	0.021704579	0.056862234	0.938071219
OID01294_AOC3	0.022333667	0.05943788	0.938071219
OID00470_HAOX1	0.072451549	0.193220125	0.938071219
OID00840_GZMB	0.16218548	0.438048918	0.938071219

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00832_VEGFA	0.029406099	0.079465849	0.938071219
OID00453_MARCO	-0.026040839	0.070782602	0.938071219
OID00815_ARG1	-0.068348005	0.188845834	0.938071219
OID01280_REG3A	0.016058333	0.044459535	0.938071219
OID00630_CASP-3	0.081163667	0.224947163	0.938071219
OID00588_TLT-2	-0.030267	0.084201143	0.938071219
OID00618_PRTN3	-0.073599333	0.206437957	0.938071219
OID01255_IGFBP3	0.026830667	0.076931444	0.941766401
OID00463_LEP	0.022295216	0.064424694	0.941766401
OID01226_ANG	0.024787	0.07251391	0.942267579
OID00645_RARRES2	0.017172667	0.051806496	0.947362732
OID00654_CCL16	0.026721	0.081333837	0.947362732
OID00777_NOS3	0.021210003	0.065037769	0.947362732
OID00646_ICAM-2	0.023408667	0.072693055	0.947362732
OID00806_CX3CL1	0.015450081	0.049045698	0.947362732
OID00625_JAM-A	0.038432333	0.122529263	0.947362732
OID00769_TRAIL	0.015733886	0.050637057	0.947362732
OID00412_RAGE	0.019914798	0.06458385	0.947362732
OID00783_GZMH	0.161430413	0.5279936	0.947362732
OID00438_PSGL-1	0.009623564	0.032845652	0.955941158
OID01248_CD59	0.020857333	0.072298134	0.955941158
OID00609_PI3	0.024493	0.085944753	0.955941158
OID01287_SPARCL1	0.019452333	0.068793591	0.955941158
OID00823_PTN	0.057826748	0.210996398	0.959852897
OID01281_EFEMP1	-0.022029667	0.081077557	0.959852897
OID01260_TNXB	0.012834	0.04891135	0.964086275
OID00804_GZMA	0.047248473	0.183952012	0.964086275
OID01228_PROC	0.025126667	0.099051423	0.964086275
OID01303_MEGF9	0.017600667	0.069447669	0.964086275
OID00466_CD4	-0.017620847	0.071489927	0.967358388
OID00770_FGF2	0.026459904	0.109222138	0.968017647
OID01243_MBL2	0.020129333	0.0842637	0.968017647
OID01238_MET	0.013289667	0.057424921	0.971372738
OID01261_CA4	0.019438333	0.085704582	0.971372738
OID01304_CRTAC1	-0.01859	0.085174552	0.971372738
OID00801_CXCL5	0.056591761	0.262102277	0.971372738
OID01284_PTPRS	0.011904667	0.05543003	0.971372738
OID00814_MMP7	-0.050284608	0.238470988	0.971372738
OID01283_PLA2G7	0.014076	0.066799305	0.971372738
OID00791_PDCD1	0.012354318	0.05997784	0.971372738

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00787_TNFSF14	0.031983891	0.156399738	0.971372738
OID00399_TF	-0.011279774	0.056725354	0.973390336
OID00458_PD-L2	0.008875363	0.046629906	0.975615977
OID01223_CA1	-0.043042667	0.227549182	0.975615977
OID00599_SPON1	-0.010126333	0.057554143	0.975615977
OID00396_TRAIL-R2	0.008901094	0.051666953	0.975615977
OID00639_CD93	0.010195667	0.061627463	0.975615977
OID00407_GIF	0.01310941	0.079182483	0.975615977
OID01282_FAP	-0.009561333	0.061457061	0.975615977
OID00420_CD84	0.015119928	0.09894397	0.975615977
OID00597_AZU1	-0.051385333	0.336411693	0.975615977
OID00566_IL-17RA	0.009372333	0.064271708	0.975615977
OID00419_GLO1	-0.021068509	0.144510605	0.975615977
OID00583_LTBR	0.00885	0.060855033	0.975615977
OID00600_MPO	0.017239333	0.119364038	0.975615977
OID00582_PLC	0.007275667	0.051541819	0.975615977
OID00392_STK4	-0.050844966	0.360811722	0.975615977
OID01277_DEFA1	-0.031735667	0.227241889	0.975615977
OID00786_CXCL1	0.024396087	0.176103843	0.975615977
OID00584_Notch 3	0.010722333	0.080281943	0.975615977
OID01216_CHL1	-0.008969	0.068705532	0.975615977
OID00610_Ep-CAM	0.019945333	0.158357002	0.975615977
OID00837_CCL20	0.019375057	0.15870762	0.975615977
OID00587_CDH5	0.008851667	0.072800002	0.975615977
OID00132_MEPE	-0.010634	0.092811452	0.976929558
OID00425_MERTK	0.007345812	0.06678953	0.976929558
OID05026_GP6	0.012353667	0.114771133	0.976929558
OID00411_PIgR	-0.001943386	0.018345758	0.976929558
OID00450_GDF-2	-0.007581038	0.076764578	0.976929558
OID00404_CXCL1	0.017759519	0.188309294	0.976929558
OID00776_CD4	-0.006988561	0.075734692	0.976929558
OID00424_DECR1	-0.029328541	0.319225554	0.976929558
OID00650_IGFBP-2	0.006257	0.069777593	0.976929558
OID00426_KIM1	0.00586703	0.071577937	0.980553338
OID00570_IL2-RA	-0.004101667	0.055004635	0.98382739
OID00578_Gal-3	0.005554	0.081123359	0.986063675
OID01278_LCN2	-0.006250667	0.097253043	0.986718044
OID01241_KIT	-0.003346333	0.063589763	0.989467808
OID01246_CCL5	-0.010164667	0.196356505	0.989467808
OID00402_IL-27	0.001777875	0.035033103	0.989467808

Epeleuton 1g/day			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	***p-value*** **Benjamini-Hochberg corrected**
OID00753_TNFRSF9	0.001992647	0.050971719	0.992909397
OID00469_PARP-1	-0.014591034	0.377402461	0.992909397
OID00415_FGF-23	-0.003367724	0.094322237	0.992909397
OID01235_CA3	0.003801333	0.12800611	0.992909397
OID00586_CNTN1	-0.002218667	0.078224244	0.992909397
OID00569_EPHB4	0.001558333	0.059904611	0.992909397
OID00812_CD5	-0.002208879	0.108389547	0.994051807
OID00820_MIC-A/B	0.000788102	0.047799928	0.994051807
OID00596_SELE	-0.000882	0.064180309	0.994051807
OID00421_PAPPA	-0.000719127	0.08177009	0.994051807
OID01285_MFAP5	-0.000511667	0.068064307	0.994051807

npx denotes normalised protein expression. **TLT-2** indicates trem-like transcript 2 protein; **SAA4**, serum amyloid A4; **PLTP**, phospholipid transfer protein; **TR**, transferrin receptor 1; **ST6GAL1**, beta-galactoside alpha-2,6-sialyltransferase 1; **PI3**, elafin; **PAI**, plasminogen activator inhibitor; **TIMP**, tissue inhibitor of metalloproteinases; **LILRB**, leukocyte immunoglobulin-like receptor subfamily B member; **CCL**, chemokine (C-C motif) ligand; **MCP**, monocyte chemoattractant protein; **DPP4**, dipeptidyl peptidase 4; **TNFRSF**, tumor necrosis factor receptor superfamily member; **ICAM**, intercellular adhesion molecule; **hOSCAR**, osteoclast-associated immunoglobulin-like receptor; **AOC3**, amine oxidase copper containing 3 / vascular adhesion protein 1; **SCF**, stem cell factor; **SORT1**, sortilin; **ACE2**, angiotensin-converting enzyme 2; **AMBP**; alpha-1-microglobulin/bikunin precursor; **CA5A**, carbonic anhydrase 5A, mitochondrial; **VCAM-1**, vascular cell adhesion molecule 1; **TNF-R**, tumor necrosis factor receptor; **IL1RL2**, interleukin-1 receptor-like 2; **IL7R**, interleukin-7 receptor subunit alpha; **FAS**, tumor necrosis factor receptor superfamily member 6; **ALCAM**, activated leukocyte cell adhesion molecule; **CTSL1**, cathepsin L1; **TIE2**, angiopoietin-1 receptor; **TIE1**, tyrosine-protein kinase receptor Tie-1; **LYVE1**, Lymphatic vessel endothelial hyaluronic acid receptor 1; **FABP**, fatty acid binding protein; **ITGB2**, integrin beta-2; **PRSS2**, trypsin-2; **PRSS8**, prostasin; **PRSS27**, serine protease 27; **NOTCH**, neurogenic locus notch homolog protein; **SELL**, L-selectin; **TM**, thrombomodulin, **CHIT**, chitotriosidase-1; **SERPINA5**, plasma serine protease inhibitor; **SERPINA7**, thyroxine-binding globulin; **SERPINA12**, visceral adipose tissue-derived serine protease inhibitor; **EPHB4**, ephrin type-B receptor 4; **C2**, complement C2; **NCAM1**, neural cell adhesion molecule 1; **TGFBI**, transforming growth factor-beta-induced protein ig-h3; **AXL**, tyrosine-protein kinase receptor UFO; **LTBR**, lymphotoxin beta receptor; **AP-N**, aminopeptidase N; **OSMR**, oncostatin-M-specific receptor subunit beta; **CR2**, complement receptor type 2; **BLM hydrolase**, bleomycin hydrolase; **IGFBP**, insulin-like growth factor-binding protein; **CSTB**, cystatin B; **CTSD**, cathepsin D; **PCOLCE**, procollagen C-endopeptidase enhancer 1; **MET**, hepatocyte growth factor receptor; **TRAIL-R2**, tumor necrosis factor related apoptosis-inducing ligand receptor 2; **IL-1RT2**, interleukin-1 receptor type 2; **IL-1RT1**, interleukin-1 receptor type 1; **NRP1**, neuropilin-1; **CST3**, cystatin-C; **PAM**, peptidyl-glycine alpha-amidating monooxygenase; **PLXNB2**, plexin-B2; **FETUB**, fetuin-B; **VASN**, vasorin; **IL-18BP**, interleukin-18-binding protein; **SHPS1**, tyrosine-protein phosphatase non-receptor type substrate 1; **CXCL**, chemokine (C-X-C motif) ligand; **PTPRS**, receptor-type tyrosine-protein phosphatase S; **FGF**,

fibroblast growth factor; **IL-1ra**, interleukin-1 receptor antagonist protein; **CES1**, liver carboxylesterase 1; **ENG**, endoglin; **IGLC2**, Ig lambda-2 chain C regions; **TIMD4**, T-cell immunoglobulin and mucin domain-containing protein 4; **REG1A**, lithostathine-1-alpha; **REG3A**, regenerating islet-derived protein 3-alpha; **MEGF9**, multiple epidermal growth factor-like domains protein 9; **F7**, coagulation factor VII; **TNXB**, tenascin-X; **RARRES2**, retinoic acid receptor responder protein 2; **F11**, coagulation factor XI; **GDF-15**, growth differentiation factor 15; **GDF-2**, growth differentiation factor 2; **SPARCL1**, SPARC-like protein 1; **SPON1**, spondin-1; **SPON2**, spondin-2; **FCGR2A**, low affinity immunoglobulin gamma Fc region receptor II-a; **FCGR3B**, low affinity immunoglobulin gamma Fc region receptor III-B; **LTBP2**, latent-transforming growth factor beta-binding protein 2; **PLC**, perlecan; **CD163**, scavenger receptor cysteine-rich type 1 protein M130; **IL2-RA**, interleukin-2 receptor subunit alpha; **CNTN1**, contactin-1; **TNFSF**, tumor necrosis factor ligand superfamily member; **KIT**, mast/stem cell growth factor receptor Kit; **PGF**, placenta growth factor; **RAGE**, receptor for advanced glycosylation end products; **Gal-4**, galectin-4; **VSIG2**, V-set and immunoglobulin domain-containing protein 2; **OPN**, osteopontin; **U-PAR**, urokinase plasminogen activator surface receptor; **LAP TGF-beta-1**, latency-associated peptide transforming growth factor beta-1; **PSP-D**, pulmonary surfactant-associated protein D; **PRCP**, lysosomal Pro-X carboxypeptidase; **CTSZ**, cathepsin Z; **TCN2**, transcobalamin-2; **OPG**, osteoprotegrin; **Dkk-1**, Dickkopf-related protein 1; **CD93**, complement component C1q receptor; **LDL receptor**, low-density lipoprotein receptor; **CDH5**, cadherin-5; **CD4**, T-cell surface glycoprotein CD4; **DLK-1**, protein delta homolog 1; **SLAMF7**, SLAM family member 7; **ANG**, angiogenin; **IL6**, interleukin-6; **GRN**, granulins; **DCN**, decorin; **HB-EGF**, proheparin-binding EGF-like growth factor; **CPB1**, carboxypeptidase B; **COMP**, cartilage oligomeric matrix protein; **SCGB3A2**, secretoglobin family 3A member 2; **VEGFD**, vascular endothelial growth factor D; **IgG Fc receptor II-b**, low affinity immunoglobulin gamma Fc region receptor II-b; **SOD1**, superoxide dismutase [Cu-Zn]; **PROC**, vitamin K-dependent protein C; **MB**, myoglobin; **uPA**, urokinase-type plasminogen activator; **IL7**, interleukin-7; **CDH1**, cadherin-1; **FCN2**, ficolin-2; **VEGFA**, vascular endothelial growth factor A; **Gal-3**, galectin-3; **LEP**, leptin; **TFF3**, trefoil factor 3; **HAOX1**, hydroxyacid oxidase 1; **SELE**, e-selectin; **IL-17RA**, interleukin-17 receptor A; **EGFR**, epidermal growth factor receptor; **HGF**, hepatocyte growth factor; **TNC**, tenascin; **THBS4**, thrombospondin-4; **CA**, carbonic anhydrase 1; **CD83**, CD83 antigen; **ICOSLG**, ICOS ligand; **KIM1**, kidney injury molecule 1; **CFHR5**, complement factor H-related protein 5; **IL12**, interleukin-12; **THPO**, thrombopoietin; **IL18**, interleukin-18; **PD-L1**, programmed cell death 1 ligand 1; **CHL1**, neural cell adhesion molecule L1-like protein; **TFPI**, tissue factor pathway inhibitor; **MFAP5**, microfibrillar-associated protein 5; **GAS6**, growth arrest-specific protein 6; **PLA2G7**, platelet-activating factor acetylhydrolase; **QPCT**, glutaminyl-peptide cyclotransferase; **IL-6RA**, interleukin-6 receptor subunit alpha; **NID1**, nidogen-1; **PGLYRP1**, peptidoglycan recognition protein 1; **PD-L2**, programmed cell death 1 ligand 2; **XCL1**, lymphotactin; **MMP**, matrix metalloproteinase; **CD59**, CD59 glycoprotein; **FAP**, prolyl endopeptidase FAP; **SELP**, p-selectin; **LOX-1**, lectin-like oxidized LDL receptor 1; **GP6**, platelet glycoprotein VI; **EFEMP1**, EGF-containing fibulin-like extracellular matrix protein 1; **PDGF subunit A**, platelet-derived growth factor subunit A; **ARG1**, arginase-1; **TF**, tissue factor; **TGM2**, protein-glutamine gamma-glutamyltransferase 2; **CD40-L**, CD40 ligand; **CD84**, SLAM family member 5; **ST2**, ST2 protein; **MERTK**, tyrosine-protein kinase Mer; **CASP-8**, caspase-8; **CA3**, carbonic anhydrase 3; **APOM**, apolipoprotein M; **PDCD1**, programmed cell death protein 1; **CPA1**, carboxypeptidase A1; **UMOD**, uromodulin; **REN**, renin; **FS**, follistatin; **NCR1**, natural cytotoxicity triggering receptor 1; **HSP 27**, heat shock 27 kDa protein; **SRC**, proto-oncogene tyrosine-protein kinase Src; **LCN2**, neutrophil gelatinase-associated lipocalin; **PARP-1**, poly [ADP-ribose] polymerase 1; **TNF**, tumor necrosis factor; **IL-4RA**, interleukin-4 receptor subunit alpha; **COL18A1**, collagen alpha-1(XVIII) chain; **TWEAK**, tumor necrosis factor (Ligand) superfamily, member 12; **MARCO**, Macrophage receptor MARCO; **CD46**, membrane cofactor protein; **PDGF subunit B**, platelet-derived growth factor subunit B; **CD244**, natural killer cell

receptor 2B4; **CD28**, T-cell-specific surface glycoprotein CD28; **Gal-9**, galectin-9; **ADGRG1**, adhesion G-protein coupled receptor G1; **CD27**, CD27 antigen; **CSF-1**, macrophage colony-stimulating factor 1; **ANGPTL3**, angiopoietin-related protein 3; **CD70**, CD70 antigen; **t-PA**, tissue-type plasminogen activator; **HO-1**, heme oxygenase 1; **GP1BA**, platelet glycoprotein Ib alpha chain; **IL-27**, interleukin-27; **CASP-3**, caspase-3; **CX3CL1**, fractalkine; **AZU1**, azurocidin; **EGF**, pro-epidermal growth factor; **MPO**, myeloperoxidase; **GH**, growth hormone; **RETN**, resistin; **PRTN3**, myeloblastin; **LAMP3**, lysosome-associated membrane glycoprotein 3; **LPL**, lipoprotein lipase; **ITGB1BP2**, melusin; **STK4**, serine/threonine-protein kinase 4; **TR-AP**, tartrate-resistant acid phosphatase type 5; **CD40**, CD40 ligand receptor; **IL12RB1**, interleukin-12 receptor subunit beta-1; **C1QTNF1**, complement C1q tumor necrosis factor-related protein 1; **CEACAM8**, carcinoembryonic antigenrelated cell adhesion molecule 8; **PECAM-1**, platelet endothelial cell adhesion molecule; **NOS3**, nitric oxide synthase, endothelial; **CHI3L1**, chitinase-3-like protein 1; **FASLG**, tyrosine-protein kinase Fgr; **MIC-A/B**, MHC class I polypeptide-related sequence A/B; **GLO1**, lactoylglutathione lyase; **PRELP**, prolargin; **VEGFC**, vascular endothelial growth factor c; **GNLY**, granulysin; **JAM-A**, junctional adhesion molecule A; **COL1A1**, collagen alpha-1(I) chain; **MBL2**, mannose-binding protein C; **IL-35**, interleukin-35; **IFN-gamma**, interferon gamma; **ADAM-TS13**, A disintegrin and metalloproteinase with thrombospondin motifs 13; **DEFA1**, neutrophil defensin 1; **PSGL-1**, p-selectin glycoprotein ligand 1; **KLK6**, kallikrein-6; **IL-8**, interleukin-8; **Gal-1**, galectin-1; **CRTAM**, cytotoxic and regulatory T-cell molecule; **AGRP**, agouti-related protein; **BOC**, brother of CDO; **PAR-1**; proteinase-activated receptor 1; **CA4**, carbonic anhydrase 4; **IL16**, pro-interleukin-16; **GZMH**, granzyme H; **DECR1**, 2,4-dienoyl-CoA reductase, mitochondrial; **CTRC**, chymotrypsin C; **SOD2**, superoxide dismutase [Mn], mitochondrial; **ANG-1**, angiopoietin-1; **TGFBR3**, transforming growth factor beta receptor type 3; **TRAIL**, TNF-related apoptosis-inducing ligand; **IL-17D**, interleukin-17D; **PTX3**, pentraxin-related protein PTX3; **IL33**, interleukin-33; **GZMB**, granzyme B; **IDUA**, alpha-L-iduronidase; **ADA**, adenosine deaminase; **GT**, gastrotropin; **PAPPA**, pappalysin-1; **MEPE**, matrix extracellular phosphoglycoprotein; **vWF**, von Willebrand factor; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **PON3**, paraoxonase; **CD5**, T-cell surface glycoprotein CD5; **IL2**, interleukin-2; **CRTAC1**, cartilage acidic protein 1; **ANGPT2**, angiopoietin-2; **ITGAM**, integrin alpha-M; **IL-21**, interleukin-21; **IL10**, interleukin-10; **IFN-beta**, interferon beta; **GZMA**, granzyme A; **VEGFR-2**, vascular endothelial growth factor receptor 2; **IL4**, interleukin-4; **CD8A**, T-cell surface glycoprotein CD8 alpha chain; **NEMO**, NF-kappa-B essential modulator; **CNDP1**, Beta-Ala-His dipeptidase; **PTN**, pleiotrophin; **KLRD1**, natural killer cells antigen CD94; **CAIX**, carbonic anhydrase IX; **IL-1 alpha**, interleukin-1 alpha; **BMP-6**, bone morphogenetic protein 6; **Ep-CAM**, epithelial cell adhesion molecule; **GIF**, gastric intrinsic factor; **ADM**, adrenomedullin; **IL13**, interleukin-13; **PlgR**, polymeric immunoglobulin receptor; **NT-proBNP**, N-terminal prohormone brain natriuretic peptide; **THBS2**, thrombospondin-2; **IL5**, interleukin-5; **BNP**, brain natriuretic peptide.

Table S8. Change in the expression of serum proteomic biomarkers at week 16 – Placebo group

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00593_TR	0.435598719	0.109732793	0.132812245
OID00449_HB-EGF	0.615928761	0.167839062	0.132812245
OID01269_SAA4	0.448531686	0.122880748	0.132812245
OID00435_SORT1	0.18552057	0.055814772	0.209732708
OID00445_Dkk-1	0.419612353	0.130465872	0.209732708
OID00439_CCL17	0.520573384	0.162237675	0.209732708
OID00767_CXCL11	0.452951506	0.145629937	0.227196507
OID00408_SCF	0.26136444	0.087260927	0.238654888
OID00588_TLT-2	0.172282596	0.057882677	0.238654888
OID00648_PDGF subunit A	0.430936498	0.146264996	0.238654888
OID00581_BLM hydrolase	0.178618799	0.062976707	0.274122198
OID00784_VEGFC	0.323567441	0.11653892	0.274122198
OID00423_REN	0.273220218	0.099562714	0.274122198
OID01252_ST6GAL1	0.303602794	0.114670198	0.274122198
OID00785_LAP TGF-beta-1	0.226714249	0.086273969	0.274122198
OID00440_CCL3	0.28806121	0.110191997	0.274122198
OID01224_TIMP1	0.244850077	0.094054908	0.274122198
OID00398_TIE2	0.154562359	0.059956279	0.274122198
OID00795_MCP-2	0.242772241	0.094352646	0.274122198
OID00574_SELP	0.207191777	0.081379865	0.274122198
OID00615_FAS	0.139210695	0.055685687	0.274122198
OID00811_CCL23	0.214666715	0.085971849	0.274122198
OID00821_CCL17	0.378345789	0.151967486	0.274122198
OID00654_CCL16	0.160234051	0.064652556	0.274122198
OID00779_Gal-9	0.095797795	0.038626334	0.274122198
OID00611_AP-N	0.130757816	0.052940587	0.274122198
OID00460_hOSCAR	0.109853806	0.044471196	0.274122198
OID00796_CCL4	0.241107547	0.10058552	0.289367528
OID00578_Gal-3	0.14209637	0.059603393	0.289367528
OID00131_NT-proBNP	0.367695393	0.154797566	0.289367528
OID00837_CCL20	0.476130501	0.201461361	0.289367528
OID00761_IL7	0.297041454	0.12633441	0.289367528
OID00579_GRN	0.120741082	0.051357575	0.289367528
OID00575_CSTB	0.20058691	0.085616196	0.289367528
OID01248_CD59	0.160147989	0.071010376	0.29561736
OID00565_ITGB2	0.23783741	0.103504969	0.296295489
OID00382_CD40-L	0.694185862	0.302846439	0.296295489
OID00825_IFN-gamma	0.103066111	0.046893764	0.30915488

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID01246_CCL5	0.401763832	0.18176548	0.30915488
OID00432_HO-1	0.242424333	0.109884226	0.30915488
OID00566_IL-17RA	0.104112407	0.04731051	0.30915488
OID00454_GT	0.2778445	0.126976389	0.30915488
OID00755_MCP-3	0.252339543	0.11589541	0.30915488
OID00638_IGFBP-7	0.164063299	0.075662018	0.30915488
OID01292_CCL14	0.252186245	0.116696299	0.30915488
OID01278_LCN2	0.198402103	0.092026533	0.30915488
OID00621_OPN	0.208749066	0.097151547	0.30915488
OID00612_AXL	0.134158673	0.062672696	0.30915488
OID00420_CD84	0.202918233	0.094994679	0.30915488
OID01258_CR2	0.183998775	0.086268952	0.30915488
OID00590_TFPI	0.130094982	0.062476018	0.314558018
OID01251_CD46	0.157333715	0.076732915	0.314558018
OID00452_THPO	0.16922668	0.082809619	0.314558018
OID01234_GP1BA	0.184066901	0.090288161	0.314558018
OID00453_MARCO	0.188247613	0.092368688	0.314558018
OID01244_FCGR2A	0.17243996	0.085267659	0.314558018
OID00572_ALCAM	0.116040121	0.057536599	0.314558018
OID00771_CXCL9	0.33089775	0.164316315	0.314558018
OID00592_CCL24	0.159864646	0.079848543	0.314558018
OID00636_SCGB3A2	0.165520139	0.082689531	0.314558018
OID00646_ICAM-2	0.127567145	0.063792628	0.314558018
OID00788_IL33	0.09347031	0.046809147	0.314558018
OID01226_ANG	0.187393003	0.093808689	0.314558018
OID00413_SOD2	0.04219349	0.021168394	0.314558018
OID00766_CRTAM	0.177864106	0.089827763	0.314558018
OID00827_CASP-8	0.449883172	0.227892336	0.314558018
OID00394_TNFRSF11A	0.177307599	0.090010248	0.314558018
OID00768_MCP-4	0.274121742	0.140089917	0.314558018
OID00643_CTSZ	0.133280843	0.068550973	0.314558018
OID00623_PGLYRP1	0.143445384	0.073832199	0.314558018
OID00567_TNF-R2	0.133165564	0.068786397	0.314558018
OID00601_CXCL16	0.108868197	0.056343374	0.314558018
OID00409_IL18	0.170257875	0.088484971	0.314558018
OID00650_IGFBP-2	0.167745911	0.087314014	0.314558018
OID00563_TNFRSF14	0.118178177	0.061714991	0.314558018
OID01272_PRCP	0.127375499	0.066871336	0.314558018
OID01296_LILRB2	0.171467027	0.090286211	0.314558018

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID01290_FCN2	0.213951958	0.112608736	0.314558018
OID00807_CXCL10	0.245444023	0.129384067	0.314558018
OID00754_TIE2	0.123101028	0.065592889	0.314558018
OID00397_PRSS27	0.170042757	0.090648899	0.314558018
OID00430_AMBP	0.057577394	0.030737979	0.314558018
OID00412_RAGE	0.128890813	0.068919102	0.314558018
OID01266_DPP4	0.163082971	0.087521189	0.314558018
OID00756_CD40-L	0.618670961	0.333732678	0.314558018
OID00455_BNP	0.168004773	0.090738833	0.314558018
OID01245_CDH1	0.17809292	0.096406507	0.314558018
OID00406_Gal-9	0.091909873	0.049857452	0.314558018
OID00589_FABP4	0.257168629	0.139499909	0.314558018
OID00459_CTSL1	0.151009641	0.082160713	0.314558018
OID00634_ST2	0.153115159	0.084200794	0.314774952
OID01291_TGFBI	0.189085443	0.104568729	0.314774952
OID00389_IL-1ra	0.222418098	0.123008749	0.314774952
OID00626_Gal-4	0.157012003	0.086946523	0.314774952
OID00793_CD28	0.067692161	0.037571811	0.314774952
OID00782_IL18	0.115086628	0.06398052	0.314774952
OID00401_PDGF subunit B	0.32128556	0.178956445	0.314774952
OID00640_IL-18BP	0.116925073	0.065164134	0.314774952
OID01232_SERPINA7	0.154154346	0.087244558	0.319454873
OID01303_MEGF9	0.169657291	0.096119376	0.319454873
OID00587_CDH5	0.123659232	0.070173728	0.319454873
OID00469_PARP-1	0.67850139	0.385822913	0.319454873
OID00757_IL-1 alpha	0.195243074	0.112032965	0.319454873
OID01276_CCL18	0.216354629	0.124330082	0.319454873
OID00576_MCP-1	0.145501289	0.084070058	0.319454873
OID05026_GP6	0.170513354	0.098645527	0.319454873
OID00839_KLRD1	0.141333033	0.081856813	0.319454873
OID00570_IL2-RA	0.097499248	0.056571846	0.319454873
OID00591_PAI	0.270197898	0.157028395	0.319454873
OID00602_IL-6RA	0.094627934	0.055054764	0.319454873
OID01218_PLXNB2	0.101094103	0.058901355	0.319454873
OID00791_PDCD1	0.151289675	0.088237973	0.319454873
OID01254_ENG	0.13157808	0.076887612	0.319454873
OID00799_PD-L1	0.148093915	0.0876439	0.329135596
OID00380_ANG-1	0.291120674	0.172612765	0.329135596
OID01262_GNLY	0.210242521	0.124652049	0.329135596

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID01250_NID1	0.157894342	0.094176111	0.330450509
OID00599_SPON1	0.091888371	0.055130098	0.331776072
OID00622_CTSD	0.102409759	0.061674189	0.331776072
OID00571_OPG	0.11301993	0.068251407	0.331776072
OID00826_LAMP3	0.152510307	0.092223152	0.331776072
OID00441_MMP7	-0.330535342	0.199859818	0.331776072
OID01267_ICAM3	0.133334013	0.081246603	0.332824864
OID00577_CD163	0.111104447	0.067682696	0.332824864
OID00466_CD4	0.091365767	0.05640961	0.339567112
OID00805_HO-1	0.168053812	0.103939849	0.339567112
OID00841_CD83	0.108824157	0.067269917	0.339567112
OID00777_NOS3	0.160508087	0.100489408	0.344397398
OID01275_PLTP	0.110312654	0.069071848	0.344397398
OID01230_ICAM1	0.143468548	0.090052136	0.344397398
OID00814_MMP7	-0.301707334	0.190339197	0.344397398
OID00573_TFF3	0.092679086	0.058453616	0.344397398
OID00399_TF	0.117142676	0.073896933	0.344397398
OID00461_TNFRSF13B	0.11426111	0.072149296	0.344716453
OID00132_MEPE	0.193154093	0.123319327	0.344716453
OID00569_EPHB4	0.093983175	0.060031637	0.344716453
OID00457_ACE2	0.146339891	0.093741713	0.344716453
OID01277_DEFA1	0.338719815	0.217412914	0.344716453
OID00428_TM	0.113279393	0.072823535	0.344716453
OID00789_TWEAK	0.113170251	0.072796942	0.344716453
OID01297_LILRB1	0.125183434	0.080665608	0.344716453
OID01222_SOD1	0.242664569	0.156932436	0.345494078
OID00772_CD8A	-0.198124275	0.128660472	0.345850566
OID01261_CA4	0.146365447	0.095370322	0.345850566
OID00628_SHPS-1	0.086684188	0.056478063	0.345850566
OID00830_CXCL13	0.147372803	0.09641997	0.346508052
OID01217_NRP1	0.064875803	0.042538006	0.346508052
OID00595_GDF-15	0.105565229	0.069313751	0.346508052
OID01247_NCAM1	0.128433483	0.084698967	0.347492623
OID00759_EGF	0.578224297	0.383928987	0.349786844
OID01253_IL7R	0.15900613	0.105958105	0.349786844
OID00639_CD93	0.077736176	0.0519392	0.349786844
OID00647_KLK6	0.08258259	0.055207997	0.349786844
OID00603_RETN	0.16083998	0.107824847	0.349786844
OID00645_RARRES2	0.077021486	0.051661523	0.349786844

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00760_ANG-1	0.248968926	0.167919827	0.352671238
OID00386_BOC	0.112610496	0.076458488	0.353109984
OID01257_VCAM1	0.134342456	0.091471702	0.353109984
OID01231_REG1A	0.186369628	0.127239957	0.353109984
OID00405_LOX-1	0.304413842	0.207820641	0.353109984
OID00425_MERTK	0.15074475	0.103017446	0.353109984
OID01220_LILRB5	0.115447576	0.079051636	0.35349432
OID01241_KIT	0.121505513	0.083474989	0.354978468
OID00627_IL-1RT2	0.089148884	0.061458169	0.354978468
OID00838_TNF	0.119952114	0.083578524	0.362665451
OID01219_FCGR3B	0.13255314	0.092621391	0.362665451
OID00444_DCN	0.11813168	0.082896405	0.3643378
OID00384_PGF	0.1211674	0.085582971	0.367360274
OID01233_C2	0.165230741	0.11694426	0.367432744
OID00597_AZU1	0.512606478	0.364886664	0.370654048
OID00815_ARG1	0.182111718	0.130042548	0.371259854
OID00828_ICOSLG	0.169752077	0.122253159	0.378493915
OID00752_IL8	0.304638523	0.220419978	0.378493915
OID01249_SELL	0.127205043	0.092290982	0.378854374
OID00617_TNFSF13B	0.073737141	0.053630669	0.379097767
OID00434_IL16	0.263980273	0.192756949	0.380504481
OID00810_TNFRSF12A	0.122614359	0.090005257	0.383166989
OID00637_EGFR	0.076982639	0.056893066	0.385703728
OID00616_MB	0.175480999	0.129889415	0.385703728
OID01270_TIE1	0.073960445	0.05507176	0.388774454
OID00426_KIM1	0.124422935	0.093350344	0.394234429
OID01264_IGFBP6	0.127996356	0.097529693	0.400588477
OID00468_VEGFD	0.072805365	0.055406132	0.400588477
OID00813_CCL3	0.117445093	0.089485651	0.400588477
OID01227_F11	0.114254251	0.087382792	0.401241408
OID00624_CPA1	-0.128770834	0.098705852	0.401241408
OID01240_IGLC2	0.12049841	0.092990382	0.402143107
OID00823_PTN	0.283836126	0.218842336	0.402143107
OID00436_CEACAM8	0.315447342	0.243784124	0.402143107
OID00774_IFN-beta	0.084630594	0.065706461	0.403718298
OID00790_PDGF subunit B	0.18051741	0.140512362	0.403769678
OID00400_IL1RL2	0.098488353	0.077097594	0.407151944
OID01294_AOC3	0.085099613	0.06709046	0.408320762
OID01216_CHL1	0.105557167	0.083245659	0.408320762

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00442_IgG Fc receptor II-b	0.081535787	0.064640566	0.409400431
OID00801_CXCL5	0.296680496	0.236280813	0.409400431
OID00818_TNFRSF21	0.063255396	0.050414863	0.409400431
OID00383_SLAMF7	0.119752198	0.095576633	0.409400431
OID00817_DCN	0.093693631	0.074876446	0.409400431
OID01225_CST3	0.141207041	0.11343219	0.411265323
OID01295_VASN	0.093454408	0.075451686	0.412968409
OID01265_TNC	0.114154169	0.092556434	0.412968409
OID00625_JAM-A	0.200844323	0.163148567	0.412968409
OID00780_VEGFR-2	0.066338763	0.054288362	0.412968409
OID00630_CASP-3	0.292380943	0.23959625	0.412968409
OID00816_NCR1	0.077557743	0.063773825	0.412968409
OID00794_CCL19	0.134639307	0.111029719	0.412968409
OID00391_TNFRSF10A	0.073539764	0.060709924	0.412968409
OID00765_MCP-1	0.104798563	0.086762108	0.412968409
OID01228_PROC	0.128785998	0.107006813	0.412968409
OID01238_MET	0.086222362	0.071672126	0.412968409
OID00465_HSP 27	0.152478053	0.126897497	0.412968409
OID00418_FS	0.09995685	0.083276294	0.412968409
OID00619_PCSK9	0.107344418	0.088928002	0.412968409
OID01273_NOTCH1	0.097124213	0.08115142	0.412968409
OID01271_COL18A1	0.133595694	0.111969502	0.412968409
OID00783_GZMH	0.540341124	0.453222584	0.412968409
OID00840_GZMB	0.486686225	0.412722985	0.419438436
OID00620_U-PAR	0.08979606	0.076579025	0.421676001
OID00798_Gal-1	0.064073869	0.054818102	0.422105024
OID00644_MMP-3	0.116472579	0.100545337	0.427441072
OID00415_FGF-23	0.131850748	0.114330639	0.428812128
OID01242_ITGAM	0.171816068	0.150705715	0.436451718
OID00808_CD70	0.084629376	0.074513298	0.436708044
OID01305_FETUB	0.125123932	0.110566416	0.437436006
OID00586_CNTN1	0.080039231	0.071277673	0.439854637
OID01239_F7	0.103011535	0.091787194	0.439854637
OID00609_PI3	0.112081145	0.100382165	0.441694785
OID00753_TNFRSF9	0.072595844	0.065206113	0.441694785
OID00422_SERPINA12	0.125845673	0.113255639	0.441694785
OID01256_PAM	0.112376442	0.101414786	0.441694785
OID00618_PRTN3	0.246834266	0.224248764	0.445061791
OID01259_TCN2	0.09091406	0.08340742	0.450195888

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00843_CSF-1	0.055854238	0.051555766	0.451631823
OID01229_SERPINA5	0.119243832	0.110119479	0.451631823
OID00781_CD40	0.089930034	0.083354289	0.452448646
OID00652_PECAM-1	0.094082991	0.087825174	0.455409758
OID00629_CCL15	0.065412498	0.061397409	0.456858536
OID00803_HGF	0.075504856	0.070958725	0.456858536
OID01255_IGFBP3	0.094736747	0.089446615	0.458157469
OID00600_MPO	0.1740741	0.167375673	0.469165388
OID00448_AGRP	0.086963581	0.083428023	0.469218054
OID01307_LYVE1	0.082239757	0.079495684	0.469218054
OID00605_CHIT1	0.097745211	0.094973621	0.471310519
OID00403_IL-17D	0.069401715	0.068500696	0.480354876
OID01274_COMP	0.104683641	0.103635345	0.480354876
OID00396_TRAIL-R2	0.06811692	0.067725998	0.481636784
OID00775_ADA	0.098592699	0.098317665	0.481636784
OID00758_CD244	0.083000753	0.083522804	0.486154959
OID00462_TGM2	0.137800205	0.139504316	0.486758788
OID00832_VEGFA	0.061428046	0.062174947	0.486758788
OID00651_vWF	-0.205082498	0.211483784	0.497396386
OID00596_SELE	0.070314308	0.072964184	0.499856774
OID01223_CA1	0.198484347	0.218221992	0.535246053
OID00649_TNF-R1	0.060630381	0.066637078	0.535246053
OID00431_PRELP	0.053214724	0.059138989	0.540983673
OID00792_FASLG	0.071288261	0.081099816	0.554073701
OID00613_IL-1RT1	0.063511291	0.07274554	0.55639757
OID00447_PRSS8	0.048431347	0.055818878	0.558946417
OID00381_ADM	0.164185575	0.191248994	0.56366432
OID01302_CFHR5	0.100036348	0.117218742	0.565033194
OID00631_uPA	0.050632281	0.059722738	0.566760324
OID00822_ANGPT2	-0.113467579	0.134644184	0.566760324
OID00411_PIgR	0.022392398	0.026684959	0.566760324
OID00438_PSGL-1	0.025285462	0.0301434	0.566760324
OID00407_GIF	0.099897948	0.119163894	0.566760324
OID01287_SPARCL1	0.080834389	0.096990149	0.567601454
OID00583_LTBR	0.05162037	0.062399456	0.570591627
OID01235_CA3	0.095893816	0.119449813	0.586626372
OID01268_THBS4	0.088059254	0.110745136	0.590537539
OID00835_IL12RB1	0.042542551	0.054266065	0.597254065
OID00842_IL12	0.067654036	0.0874892	0.603838079

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00786_CXCL1	0.157599598	0.211740847	0.616176729
OID00395_PAR-1	0.081868915	0.110056615	0.616176729
OID01221_APOM	0.066862959	0.089919877	0.616176729
OID00404_CXCL1	0.17589403	0.236822155	0.616176729
OID00582_PLC	0.038552521	0.052148243	0.616176729
OID00614_MMP-2	0.059332905	0.080632269	0.616176729
OID00564_LDL receptor	0.055064344	0.075388575	0.616176729
OID00608_PSP-D	0.042744699	0.058520961	0.616176729
OID00819_TNFRSF4	0.054019194	0.074003639	0.616176729
OID00635_t-PA	0.109519151	0.150257282	0.616176729
OID01236_PRSS2	0.052850289	0.07300573	0.616176729
OID00824_CXCL12	-0.131188942	0.182602745	0.616176729
OID00802_IL5	0.215456013	0.300923983	0.618190384
OID00388_SRC	0.19908791	0.278257953	0.618190384
OID00584_Notch 3	0.052168931	0.073949731	0.623799337
OID00820_MIC-A/B	0.039265013	0.059262791	0.655780725
OID00834_IL-21	-0.035803096	0.055037011	0.659903013
OID00800_CD27	0.039717309	0.061065749	0.659903013
OID00392_STK4	0.223356917	0.34424372	0.659903013
OID00804_GZMA	0.129432495	0.207832177	0.677251984
OID00633_CHI3L1	-0.054705471	0.088175169	0.677251984
OID00456_MMP12	0.056718247	0.092427331	0.677251984
OID01282_FAP	0.052387332	0.085649272	0.677251984
OID00833_IL4	0.052200049	0.085372155	0.677251984
OID00463_LEP	0.046438576	0.076020159	0.677251984
OID01283_PLA2G7	0.051257933	0.08458707	0.678523418
OID00424_DECR1	0.22599994	0.376078183	0.680220826
OID00419_GLO1	0.106929452	0.180872214	0.685921571
OID00809_IL10	-0.054606625	0.093274251	0.68835166
OID01288_LTBP2	-0.042102676	0.073708604	0.697529564
OID00464_CA5A	0.11633696	0.208225035	0.699757625
OID00632_CPB1	-0.050862781	0.091102773	0.699757625
OID00641_COL1A1	0.030130917	0.053982419	0.699757625
OID00437_PTX3	0.062659534	0.113054836	0.699757625
OID00433_XCL1	0.055677592	0.100784993	0.699757625
OID00379_BMP-6	0.098592369	0.178706062	0.699757625
OID01284_PTPRS	0.039581004	0.072415678	0.701489353
OID00787_TNFSF14	0.115017124	0.221054235	0.71956367
OID01289_PCOLCE	0.055637282	0.107380459	0.71956367

Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00604_IGFBP-1	0.097504053	0.189014775	0.71956367
OID00585_TIMP4	0.035924952	0.070618736	0.723040374
OID00762_PGF	0.029985112	0.061561198	0.73836906
OID01281_EFEMP1	0.047783885	0.100556835	0.744083349
OID01300_OSMR	0.022945382	0.048370981	0.744083349
OID00387_IL-4RA	0.034229038	0.074208178	0.7510043
OID01237_UMOD	0.025343933	0.055110318	0.7510043
OID00831_PD-L2	0.03859584	0.084395546	0.7510043
OID00427_THBS2	-0.016244159	0.036227813	0.756226788
OID00416_SPON2	-0.031204056	0.071910004	0.75971485
OID01260_TNXB	0.02740461	0.063206904	0.75971485
OID01293_QPCT	0.040823959	0.094261044	0.75971485
OID01286_GAS6	0.049690811	0.115383976	0.75971485
OID00421_PAPPA	0.053657784	0.124940006	0.75971485
OID00458_PD-L2	0.034480846	0.083263178	0.769974331
OID00769_TRAIL	0.024543652	0.061517554	0.779828665
OID00806_CX3CL1	0.030328116	0.077698726	0.784516568
OID00390_IL6	0.038659935	0.103069319	0.792837233
OID00797_IL-35	0.059326612	0.158483797	0.792837233
OID00568_MMP-9	-0.040910642	0.111718475	0.797176646
OID01301_C1QTNF1	0.066370615	0.185064239	0.800902083
OID00467_NEMO	0.092625695	0.261948889	0.802621635
OID01299_CNDP1	0.059503749	0.178358187	0.814793716
OID01279_TGFBR3	0.0478612	0.143738752	0.814793716
OID00763_IL6	0.028174842	0.087640882	0.821774217
OID00778_IL2	-0.021684572	0.069409872	0.825916457
OID00402_IL-27	0.024422452	0.078658984	0.825916457
OID00776_CD4	0.01919738	0.066118825	0.840023817
OID00764_ADGRG1	0.017348699	0.063744378	0.852419926
OID00770_FGF2	0.034816184	0.131929525	0.856653994
OID00594_TNFRSF10C	0.012387064	0.04768032	0.85754696
OID00393_IDUA	0.038426851	0.149992074	0.857956609
OID00451_FABP2	0.04408778	0.177990097	0.862422307
OID01298_TIMD4	0.023299633	0.095279837	0.862498744
OID00417_GH	0.077628276	0.321328858	0.862498744
OID00410_FGF-21	-0.051287175	0.216772004	0.864041587
OID01304_CRTAC1	0.029003569	0.124403787	0.864355778
OID00385_ADAM-TS13	0.006562149	0.029094404	0.868063928
OID00443_ITGB1BP2	0.054873099	0.286591964	0.889519629

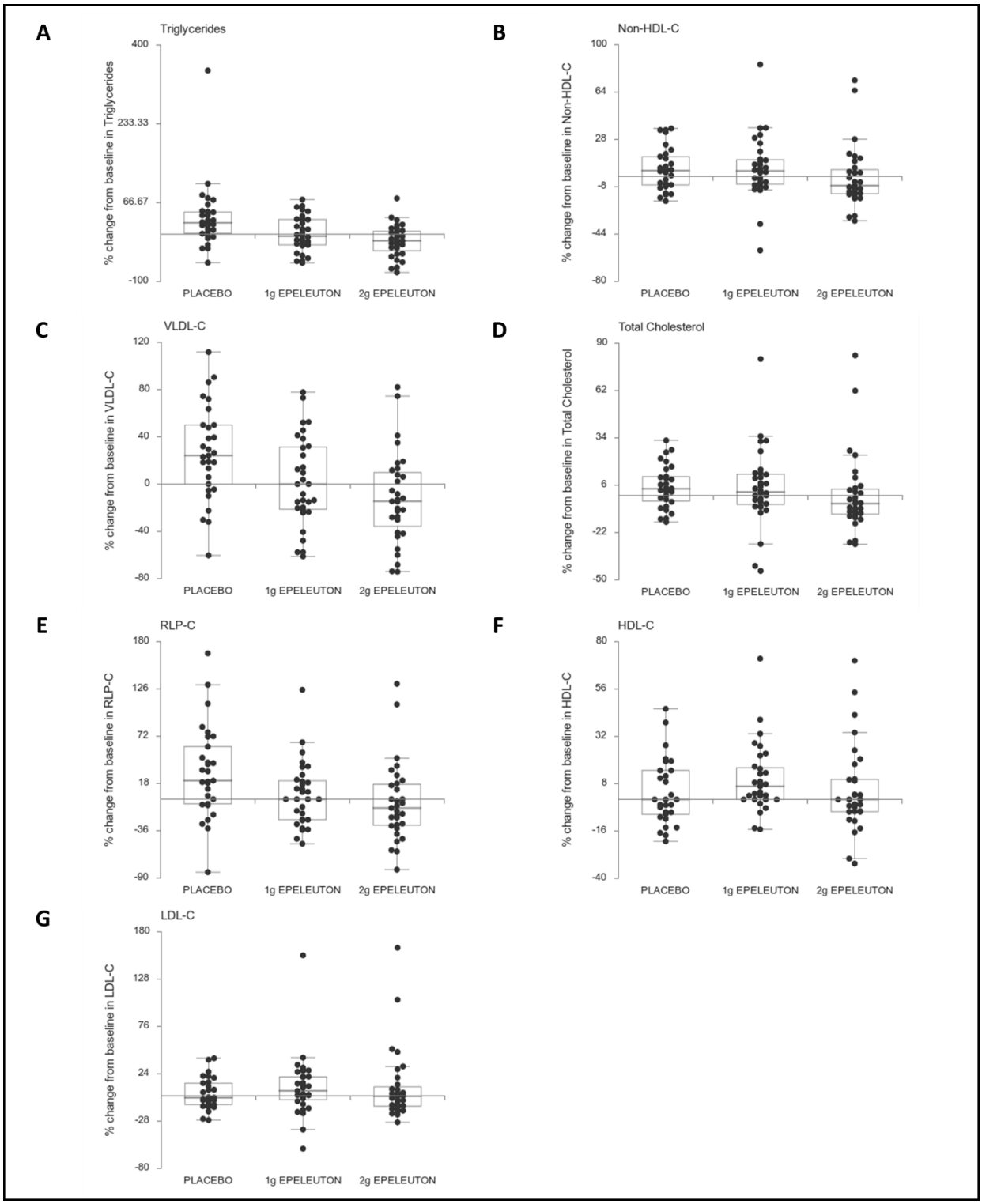
Placebo group			
Protein (OLINK ID_Name)	**Change from baseline to week 16 (npx)**	**Standard Error**	**p-value Benjamini-Hochberg corrected**
OID00829_MMP12	0.019047513	0.100187096	0.889519629
OID00812_CD5	0.027085172	0.142700064	0.889519629
OID00836_IL13	0.022332884	0.130439357	0.901427803
OID00414_CTRC	0.014635487	0.089404703	0.905655161
OID00610_Ep-CAM	0.018783946	0.125668732	0.914586161
OID01306_ANGPTL3	0.01520538	0.108255031	0.916965709
OID01263_CES1	0.020813734	0.148476456	0.916965709
OID00450_GDF-2	0.012725068	0.094350623	0.918691092
OID00642_PON3	-0.012963988	0.101143188	0.920232498
OID01243_MBL2	0.018290309	0.144529905	0.920232498
OID00470_HAOX1	0.017441693	0.208488638	0.952049484
OID01285_MFAP5	0.005767604	0.081764001	0.95991921
OID01280_REG3A	0.001949156	0.051485876	0.982124692
OID00606_TR-AP	0.002441515	0.067599829	0.982124692
OID00446_LPL	-0.001692217	0.126202932	0.996235884
OID00598_DLK-1	0.000968717	0.083441486	0.996235884
OID00429_VSIG2	-0.000758928	0.098129205	0.996593707
OID00773_CAIX	0.000281421	0.099183765	0.997756748

npx denotes normalised protein expression. **TLT-2** indicates trem-like transcript 2 protein; **SAA4**, serum amyloid A4; **PLTP**, phospholipid transfer protein; **TR**, transferrin receptor 1; **ST6GAL1**, beta-galactoside alpha-2,6-sialyltransferase 1; **PI3**, elafin; **PAI**, plasminogen activator inhibitor; **TIMP**, tissue inhibitor of metalloproteinases; **LILRB**, leukocyte immunoglobulin-like receptor subfamily B member; **CCL**, chemokine (C-C motif) ligand; **MCP**, monocyte chemoattractant protein; **DPP4**, dipeptidyl peptidase 4; **TNFRSF**, tumor necrosis factor receptor superfamily member; **ICAM**, intercellular adhesion molecule; **hOSCAR**, osteoclast-associated immunoglobulin-like receptor; **AOC3**, amine oxidase copper containing 3 / vascular adhesion protein 1; **SCF**, stem cell factor; **SORT1**, sortilin; **ACE2**, angiotensin-converting enzyme 2; **AMBP**; alpha-1-microglobulin/bikunin precursor; **CA5A**, carbonic anhydrase 5A, mitochondrial; **VCAM-1**, vascular cell adhesion molecule 1; **TNF-R**, tumor necrosis factor receptor; **IL1RL2**, interleukin-1 receptor-like 2; **IL7R**, interleukin-7 receptor subunit alpha; **FAS**, tumor necrosis factor receptor superfamily member 6; **ALCAM**, activated leukocyte cell adhesion molecule; **CTSL1**, cathepsin L1; **TIE2**, angiopoietin-1 receptor; **TIE1**, tyrosine-protein kinase receptor Tie-1; **LYVE1**, Lymphatic vessel endothelial hyaluronic acid receptor 1; **FABP**, fatty acid binding protein; **ITGB2**, integrin beta-2; **PRSS2**, trypsin-2; **PRSS8**, prostasin; **PRSS27**, serine protease 27; **NOTCH**, neurogenic locus notch homolog protein; **SELL**, L-selectin; **TM**, thrombomodulin, **CHIT**, chitotriosidase-1; **SERPINA5**, plasma serine protease inhibitor; **SERPINA7**, thyroxine-binding globulin; **SERPINA12**, visceral adipose tissue-derived serine protease inhibitor; **EPHB4**, ephrin type-B receptor 4; **C2**, complement C2; **NCAM1**, neural cell adhesion molecule 1; **TGFBI**, transforming growth factor-beta-induced protein ig-h3; **AXL**, tyrosine-protein kinase receptor UFO; **LTBR**, lymphotoxin beta receptor; **AP-N**, aminopeptidase N; **OSMR**, oncostatin-M-specific receptor subunit beta; **CR2**, complement receptor type 2; **BLM hydrolase**, bleomycin hydrolase;

IGFBP, insulin-like growth factor-binding protein; **CSTB**, cystatin B; **CTSD**, cathepsin D; **PCOLCE**, procollagen C-endopeptidase enhancer 1; **MET**, hepatocyte growth factor receptor; **TRAIL-R2**, tumor necrosis factor related apoptosis-inducing ligand receptor 2; **IL-1RT2**, interleukin-1 receptor type 2; **IL-1RT1**, interleukin-1 receptor type 1; **NRP1**, neuropilin-1; **CST3**, cystatin-C; **PAM**, peptidyl-glycine alpha-amidating monooxygenase; **PLXNB2**, plexin-B2; **FETUB**, fetuin-B; **VASN**, vasorin; **IL-18BP**, interleukin-18-binding protein; **SHPS1**, tyrosine-protein phosphatase non-receptor type substrate 1; **CXCL**, chemokine (C-X-C motif) ligand; **PTPRS**, receptor-type tyrosine-protein phosphatase S; **FGF**, fibroblast growth factor; **IL-1ra**, interleukin-1 receptor antagonist protein; **CES1**, liver carboxylesterase 1; **ENG**, endoglin; **IGLC2**, Ig lambda-2 chain C regions; **TIMD4**, T-cell immunoglobulin and mucin domain-containing protein 4; **REG1A**, lithostathine-1-alpha; **REG3A**, regenerating islet-derived protein 3-alpha; **MEGF9**, multiple epidermal growth factor-like domains protein 9; **F7**, coagulation factor VII; **TNXB**, tenascin-X; **RARRES2**, retinoic acid receptor responder protein 2; **F11**, coagulation factor XI; **GDF-15**, growth differentiation factor 15; **GDF-2**, growth differentiation factor 2; **SPARCL1**, SPARC-like protein 1; **SPON1**, spondin-1; **SPON2**, spondin-2; **FCGR2A**, low affinity immunoglobulin gamma Fc region receptor II-a; **FCGR3B**, low affinity immunoglobulin gamma Fc region receptor III-B; **LTBP2**, latent-transforming growth factor beta-binding protein 2; **PLC**, perlecan; **CD163**, scavenger receptor cysteine-rich type 1 protein M130; **IL2-RA**, interleukin-2 receptor subunit alpha; **CNTN1**, contactin-1; **TNFSF**, tumor necrosis factor ligand superfamily member; **KIT**, mast/stem cell growth factor receptor Kit; **PGF**, placenta growth factor; **RAGE**, receptor for advanced glycosylation end products; **Gal-4**, galectin-4; **VSIG2**, V-set and immunoglobulin domain-containing protein 2; **OPN**, osteopontin; **U-PAR**, urokinase plasminogen activator surface receptor; **LAP TGF-beta-1**, latency-associated peptide transforming growth factor beta-1; **PSP-D**, pulmonary surfactant-associated protein D; **PRCP**, lysosomal Pro-X carboxypeptidase; **CTSZ**, cathepsin Z; **TCN2**, transcobalamin-2; **OPG**, osteoprotegrin; **Dkk-1**, Dickkopf-related protein 1; **CD93**, complement component C1q receptor; **LDL receptor**, low-density lipoprotein receptor; **CDH5**, cadherin-5; **CD4**, T-cell surface glycoprotein CD4; **DLK-1**, protein delta homolog 1; **SLAMF7**, SLAM family member 7; **ANG**, angiogenin; **IL6**, interleukin-6; **GRN**, granulins; **DCN**, decorin; **HB-EGF**, proheparin-binding EGF-like growth factor; **CPB1**, carboxypeptidase B; **COMP**, cartilage oligomeric matrix protein; **SCGB3A2**, secretoglobin family 3A member 2; **VEGFD**, vascular endothelial growth factor D; **IgG Fc receptor II-b**, low affinity immunoglobulin gamma Fc region receptor II-b; **SOD1**, superoxide dismutase [Cu-Zn]; **PROC**, vitamin K-dependent protein C; **MB**, myoglobin; **uPA**, urokinase-type plasminogen activator; **IL7**, interleukin-7; **CDH1**, cadherin-1; **FCN2**, ficolin-2; **VEGFA**, vascular endothelial growth factor A; **Gal-3**, galectin-3; **LEP**, leptin; **TFF3**, trefoil factor 3; **HAOX1**, hydroxyacid oxidase 1; **SELE**, e-selectin; **IL-17RA**, interleukin-17 receptor A; **EGFR**, epidermal growth factor receptor; **HGF**, hepatocyte growth factor; **TNC**, tenascin; **THBS4**, thrombospondin-4; **CA**, carbonic anhydrase 1; **CD83**, CD83 antigen; **ICOSLG**, ICOS ligand; **KIM1**, kidney injury molecule 1; **CFHR5**, complement factor H-related protein 5; **IL12**, interleukin-12; **THPO**, thrombopoietin; **IL18**, interleukin-18; **PD-L1**, programmed cell death 1 ligand 1; **CHL1**, neural cell adhesion molecule L1-like protein; **TFPI**, tissue factor pathway inhibitor; **MFAP5**, microfibrillar-associated protein 5; **GAS6**, growth arrest-specific protein 6; **PLA2G7**, platelet-activating factor acetylhydrolase; **QPCT**, glutaminyl-peptide cyclotransferase; **IL-6RA**, interleukin-6 receptor subunit alpha; **NID1**, nidogen-1; **PGLYRP1**, peptidoglycan recognition protein 1; **PD-L2**, programmed cell death 1 ligand 2; **XCL1**, lymphotactin; **MMP**, matrix metalloproteinase; **CD59**, CD59 glycoprotein; **FAP**, prolyl endopeptidase FAP; **SELP**, p-selectin; **LOX-1**, lectin-like oxidized LDL receptor 1; **GP6**, platelet glycoprotein VI; **EFEMP1**, EGF-containing fibulin-like extracellular matrix protein 1; **PDGF subunit A**, platelet-derived growth factor subunit A; **ARG1**, arginase-1; **TF**, tissue factor; **TGM2**, protein-glutamine gamma-glutamyltransferase 2; **CD40-L**, CD40 ligand; **CD84**, SLAM family member 5; **ST2**, ST2 protein; **MERTK**, tyrosine-protein kinase Mer; **CASP-8**, caspase-8; **CA3**, carbonic anhydrase 3; **APOM**, apolipoprotein

M; **PDCD1**, programmed cell death protein 1; **CPA1**, carboxypeptidase A1; **UMOD**, uromodulin; **REN**, renin; **FS**, follistatin; **NCR1**, natural cytotoxicity triggering receptor 1; **HSP 27**, heat shock 27 kDa protein; **SRC**, proto-oncogene tyrosine-protein kinase Src; **LCN2**, neutrophil gelatinase-associated lipocalin; **PARP-1**, poly [ADP-ribose] polymerase 1; **TNF**, tumor necrosis factor; **IL-4RA**, interleukin-4 receptor subunit alpha; **COL18A1**, collagen alpha-1(XVIII) chain; **TWEAK**, tumor necrosis factor (Ligand) superfamily, member 12; **MARCO**, Macrophage receptor MARCO; **CD46**, membrane cofactor protein; **PDGF subunit B**, platelet-derived growth factor subunit B; **CD244**, natural killer cell receptor 2B4; **CD28**, T-cell-specific surface glycoprotein CD28; **Gal-9**, galectin-9; **ADGRG1**, adhesion G-protein coupled receptor G1; **CD27**, CD27 antigen; **CSF-1**, macrophage colony-stimulating factor 1; **ANGPTL3**, angiopoietin-related protein 3; **CD70**, CD70 antigen; **t-PA**, tissue-type plasminogen activator; **HO-1**, heme oxygenase 1; **GP1BA**, platelet glycoprotein Ib alpha chain; **IL-27**, interleukin-27; **CASP-3**, caspase-3; **CX3CL1**, fractalkine; **AZU1**, azurocidin; **EGF**, pro-epidermal growth factor; **MPO**, myeloperoxidase; **GH**, growth hormone; **RETN**, resistin; **PRTN3**, myeloblastin; **LAMP3**, lysosome-associated membrane glycoprotein 3; **LPL**, lipoprotein lipase; **ITGB1BP2**, melusin; **STK4**, serine/threonine-protein kinase 4; **TR-AP**, tartrate-resistant acid phosphatase type 5; **CD40**, CD40 ligand receptor; **IL12RB1**, interleukin-12 receptor subunit beta-1; **C1QTNF1**, complement C1q tumor necrosis factor-related protein 1; **CEACAM8**, carcinoembryonic antigenrelated cell adhesion molecule 8; **PECAM-1**, platelet endothelial cell adhesion molecule; **NOS3**, nitric oxide synthase, endothelial; **CHI3L1**, chitinase-3-like protein 1; **FASLG**, tyrosine-protein kinase Fgr; **MIC-A/B**, MHC class I polypeptide-related sequence A/B; **GLO1**, lactoylglutathione lyase; **PRELP**, prolargin; **VEGFC**, vascular endothelial growth factor c; **GNLY**, granulysin; **JAM-A**, junctional adhesion molecule A; **COL1A1**, collagen alpha-1(I) chain; **MBL2**, mannose-binding protein C; **IL-35**, interleukin-35; **IFN-gamma**, interferon gamma; **ADAM-TS13**, A disintegrin and metalloproteinase with thrombospondin motifs 13; **DEFA1**, neutrophil defensin 1; **PSGL-1**, p-selectin glycoprotein ligand 1; **KLK6**, kallikrein-6; **IL-8**, interleukin-8; **Gal-1**, galectin-1; **CRTAM**, cytotoxic and regulatory T-cell molecule; **AGRP**, agouti-related protein; **BOC**, brother of CDO; **PAR-1**; proteinase-activated receptor 1; **CA4**, carbonic anhydrase 4; **IL16**, pro-interleukin-16; **GZMH**, granzyme H; **DECR1**, 2,4-dienoyl-CoA reductase, mitochondrial; **CTRC**, chymotrypsin C; **SOD2**, superoxide dismutase [Mn], mitochondrial; **ANG-1**, angiopoietin-1; **TGFBR3**, transforming growth factor beta receptor type 3; **TRAIL**, TNF-related apoptosis-inducing ligand; **IL-17D**, interleukin-17D; **PTX3**, pentraxin-related protein PTX3; **IL33**, interleukin-33; **GZMB**, granzyme B; **IDUA**, alpha-L-iduronidase; **ADA**, adenosine deaminase; **GT**, gastrotropin; **PAPPA**, pappalysin-1; **MEPE**, matrix extracellular phosphoglycoprotein; **vWF**, von Willebrand factor; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **PON3**, paraoxonase; **CD5**, T-cell surface glycoprotein CD5; **IL2**, interleukin-2; **CRTAC1**, cartilage acidic protein 1; **ANGPT2**, angiopoietin-2; **ITGAM**, integrin alpha-M; **IL-21**, interleukin-21; **IL10**, interleukin-10; **IFN-beta**, interferon beta; **GZMA**, granzyme A; **VEGFR-2**, vascular endothelial growth factor receptor 2; **IL4**, interleukin-4; **CD8A**, T-cell surface glycoprotein CD8 alpha chain; **NEMO**, NF-kappa-B essential modulator; **CNDP1**, Beta-Ala-His dipeptidase; **PTN**, pleiotrophin; **KLRD1**, natural killer cells antigen CD94; **CAIX**, carbonic anhydrase IX; **IL-1 alpha**, interleukin-1 alpha; **BMP-6**, bone morphogenetic protein 6; **Ep-CAM**, epithelial cell adhesion molecule; **GIF**, gastric intrinsic factor; **ADM**, adrenomedullin; **IL13**, interleukin-13; **PlgR**, polymeric immunoglobulin receptor; **NT-proBNP**, N-terminal prohormone brain natriuretic peptide; **THBS2**, thrombospondin-2; **IL5**, interleukin-5; **BNP**, brain natriuretic peptide.

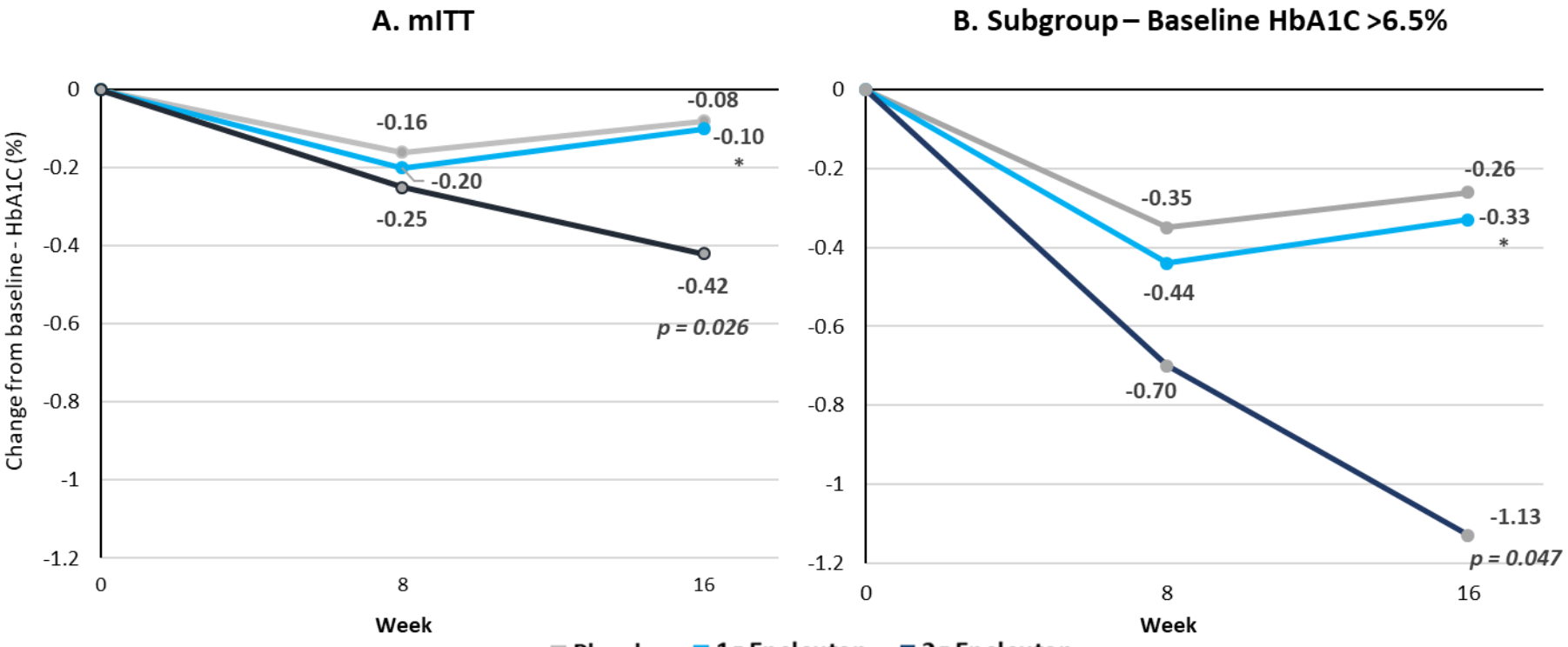
Figure S1. Percentage change in lipid levels at week 16, box/scatter plots



A. Percent change in triglycerides in placebo and epeleuton groups. **B.** Percent change in Non-HDL-C in placebo and epeleuton groups. **C.** Percent change in VLDL-C in placebo and epeleuton groups. **D.** Percent change in total cholesterol in placebo and epeleuton groups. **E.** Percent change in RLP-C in placebo and epeleuton groups. **F.** Percent change in HDL-C in placebo and epeleuton groups. **G.**

Percent change in LDL-C in placebo and epeleuton groups. Non-HDL-C indicates non-high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; RLP-C, remnant lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol and LDL-C, low-density lipoprotein cholesterol.

Figure S2.Mean changes in HbA1C (%) over time from baseline to end of treatment in the mITT population and patients with HbA1C >6.5% at baseline

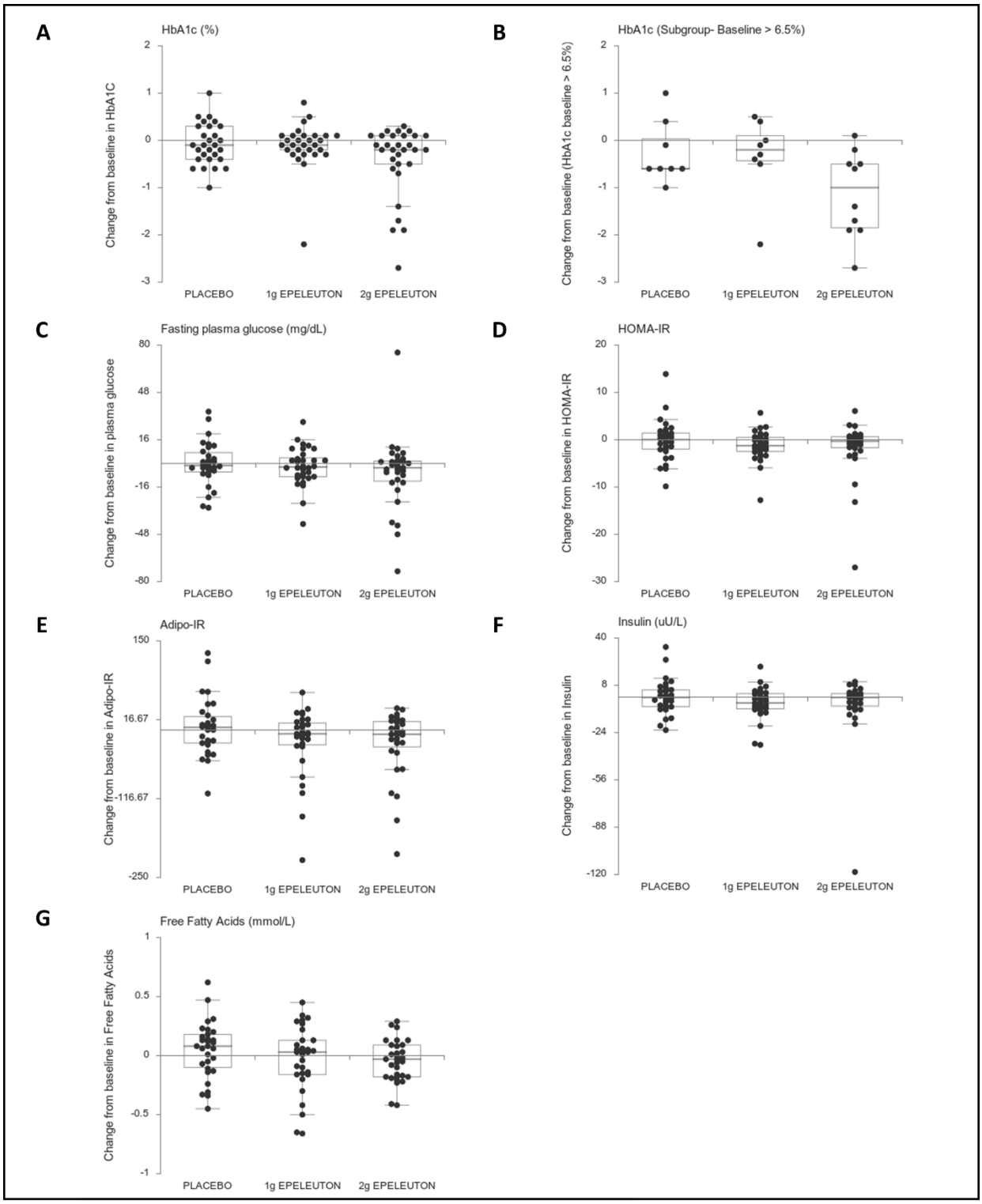


	2g Epeleuton	1g Epeleuton	Placebo
Mean Baseline HbA1C (%)	6.3	6.2	6.2

	2g Epeleuton	1g Epeleuton	Placebo
Mean Baseline HbA1C (%)	7.9	7.8	7.6

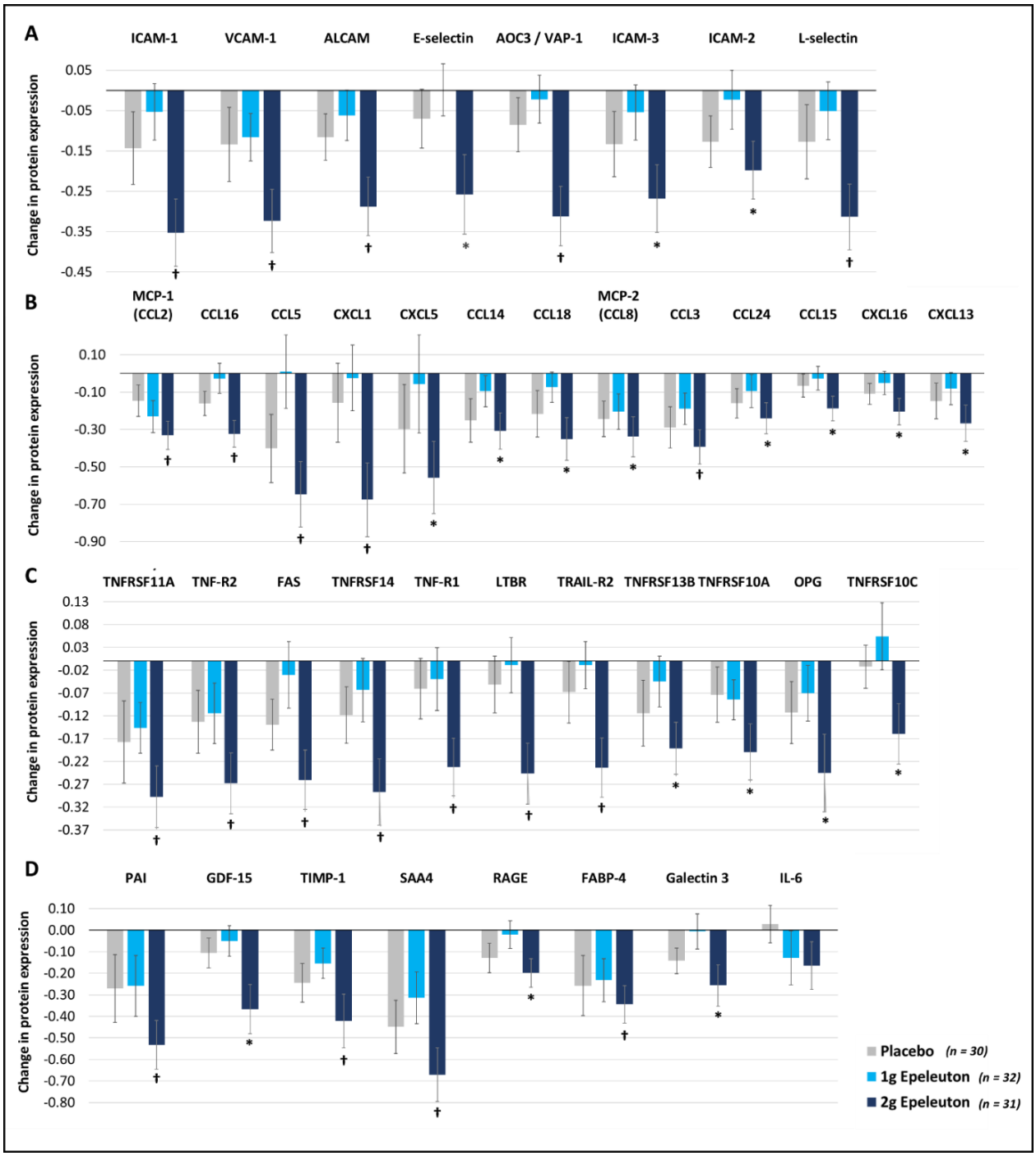
A. Mean change in HbA1C (%) from baseline to end-of-treatment in the mITT population. **B.** Mean change in HbA1C (%) from baseline to end-of-treatment in patients with HbA1C >6.5% at baseline. HbA1C indicates haemoglobin A1c; mITT indicates modified intention-to-treat.

Figure S3. Change in glycemic and insulin resistance parameters at week 16, box/scatter plot



A. Change in HbA1C (%) in placebo and epeleuton groups. **B.** Change in HbA1C (%) in patients with HbA1C >6.5% at baseline in placebo and epeleuton groups. **C.** Change in fasting plasma glucose in placebo and epeleuton groups. **D.** Change in HOMA-IR in placebo and epeleuton groups. **E.** Change in Adipo-IR in placebo and epeleuton groups. **F.** Change in insulin in placebo and epeleuton groups. **G.** Change in free fatty acids in placebo and epeleuton groups. HbA1c indicates hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance and Adipo-IR, adipose tissue insulin resistance.

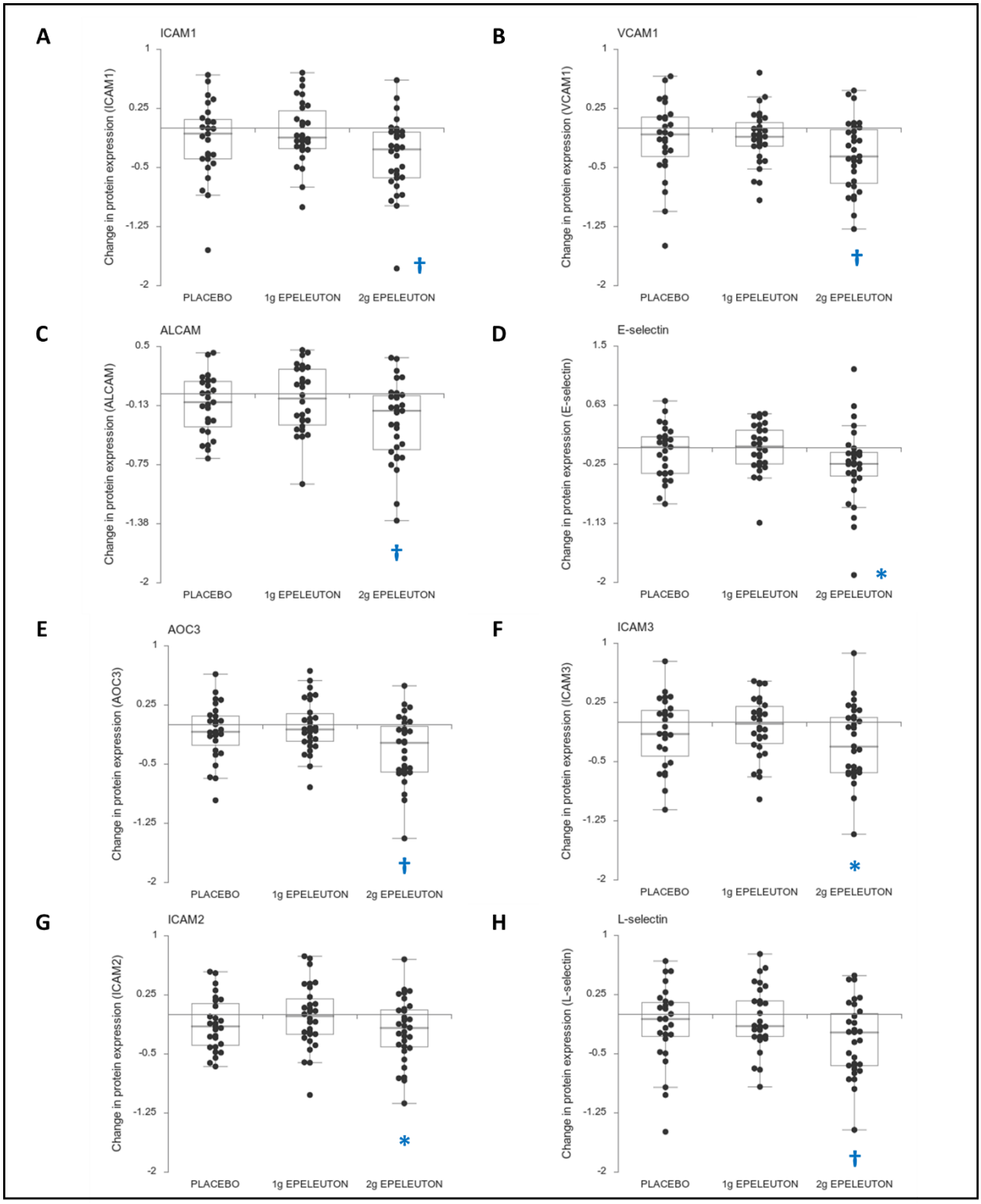
Figure S4. Change in the expression of serum proteomic biomarkers at week 16.



A. Change in cellular adhesion molecules in placebo and epeleuton groups. **B.** Change in chemokines in placebo and epeleuton groups. **C.** Change in tumor necrosis factor receptor superfamily members in placebo and epeleuton groups. **D.** Change in biomarkers of cardiovascular risk and diabetes in placebo and epeleuton groups. * denotes $p < 0.05$ and † denotes $p < 0.01$. All p-values for placebo and epeleuton 1g/day are > 0.05. Error bars denote standard error. ICAM indicates intercellular adhesion molecule; VCAM-1, vascular cell adhesion molecule 1; ALCAM, activated leukocyte cell adhesion molecule; AOC3/VAP-1, amine oxidase copper containing 3 / vascular adhesion protein 1;

MCP, monocyte chemoattractant protein; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; RANK, receptor activator of nuclear factor κ B; TNFRSF, tumor necrosis factor receptor superfamily member; TNF-R, tumor necrosis factor receptor; FAS, tumor necrosis factor receptor superfamily member 6; LTBR, lymphotoxin beta receptor; TRAIL-R, tumor necrosis factor related apoptosis-inducing ligand receptor; OPG, osteoprotegrin; PAI, plasminogen activator inhibitor; GDF-15, growth differentiation factor 15; TIMP-1, tissue inhibitor of metalloproteinases; SAA4, serum amyloid A4; sRAGE, soluble receptor for advanced glycosylation end products, FABP-4, fatty acid binding protein 4 and IL-6, interleukin 6.

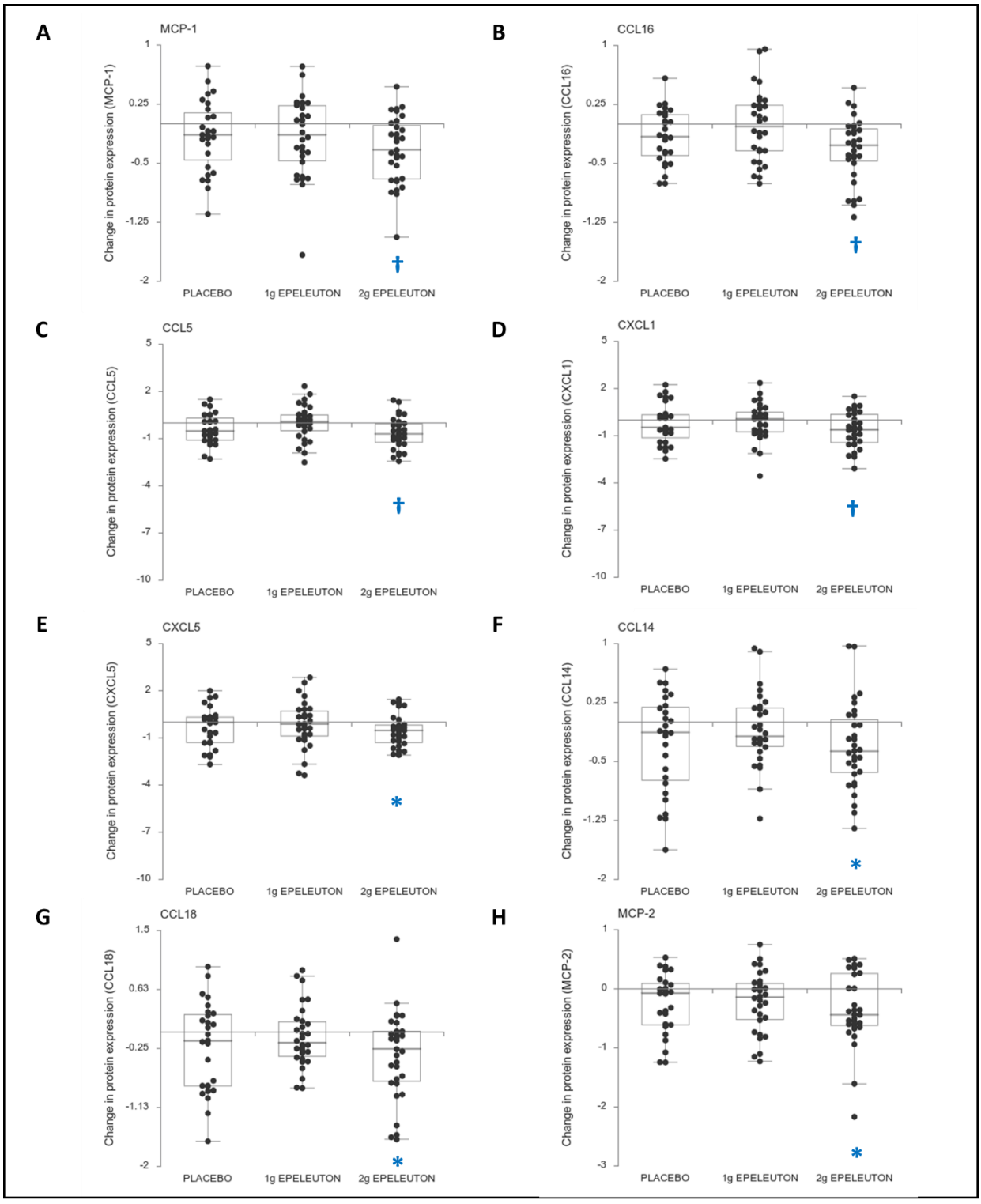
Figure S5. Change in the expression of circulating cellular adhesion molecules at week 16, box/scatter plot

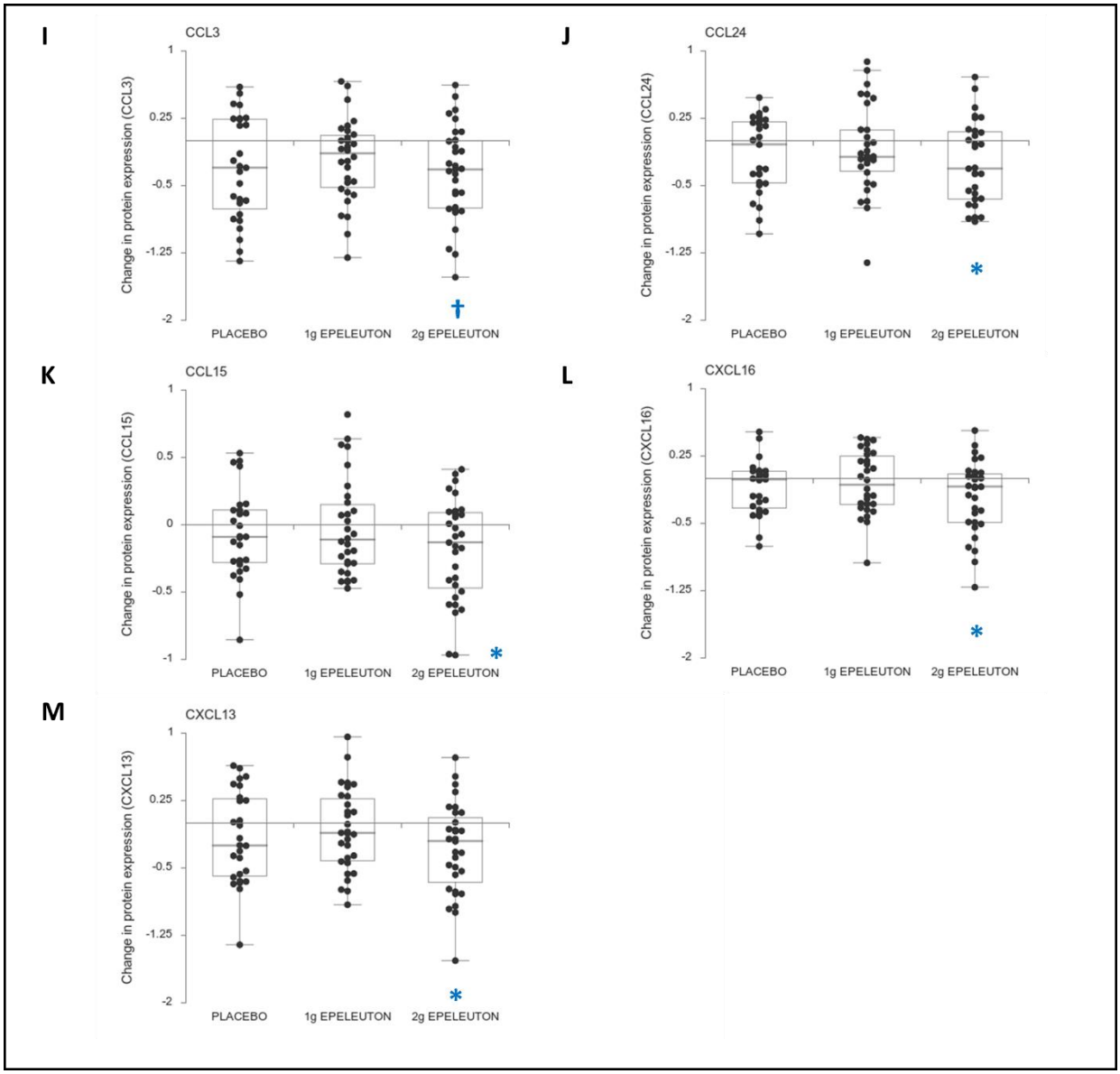


A. Change in ICAM1 in placebo and epeleuton groups. **B.** Change in VCAM1 in placebo and epeleuton groups. **C.** Change in ALCAM in placebo and epeleuton groups. **D.** Change in E-selectin in placebo and epeleuton groups. **E.** Change in AOC3 in placebo and epeleuton groups. **F.** Change in ICAM3 in

placebo and epeleuton groups. **G.** Change in ICAM2 in placebo and epeleuton groups. **H.** Change in L-selectin in placebo and epeleuton groups. ICAM indicates intercellular adhesion molecule; VCAM-1, vascular cell adhesion molecule 1; ALCAM, activated leukocyte cell adhesion molecule and AOC3, amine oxidase copper containing 3 / vascular adhesion protein 1. ***** denotes $p < 0.05$ and **†** denotes $p < 0.01$. All p-values for placebo and epeleuton 1g/day are > 0.05.

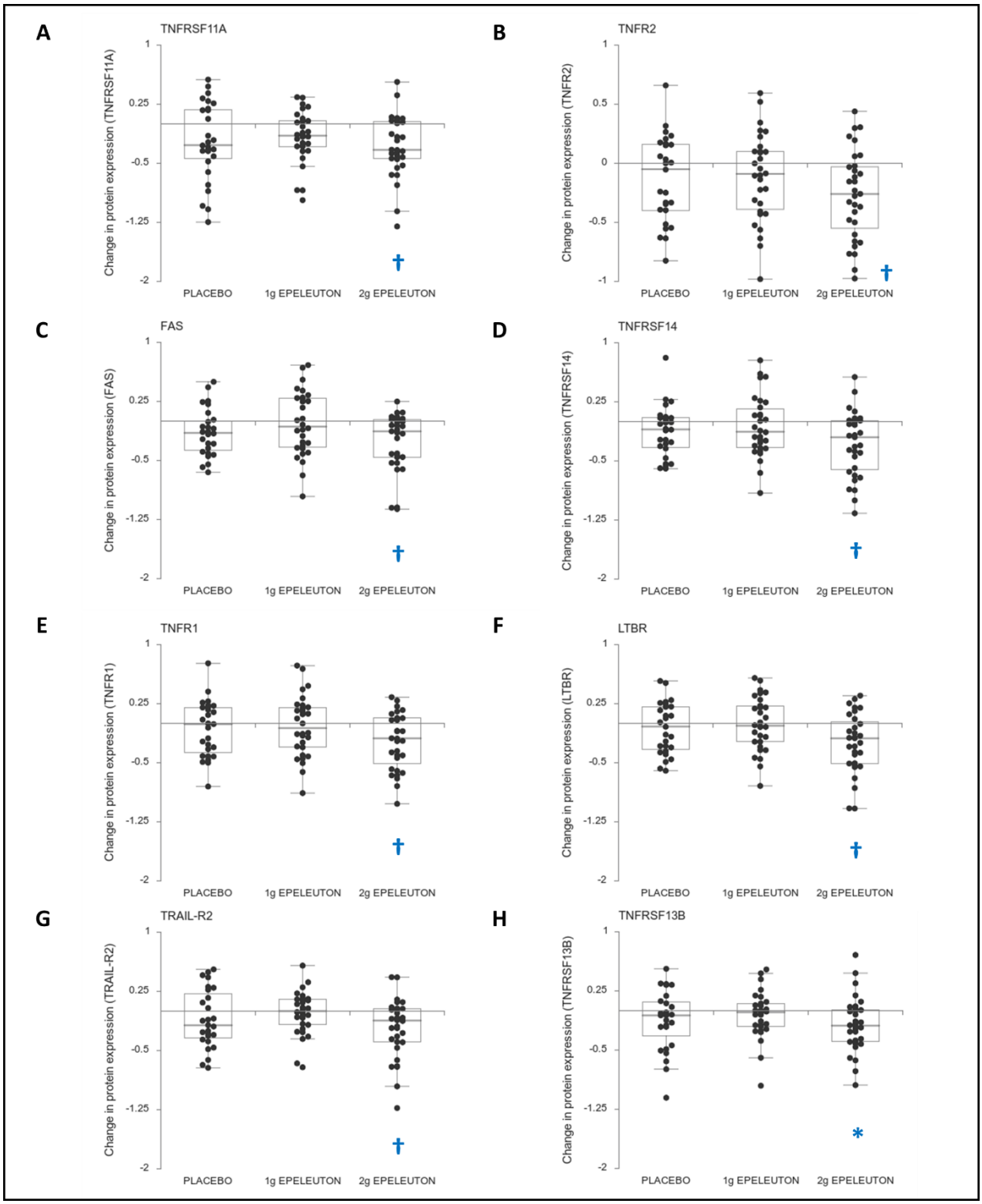
Figure S6. Change in the expression of circulating chemokines at week 16, box/scatter plot

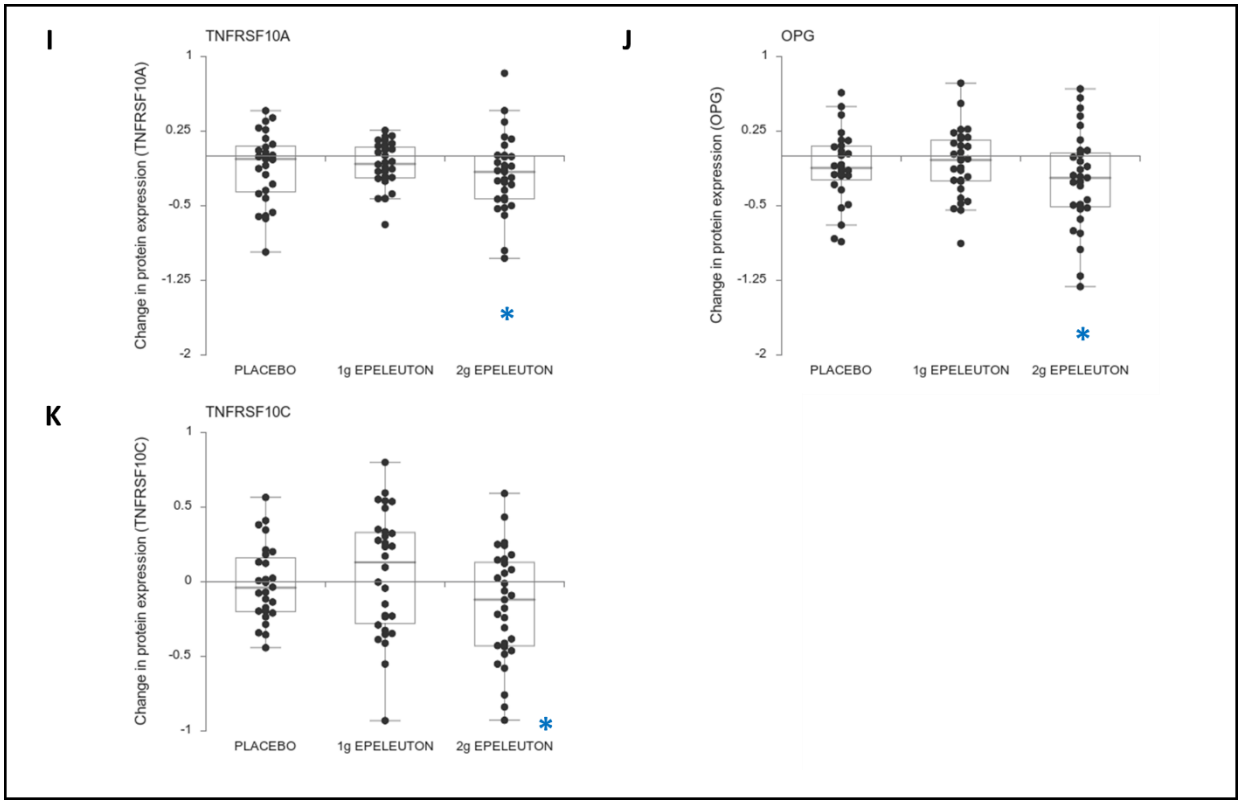




A. Change in MCP-1 in placebo and epeleuton groups. **B.** Change in CCL16 in placebo and epeleuton groups. **C.** Change in CCL5 in placebo and epeleuton groups. **D.** Change in CXCL1 in placebo and epeleuton groups. **E.** Change in CXCL5 in placebo and epeleuton groups. **F.** Change in CCL14 in placebo and epeleuton groups. **G.** Change in CCL18 in placebo and epeleuton groups. **H.** Change in MCP-2 in placebo and epeleuton groups. **I.** Change in CCL3 in placebo and epeleuton groups. **J.** Change in CCL24 in placebo and epeleuton groups. **K.** Change in CCL15 in placebo and epeleuton groups. **L.** Change in CXCL16 in placebo and epeleuton groups. **M.** Change in CXCL13 in placebo and epeleuton groups. MCP indicates monocyte chemoattractant protein; CCL, chemokine (C-C motif) ligand and CXCL, chemokine (C-X-C motif) ligand. * denotes $p < 0.05$ and † denotes $p < 0.01$. All p-values for placebo and epeleuton 1g/day are > 0.05.

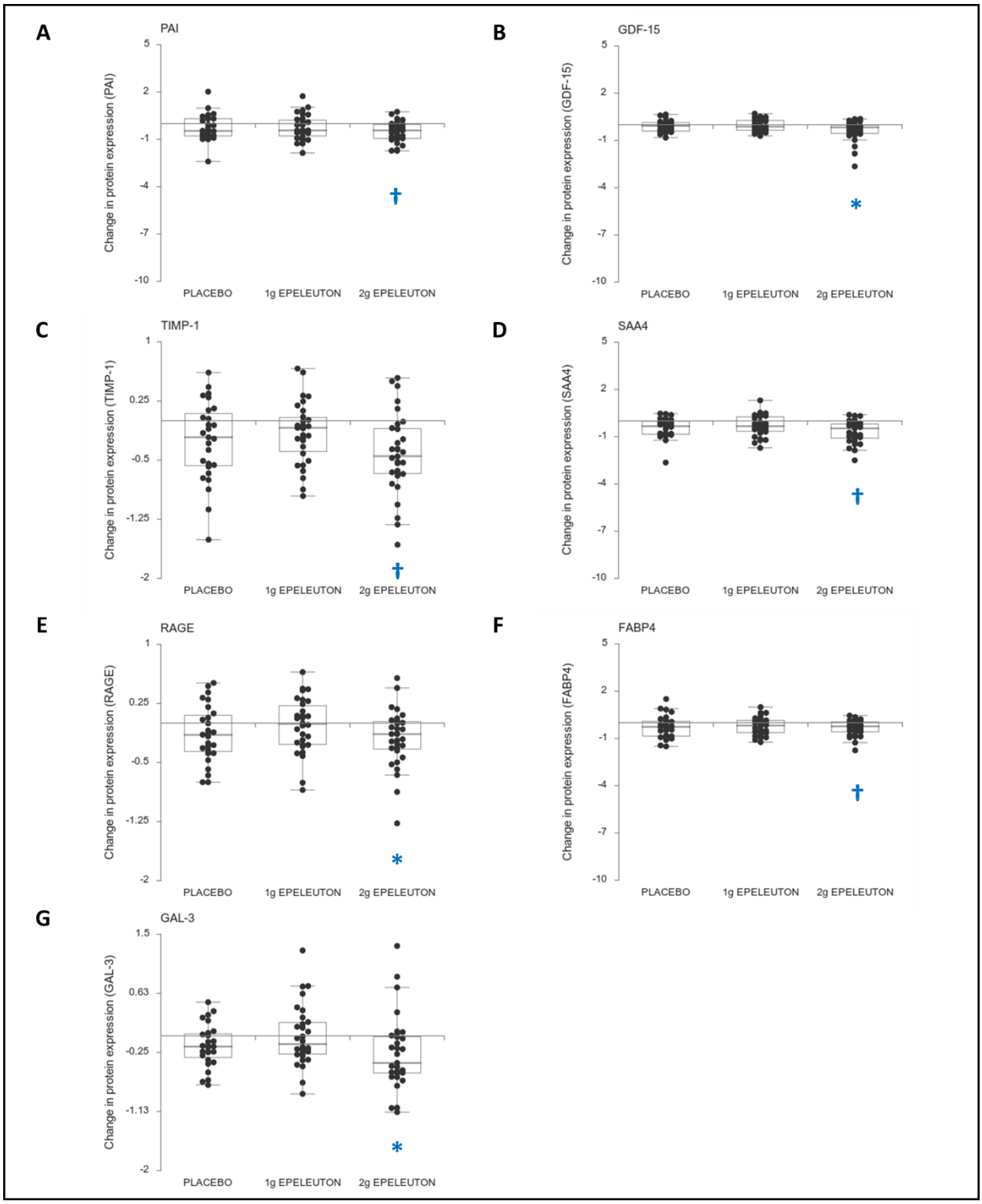
Figure S7. Change in the expression of circulating tumor necrosis factor receptor superfamily members at week 16, box/scatter plot





A. Change in TNFRSF11A in placebo and epeleuton groups. **B.** Change in TNFR2 in placebo and epeleuton groups. **C.** Change in FAS in placebo and epeleuton groups. **D.** Change in TNFRSF14 in placebo and epeleuton groups. **E.** Change in TNFR1 in placebo and epeleuton groups. **F.** Change in LTBR in placebo and epeleuton groups. **G.** Change in TRAIL-R2 in placebo and epeleuton groups. **H.** Change in TNFRSF13B in placebo and epeleuton groups. **I.** Change in TNFRSF10A in placebo and epeleuton groups. **J.** Change in OPG in placebo and epeleuton groups. **K.** Change in TNFRSF10C in placebo and epeleuton groups. TNFRSF indicates tumor necrosis factor receptor superfamily member; TNFR, tumor necrosis factor receptor; FAS, tumor necrosis factor receptor superfamily member 6; LTBR, lymphotoxin beta receptor; TRAIL-R, tumor necrosis factor related apoptosis-inducing ligand receptor and OPG, osteoprotegrin. ***** denotes $p < 0.05$ and **†** denotes $p < 0.01$. All p-values for placebo and epeleuton 1g/day are > 0.05.

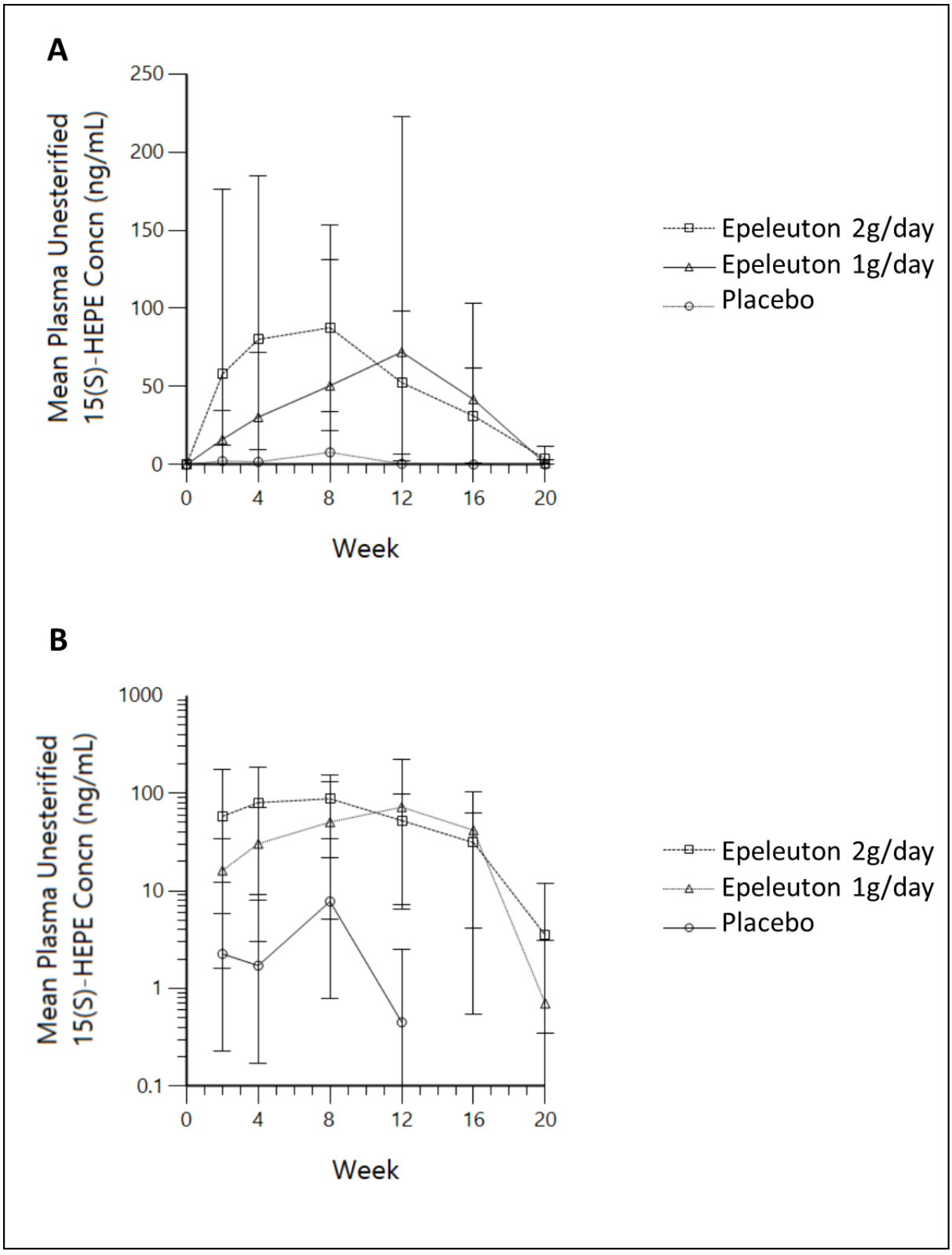
Figure S8. Change in the expression of circulating markers of cardiovascular risk and diabetes at week 16, box/scatter plot



A. Change in PAI in placebo and epeleuton groups. **B.** Change in GDF-15 in placebo and epeleuton groups. **C.** Change in TIMP-1 in placebo and epeleuton groups. **D.** Change in SAA4 in placebo and epeleuton groups. **E.** Change in RAGE in placebo and epeleuton groups. **F.** Change in FABP4 in placebo and epeleuton groups. **G.** Change in GAL-3 in placebo and epeleuton groups. PAI indicates

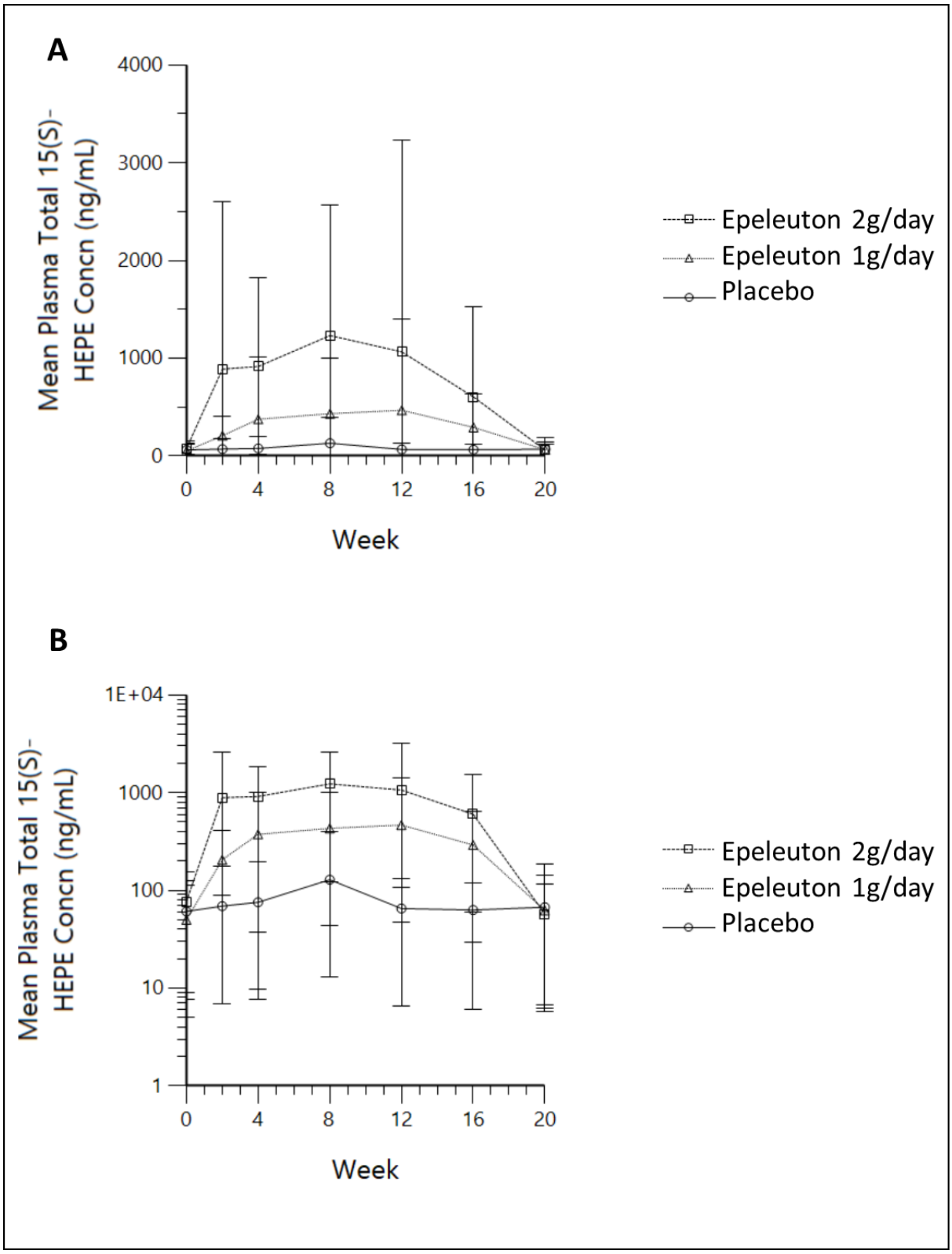
plasminogen activator inhibitor; GDF-15, growth differentiation factor 15; TIMP-1, tissue inhibitor of metalloproteinases; SAA4, serum amyloid A4; RAGE, receptor for advanced glycosylation end products; FABP-4, fatty acid binding protein 4 and GAL-3, galectin 3. ***** denotes $p < 0.05$ and **†** denotes $p < 0.01$. All p-values for placebo and epeleuton 1g/day are > 0.05.

Figure S9. Mean (+/- SD) plasma unesterified 15(S)-HEPE concentrations (ng/mL) versus time (linear and semilogarithmic scales) for epeleuton 1g/day, epeleuton 2g/day and placebo treated patients



A. Mean plasma unesterified 15(S)-HEPE concentrations (ng/mL) versus time (linear scale). B. Mean plasma unesterified 15(S)-HEPE concentrations (ng/mL) versus time (semi-logarithmic scale). 15(S)-HEPE indicates 15-hydroxy eicosapentaenoic acid and SD, standard deviation.

Figure S10. Mean (+/- SD) plasma total 15(S)-HEPE concentrations (ng/mL) versus time (linear and semilogarithmic scales) for epeleuton 1g/day, epeleuton 2g/day and placebo treated patients



A. Mean plasma total 15(S)-HEPE concentrations (ng/mL) versus time (linear scale). **B.** Mean plasma total 15(S)-HEPE concentrations (ng/mL) versus time (semi-logarithmic scale). 15(S)-HEPE indicates 15-hydroxy eicosapentaenoic acid and SD, standard deviation.