Published in final edited form as:

Obesity (Silver Spring). 2022 August ; 30(8): 1608–1620. doi:10.1002/oby.23481.

Effects of Liraglutide on Gastrointestinal Functions and Weight in Obesity: A Randomized Clinical and Pharmacogenomic Trial

Daniel Maselli, MD[*],
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Jessica Atieh, MD[*],
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Matthew M. Clark, PhD[@], **Deborah Eckert, RN, BSN**,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Ann Taylor, CCRP,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Paula Carlson, BS,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Address for correspondence: Michael Camilleri, M.D., Mayo Clinic, Charlton Bldg., Rm. 8-110, 200 First St. S.W., Rochester, MN 55905, Telephone: 507-266-2305, camilleri.michael@mayo.edu.
[*]These authors contributed equally to this work.

Authors' contributions:
D. Maselli and J. Atieh: fellow investigators, patient screening, first line care of patients in clinical research unit, joint 1st authors
D. Eckert and A. Taylor: recruitment and management of patient schedules
P. Carlson: Genotyping assays and co-authorship
M. M. Clark: standardization of dietary and behavioral treatment; co-authorship
D. D. Burton, I. Busciglio: technical measurements of gastric functions, analysis and co-authorship
A. Acosta: staff co-investigator, supervision of patient care; co-authorship
A. Vella: GLP-1 and genotyping expertise; co-authorship
W. Scott Harmsen: study statistician
M. Camilleri: principal investigator, NIH grant recipient, supervision of all aspects of study; authorship

Clinical trial registration: ClinicalTrials.gov #NCT02647944, (https://clinicaltrials.gov/ct2/show/NCT02647944?term=NCT02647944&rank=1)

Disclosures:
A. Acosta is a stockholder in Gila Therapeutics, Phenomix Sciences and Lipiquester; he serves as a consultant for Rhythm Pharmaceuticals, General Mills, Gila Therapeutics.
M. Camilleri is a stockholder in Phenomix Sciences (with current shares valued at less than U.S.$1.00) and serves as a consultant to Kallyope (with consulting fee paid to his employer, Mayo Clinic).
The other authors have no conflicts of interest.

Duane D. Burton, MHA,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Irene Busciglio, BS,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

W. Scott Harmsen, MS[†], **Adrian Vella, MD**[^], **Andres Acosta, MD, PhD**,
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Michael Camilleri, MD
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

[@]Department of Psychiatry and Psychology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

[†]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

[^]Division of Endocrinology; Mayo Clinic, 200 First St. S.W., Rochester, Minnesota, 55905, USA

Abstract

Objective: To determine the effects of long-acting GLP-1 receptor agonist, liraglutide, and placebo SQ over 16 weeks on weight and gastric functions and to evaluate associations of single nucleotide polymorphisms (SNPs) in *GLP-1R* (rs6923761) and *TCF7L2* (rs7903146) with effects of liraglutide.

Methods: We conducted a randomized, parallel-group, placebo-controlled, 16-week trial of liraglutide, escalated to 3mg SQ daily in 136 otherwise healthy adults with obesity. Weight, GES, gastric volumes (GV), satiation, and body composition measured at baseline and after treatment were compared in 2 treatment groups using ANCOVA.

Results: Liraglutide (n=59) and placebo (n=65) groups completed treatment. Relative to placebo, liraglutide increased weight loss at 5 and 16 weeks (both $p<0.05$), slowed GES $T_{1/2}$ at 5 and 16 weeks (both $p<0.001$), increased fasting GV ($p=0.01$) and satiation ($p<0.01$)] at 16 weeks. GES $T_{1/2}$ was positively correlated with weight loss on liraglutide (both $p<0.001$). After 16 weeks of liraglutide, *GLP-1R* rs6923761 (AG/AA vs. GG) was associated with reduced percentage body fat ($p=0.062$), and *TCF7L2* rs7903146 (CC vs. CT/TT) with lower body weight ($p=0.015$).

Conclusions: Liraglutide, 3mg, induces weight loss with delay in GES $T_{1/2}$ and reduces calorie intake. Slowing GES and variations in *GLP-1R* and *TCF7L2* are associated with liraglutide effects in obesity.

INTRODUCTION

The prevalence of obesity is increasing in most countries, and response to treatments with diet, exercise, and medications is highly variable. In addition to the impact of energy expenditure and hedonic mechanisms that influence daily caloric balance, gastrointestinal traits (such as gastric volume and emptying, satiation, and incretin responses) may constitute relevant pathophysiological mechanisms in obesity and potential targets for therapy.[1]

Endogenous glucagon-like peptide-1 (GLP-1) pathways influence these gastrointestinal traits, and GLP-1 receptor agonists and analogs induce weight loss which is likely mediated through multiple peripheral and central mechanisms. The peripheral effects include delay in gastric emptying,[2] activation of the ileal brake, increase in satiation, increase in resting energy expenditure, increase in glucose-dependent insulin release and pancreatic β cell growth (latter effect in experimental animals), and decrease in glucagon secretion.[3] Modification of appetite results from direct effects on several regions that express GLP-1 receptors in the human central nervous system including the parietal and orbitofrontal cortex, hypothalamus,[4] and medulla.[5–8]

At a dose of 3mg/day administered subcutaneously (SQ), liraglutide, a long-acting GLP-1 receptor agonist with 97% homology to human GLP-1, is FDA-approved for weight management in adults with BMI ≥30kg/m^2, or ≥27kg/m^2 with obesity related co-morbidities, and for adolescents aged 12 to 17 years with a body weight of at least 60kg and BMI ≥30kg/m^2. A recent network meta-analysis showed that SQ liraglutide >1.8mg dose is one of the three most effective GLP-1 receptor agonists for weight loss.[9]

The mechanistic underpinnings of liraglutide in treatment of obesity are likely multifold. In our prior pilot trial of the first 40 participants in this 136-person study, 3mg liraglutide significantly delayed gastric emptying of solids at both 5 and 16 weeks, and this delay correlated with weight loss.[10] Liraglutide use is associated with nausea which may result from retardation of gastric emptying. In addition, endogenous GLP-1 slows gastric emptying as demonstrated by administration of the specific GLP-1 antagonist, exendin(9-39) amide.[11] GLP-1 itself increases fasting and postprandial gastric volumes.[12] Thus, an effect of liraglutide on gastric accommodation (indirectly affecting appetite) could also contribute to the weight loss. Given that the pilot study involved 40 participants and was underpowered to detect effects on functions such as gastric accommodation and the potential pharmacogenomic interactions with genetic variation in *GLP-1R* (receptor gene) and the *TCF7L2* that controls endogenous GLP-1 synthesis, it is important to complete the randomized, controlled trial as proposed in the NIH-funded proposal (DK67071).

GLP-1 activity is mediated by a complex pathway of genes and their products including the product of the transcription factor 7-like 2 gene (*TCF7L2*) which drives transcription of pre-proglucagon in enteroendocrine L cells. GLP-1 signals through its cognate receptor (encoded by *GLP1R).* rs6923761 in GLP1R is associated with altered response to GLP-1.[13] The A allele (AA/AG) in comparison to GG genotype showed greater effects of liraglutide 1.8mg/day on BMI, body weight, and fat mass.[14]

*TCF7L2*rs7903146 is associated with defects in insulin secretion and type 2 diabetes mellitus,[13,15] and with more rapid gastric emptying of liquids with the CT/TT genotypes compared to CC group.[16]

To identify relevant phenotype and genotypic biomarkers in response to liraglutide, our study aims were to compare the effects of liraglutide 3mg and placebo on gastrointestinal functions and body weight over 16 weeks of treatment and second, to assess the relationship between post-treatment as well as baseline gastric emptying with weight loss; and third, to analyze pharmacogenetics of liraglutide treatment in association with common variants of *GLP1R* and *TCF7L2* genes.

METHODS

Study Design and Participants

Our study team performed a single-center (Mayo Clinic in Rochester, MN, USA), double-blind, placebo-controlled, parallel-group trial of once daily, SQ liraglutide 3mg or placebo (1:1) for a total treatment period of 16 weeks. The pilot study results in the first 40 patients were published elsewhere.[10]

Adults with obesity (BMI >30kg/m^2), 18-65 years of age residing within 125 miles of the center were recruited. Participants were otherwise healthy, with no unstable psychiatric or medical disease or treatment that could interfere with the study conduct or interpretation. The study was approved by Mayo Clinic Institutional Review Board (IRB #15-001783). All participants provided written informed consent.

Patients with delayed gastric emptying of solids (>90th percentile according to gender, <87% in males or <81% emptied at 4 hours in females[17]) were excluded, since it was considered potentially dangerous to increase the delay in gastric emptying with a GLP-1 receptor agonist.

Eligibility Criteria for Liraglutide Treatment and Permitted Concomitant Medications

Permitted concomitant medications during the study were birth control pill, estrogen and thyroxin replacement therapy, and any medication administered for co-morbidities if they did not alter gastric emptying or accommodation or satiation. Specifically, statins for hyperlipidemia, diuretics, β-adrenergic blockers, ACE inhibitors and angiotensin antagonists for hypertension, and metformin for type 2 diabetes mellitus or prediabetes were permissible. In contrast, resin sequestrants for hyperlipidemia (which may reduce gastric emptying and appetite), α2-adrenerigc agonists for hypertension, other GLP-1 receptor agonists (e.g., exenatide) or amylin analogs (e.g., pramlintide) which retard gastric emptying were not permissible.

In addition, standard FDA recommendations on use of liraglutide were followed for eligibility. Women of childbearing potential underwent pregnancy tests within 48 hours of enrollment and before each radiation exposure. In addition, since liraglutide is classified as Pregnancy Category X medication, monthly urine pregnancy testing was performed in any female participant with childbearing potential.

Eligibility for Treatment with Liraglutide

Standard FDA recommendations on use of liraglutide were followed for eligibility. Screening questionnaires assessed the presence of psychiatric symptoms,[18] alcohol use disorders,[19] eating disorders,[20] and intake of medications whether prescribed or over the counter (except multivitamins) within 7 days of the study.

Randomization and Masking

For the pilot study, 47 participants with BMI ≥27kg/m^2 were enrolled from December 18, 2015 to September 1, 2016, and 40 patients were eligible for and participated in the clinical trial. For the entire trial, 136 participants were enrolled up to May 1, 2021 and completed the studies by August 31, 2021.

A randomization schedule, computer generated by the study statistician's office, was submitted to the Mayo Clinic Research Pharmacy. The study had no stratification factors. Allocations (1:1 ratio) were concealed by the study pharmacists who assigned patients to treatment groups and were physically separated from the Clinical Research Trials Unit where the patients were enrolled by the study coordinators. The participants, study coordinators, technicians performing measurements, and physicians were blinded to assignments. All data were transmitted to the statistician for data lock.

Procedures

Study protocol—Figure 1 shows the study protocol. All study participants underwent screening visits, baseline measurements of gastrointestinal, behavioral, and psychological factors, and dose escalation (0.6mg per week for liraglutide, and similar weekly volume increments for placebo).

Measurements of gastrointestinal functions

1. **Gastric emptying of solids** was assessed by scintigraphy using a 320kcal ^{99m}Tc-radiolabeled egg, solid-liquid meal.[17] The primary endpoint was gastric half-emptying time (GE $T_{1/2}$). GE of liquids is generally regarded to be a minor factor in the context of upper gastrointestinal symptoms;[21] to reduce radiation burden, we studied exclusively GE of solids.

2. **Fasting and postprandial gastric volumes** were measured by single photon emission computed tomography (SPECT) imaging of the stomach after intravenous injection of ^{99m}Tc-pertechnetate, which is taken up by the gastric mucosa. This method was developed and validated (including performance characteristics) in our laboratory [22] and provides volume measurements during fasting and post-300mL Ensure®.

3. **Satiation** test by ingestion of Ensure® (1kcal/mL, 11% fat, 73% carbohydrate, and 16% protein) ingested at a constant rate of 30ml/minute was performed to measure volume to fullness (VTF) and maximum tolerated volume (MTV).[23] Thirty minutes after reaching MTV, symptoms of fullness, nausea, bloating, and pain were measured using 100mm horizontal visual analog scales (VAS), with the words "none" and "worst ever" anchored at each end.

4. **Satiety** test (a measure of **appetite**) by *ad libitum* meal measured total caloric intake and macronutrient distribution in the chosen foods from standard foods of known nutrient composition:[1] vegetable lasagna (Stouffers, Nestle USA, Inc., Solon, OH, USA]; vanilla pudding (Hunts, Kraft Foods North America, Tarrytown, NY, USA); and skim milk. The total kilocalories of food consumed and macronutrients ingested at the ad libitum meal were analyzed by validated software (ProNutra 3.0; Viocare Technologies Inc., Princeton, NJ, USA).

5. **Plasma peptide YY levels** by radioimmunoassay were measured fasting, and 15, 45, and 90 minutes postprandially. PYY was measured by radioimmunoassay (Millipore Research, Inc. (St. Louis, MO) PYY exists in at least 2 molecular forms, 1-36 and 3-36, both of which are physiologically active and are detected by the assay.

Measurement of body composition—Body composition was determined at baseline and at 16 weeks of treatment via dual-energy x-ray absorptiometry (DXA) technology using a Lunar iDXA (GE Healthcare, Madison, WI) as previously described.[24]

A research support technician with Limited Scope X-ray Operator certification (State of MN) performed full body scans. Scans were analyzed with enCORE software (version 15.0; GE Healthcare). Participants wore light clothing and removed all metal jewelry and other materials that could interfere with the x-ray beam. Quality control was performed daily before scanning the first participant using a phantom. The study technician analyzed all scans in an identical manner and was blind to group allocation. The Lunar iDXA is equipped for visceral and subcutaneous fat measurement. Standard DXA regions of interest (ROI) including the upper body (android) and trunk regions (which are associated with risk of chronic disease), the lower body region (gynoid, prominent in women) and total body fat (TBF) were assessed. The trunk ROI included everything except the head, arms, and legs.

Quantitative traits (see Appendix for details) of gastric emptying of solids (standardized 320-kcal solid-liquid meal [17]), satiation by ad libitum meal, volume to fullness, and maximum tolerated volume of liquid nutrient meal,[23] fasting and postprandial gastric volumes (in response to a standard volume of 300mL Ensure®[22]), and body composition by DEXA [24] were measured at baseline and at week 16. An additional scintigraphic gastric emptying test with the same solid-liquid meal was performed at week 5.

Liraglutide

Liraglutide (SAXENDA® Novo Nordisk, Inc., Plainsboro, NJ, USA) was purchased and stored in Mayo Clinic Research Pharmacy. All liraglutide and saline placebo supplies were dispensed from the Research Pharmacy directly to the participants. Liraglutide was administered as recommended by the FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014.pdf): initiated at 0.6mg daily for one week, with instructions to increase by 0.6mg weekly until 3.0mg was reached (~ over 4 weeks). Every 4 weeks, participants obtained a new supply of study medication from the Research Pharmacy. Participants received education and a “Direction for Use” pamphlet provided by the Clinical Trials Unit nurses not associated with the research study.

Standardization of Dietetic and Behavioral Advice

Patients received standardized dietetic and behavioral counseling for weight reduction therapy (Appendix **including** Appendix Table 1).

Safety and Tolerability

We assessed safety and tolerability throughout the study by evaluation of adverse events, vital signs, fasting blood glucose, and physical examination. These assessments were conducted at baseline and at visits for dose escalations at weeks 2, 3, and 4, as well as follow-up visits at weeks 8, 12 and 16.

Adverse Events

At each scheduled follow-up visit, study participants were assessed by study physicians and nurses and were given opportunity to self-report adverse events, and the study team specifically inquired about the following adverse events: nausea, abdominal pain, diarrhea, lightheadedness, injection site rash, and injection site reaction (**details in** Appendix Table 5).

Genotyping

Genotyping was performed as previously reported.[25] We used established PCR-based methods using TaqMan® SNP Genotyping Assays rs6923761 (GLP-1 [catalog no. C_25615272_20]) and rs7903146 (TCF7L2 [catalog no. C_29347861_10]; Applied Biosystems, Foster City, CA, USA) in accordance with the manufacturer's instructions. Following polymerase chain reaction amplification, end reactions were analyzed with an ABI ViiA-7 Real-Time PCR System using QuantStudio™ Real-Time PCR software (Applied Biosystems).

Outcomes

Time to half gastric emptying of solids (GES $T_{1/2}$) was the primary endpoint for analysis during the 5- and 16-week treatment periods. Secondary endpoints were weight loss at week 5 and week 16, satiation by ad libitum meal, volume to fullness and maximum tolerated volume, fasting, postprandial, accommodation gastric volumes, postprandial plasma PYY levels at 16 weeks, and percent total body and trunk fat relative to whole body composition (on DEXA imaging).

Statistical Analysis

The statistical analysis addressed the hypothesis that there was a treatment effect with liraglutide compared to placebo on the study endpoints, based on analysis of covariance. Data are provided as median (interquartile range). All available data from all randomized patients were used in the statistical analyses. In addition, data were imputed for the 12 participants who dropped out. For each missing data, we imputed the average value for all patients in the study and reduced the degrees of freedom by one for each data value imputed for that endpoint.

We analyzed the effects of liraglutide and placebo using analysis of covariance (ANCOVA), with the corresponding baseline measurement as a covariate, using an α of 0.05. We

compared the gastric emptying $T_{1/2}$ of solids at 5 and 16 weeks in participants receiving liraglutide using a paired t-test (test for normality passed using Shapiro-Wilk test). A dominant genetic model was used to assess the association of the two single nucleotide polymorphisms of interest in the *GLP1R* and *TCF7L2* genes with phenotypes, especially weight, percent fat in body composition and gastric function.

We used Spearman correlations to assess the relationship between (absolute value of) gastric emptying $T_{1/2}$ of solids at baseline, 5 and 16 weeks (as well as change between baseline and 5 or 16 weeks) and degree of weight loss on treatment. All analyses were conducted using SAS Version 9.4.

Statistical Power

The present study with 65 patients in each treatment arm had 80% power (at α=0.05) to detect a difference in absolute gastric emptying $T_{1/2}$ of 14.8 minutes between the treatment groups based on GE $T_{1/2}$ mean ± SD of 121.7 ± 29.8 minutes published previously[16] from a study of 319 healthy human volunteers. Effect sizes demonstrable for weight loss and other quantitative traits are shown in Appendix Table 2.

Data Sharing Statement

Deidentified participant data will be shared in ClinicalTrials.gov [#NCT02647944 (https://clinicaltrials.gov/ct2/show/NCT02647944?term=NCT02647944&rank=1)] and in the genotype and phenotype repository at National Institutes of Health (as required for R01-DK67071) when the article is published. Additional related documents such as the study protocol, statistical analysis plan, etc. may be made available upon request to the principal investigator upon approval of a proposal.

RESULTS

Study Evolution

Figure 2 shows the CONSORT flow chart with 182 adults assessed for eligibility, 136 randomized, and 124 completing the 16-week treatment trials (65 placebo and 59 liraglutide). Two participants did not reach full liraglutide dose at 16 weeks because of adverse effects (final doses 1.2 and 1.8mg).

The baseline demographics and measurements in the two treatment groups were not significantly different (Table 1, Appendix Table 3). The lowest BMI at baseline was 30.09 kg/m^2. The median baseline GES $T_{1/2}$ for the 136 participants was 113.6 minutes (10-90%ile 86.4, 148.9), which is consistent with the reported range for normal controls, median 120 minutes (10-90th %ile, 88, 163).[17] Participants had no co-morbidities, except for one who had type 2 diabetes (T2DM) at enrollment; a second participant was diagnosed with T2DM during the study and was treated with metformin. The distributions of alleles for the entire group were as follows: *GLP1R* rs6923761: 64 (47%) AG/AA, and 71 (53%) GG; and *TCF7L2* rs7903146: 61 (45%) CT/TT and 74 (55%) CC; the allelic distributions between the two treatment groups (Appendix Table 3) were not significantly different: *GLP1R* rs6923761 (p=0.200) and *TCF7L2* rs7903146 (p=0.329).

Effects of Treatment on Gastrointestinal Motor Functions, Weight, and Satiation

Data in the two treatment groups are shown in Tables 1 and 2, demonstrating the significant effects of liraglutide on GES $T_{1/2}$ and weight documented by changes from baseline values.

Liraglutide also prolonged (Figure 3 **upper panel**, Table 1) times for 50% and 25% gastric emptying compared to placebo. In the liraglutide-treated group, GES $T_{1/2}$ at 16 weeks was not as slow as at 5 weeks; thus, the delta of GES $T_{1/2}$ at 16 weeks minus GES $T_{1/2}$ at 5 weeks was −12.9 (IQR −62.7, 8.0) minutes ($p<0.001$).

Weight loss (Figure 4 **upper panel**, Table 1) was significantly greater for the liraglutide group compared to the placebo group at 5 weeks ($p=0.004$) and at 16 weeks ($p=0.033$).

There were significant effects of liraglutide on fasting gastric volumes at 16 weeks which was significantly higher ($p=0.01$) in the liraglutide group compared to the placebo group (Table 2); these were documented by comparison of the changes from baseline. The numerical difference in postprandial gastric volume noted in the liraglutide compared to the placebo group was not significant ($p=0.14$).

The volume to comfortable fullness ($p=0.0056$) and maximum tolerated volume ($p<0.001$) at 16 weeks were significantly lower in the liraglutide group compared to the placebo group (Figure 4 **lower panel, and** Table 2), as documented by the changes from baseline. Postprandial symptoms after the satiation drink test were not significantly different in the two treatment groups.

There was also a significant difference ($p=0.0036$) in the calories consumed during an *ad libitum* meal in the group treated with liraglutide compared to placebo (Figure 4 **lower panel**, Table 2).

There were no significant effects of liraglutide on fasting and postprandial peptide YY (Appendix Table 4).

Relationship between Gastric Emptying and Effect of Liraglutide on Weight Loss

For the entire study cohort, there were significant correlations between GES $T_{1/2}$ and weight loss, particularly between change in GES $T_{1/2}$ at 5 weeks and 16 weeks (Figure 3, **lower left panel**) and the weight loss (expressed as delta from baseline) over the 5- and 16-week periods (upper panel Figure 4) (all $p<0.001$). Appendix Figure 1 shows the significant Spearman correlations for the associations of GES $T_{1/2}$ at 5 and 16 weeks and weight loss with treatment in the two groups (both $P<0.001$).

Moreover, in the liraglutide treatment group alone, there was significant direct correlation of GES $T_{1/2}$ at 16 weeks and weight loss over the 16-week period ($Rs=0.262$, $p=0.0432$, $N=60$), but no significant correlation at 5 weeks (Figure 5).

There was borderline significant correlation between the fastest quartile of GES $T_{1/2}$ at baseline (≤97.5 min) and weight loss in response to liraglutide at week 5 ($Rs = −0.432$; $P=0.081$; $N=17$) and at week 16 ($Rs = −0.478$; $P=0.051$; $N=17$) (Figure 3 **lower right panel**). In addition, after adjusting for baseline weight, total % fat, and trunk % fat,

the fastest quartile of baseline GES $T_{1/2}$ was associated with numerically lower percent total body and percent trunk fat after treatment with liraglutide for 16 weeks (respectively p=0.059 and 0.057 based on rank scores).

Pharmacogenomics

Based on a dominant genetic model to assess the association of the two single nucleotide polymorphisms of interest (Figure 6) in the *GLP1R* and *TCF7L2* genes, *GLP1R* rs6923761 AG/AA genotype was associated with a lower % total fat in response to liraglutide (p=0.062). In addition, *TCF7L2* rs7903146 CC genotype was associated with lower weight at 16 weeks in response to liraglutide compared to the CT/TT genotype (p=0.015) No other significant associations were identified between gene SNPs and other measurements.

Withdrawals and Adverse Effects

One participant in each treatment group underwent uneventful cholecystectomy for acute cholecystitis associated with gallstones during the study; the patient in the placebo group chose to continue participation in the trial. Twelve participants withdrew from the study: 8 in the liraglutide group and 4 in the placebo group (details in Appendix).

Adverse effects in ≥5 participants are shown in Appendix Table 5; the following were significantly more prevalent in the patients on liraglutide: nausea, diarrhea, abdominal pain or discomfort, and constipation. Nausea was reported in 59.7% on liraglutide and 15.9% on placebo. Overall, patients with nausea experienced higher weight loss [4.7 (0.77-7.0) kg] compared to patients with no nausea [1.8 (−1.0-6.0) kg; p=0.044].

DISCUSSION

This randomized, controlled trial has documented important phenotypic and genotypic mechanisms in the effects of 3mg liraglutide on weight loss: retardation of gastric emptying of solids for at least 16 weeks of treatment and correlation of degree of weight loss with the retardation of gastric emptying of solids, confirming our pilot data.[10] Liraglutide also influenced appetite regulation and highlighted the association of clinically relevant endpoints (weight and percent body fat) and allelic variation in genes relevant to GLP-1.

GLP-1 agonists or analogs are generally recognized to delay gastric emptying. Our findings confirm that liraglutide slows gastric emptying in contrast to prior studies that used suboptimal measurements based on acetaminophen test or gastric emptying of liquids, which have notably different rates of emptying compared to solids in a stomach with an intact pylorus.[26–29] Our findings are consistent with a literature review[2] that documented slowing gastric emptying by GLP-1 agonists or analogs.

The absolute and the change from baseline GES $T_{1/2}$ were associated with the degree of weight loss during the first 5-week and the entire 16-week periods of liraglutide treatment. The significant correlation between degree of retardation of gastric emptying and weight loss is consistent with a mechanistic role of the gastric emptying effect on weight loss. Indeed, among the participants with obesity randomized to liraglutide, the quartile with the fastest gastric emptying at baseline showed correlation with the degree of

weight lost, suggesting that baseline gastric motor function phenotype can play a role in a patient-tailored approach to obesity management. Similarly, tolerance of GLP-1 agonists or analogs can influence patient adherence and thus the effectiveness of these medications. We excluded individuals with markedly delayed gastric emptying from study enrollment, and we observed that experience of nausea was associated with greater weight loss, as has been previously documented in trials using with exenatide once weekly and exenatide twice daily.[30]

It is interesting to note that, in large multicenter studies of liraglutide,[31,32] approximately 50% of the average weight loss was achieved in the first 8 weeks of treatment, which included the period with the greatest delay in gastric emptying of solids in our study. While GES $T_{1/2}$ correlated with concurrent weight loss at both 5 and 16 weeks, there was reduced effect on GES $T_{1/2}$ with liraglutide at 16 weeks compared to 5 weeks. This is consistent with tachyphylaxis in the effect on gastric emptying of solids as previously described with GLP-1.[33] This phenomenon reflects continuous activation of the GLP-1 receptor by the long-acting GLP-1 receptor agonist, leading to tolerance.[3,33] Nevertheless, there was still significant delay in GES $T_{1/2}$ at 16 weeks, and weight loss continued from 5 to 16 weeks, suggesting a durable treatment effect from liraglutide even with diminished perturbation in gastric motor functions related to appetite.

There is insufficient appreciation that GLP-1 analogs or agonists delay gastric emptying despite the published evidence including the current report, as well as studies of oral semaglutide,[34] or subcutaneous lixisenatide (which slows gastric emptying of liquids[35] and solids[36,37]), and the dual GLP-1 and glucagon agonist, tirzepatide.[38] This is not surprising given that both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) slow gastric emptying. This insufficient appreciation of the slowing of gastric emptying may be, in part, related to the use of area under the curve over several hours in the acetaminophen (paracetamol) absorption test to quantify gastric emptying as reported with liraglutide.[26] The acetaminophen likely empties with the liquid phase of the meal and, in fact, 1-hour acetaminophen levels were reduced with liraglutide, suggesting slower gastric emptying. Alternatively, the use of 13C-acetate as a meal marker (which may elute from the solid phase and empty with the liquid phase) documented gastric emptying rate was significantly delayed by lixisenatide, while liraglutide and dulaglutide had limited effects on gastric emptying.[39] The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has advised that, at least for one GLP-1 agonist or analog, there is a causal relationship between delayed gastric emptying and liraglutide (EMA/429077/2019).[40]

Liraglutide also increased fasting gastric volume which is consistent with pharmacological effects of GLP-1,[12] but the postprandial gastric volume was not significantly increased. Importantly, the kilocalorie intake of and liquid nutrient at a standard rate (30mL/min) and in an *ad libitum* meal were reduced by liraglutide, suggesting increased satiation without significant effect on postprandial levels of the appetite-modifying incretin, peptide YY. These observations may result from multiple mechanisms including delay in gastric emptying and activation of brainstem or hypothalamic GLP-1 receptors[6] and central appetite suppression in the absence of increased postprandial gastric volume.

Our study also provides the novel observation that SNPs impacting *GLP-1R* and *TCF7L2* are associated with percent body and trunk fat and weight responses to liraglutide treatment. While these data are limited by sample size and require confirmation in clinical trials of GLP-1 agonists or analogs, they suggest that baseline accelerated gastric emptying and these loci may serve as biomarkers of weight loss (carriers of *TCF7L2* SNP) and possibly the effect on total fat percentage (carriers of *GLP-1R* SNP). The *TCF7L2* gene variant may impact the synthesis of endogenous GLP-1 [41–44] and could impact the combined effects of the endogenous and exogenous GLP-1 receptor agonists.

In conclusion, the findings from this randomized clinical trial suggest that gastric emptying modulation, in addition to other central effects that are well-established, plays a role in weight loss with liraglutide, especially early in the treatment course. The correlation coefficients suggest that delay in gastric emptying accounts for about 20% of the variance (based on R^2) in the weight loss response, and therefore, gastric emptying is certainly not the only mechanism contributing to weight loss effects. Moreover, baseline acceleration of gastric emptying appears to predict some of the variance in the weight loss on liraglutide. Effects on calorie intake are consistent with central effects of the drug or satiation associated with delayed gastric emptying,[45] and our novel pharmacogenetic observations especially in *TCF7L2* suggest biological genetic variation may also influence weight loss with liraglutide treatment. With further support in larger studies, these observations support potential individualized approaches for selection of patients for treatment of obesity with liraglutide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank Cindy Stanislav for excellent secretarial assistance, the nurses and staff of the Mayo Clinic Clinical Research Unit for nursing support and care of patients, Mayo Clinic Research Pharmacy, and Michael Ryks and Lisa Tebay, RN for excellent technical support.

Funding support:

Michael Camilleri is supported by grant R01-DK67071 from National Institutes of Health. The study was conducted in the Clinical Trials Research Unit [supported by Mayo Clinic Center for Clinical and Translational Science (CCaTS) grant UL1-TR000135].

REFERENCES

1. Acosta A, Camilleri M, Shin A, Vazquez-Roque MI, Iturrino J, Burton D, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. Gastroenterology 2015;148:537–546.e4. [PubMed: 25486131]
2. Maselli DB, Camilleri M. Effects of GLP-1 and its analogs on gastric physiology in diabetes mellitus and obesity. Adv Exp Med Biol. 2021;1307:171–192. [PubMed: 32077010]
3. Umapathysivam MM, Lee MY, Jones KL, Annink CE, Cousins CE, Trahair LG, et al. Comparative effects of prolonged and intermittent stimulation of the glucagon-like peptide 1 receptor on gastric emptying and glycemia. Diabetes 2014;63:785–790. [PubMed: 24089511]
4. Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 2014;124:4473–4488. [PubMed: 25202980]

5. Coveleskie K, Kilpatrick LA, Gupta A, Stains J, Connolly L, Labus JS, et al. The effect of the GLP-1 analogue Exenatide on functional connectivity within an NTS-based network in women with and without obesity. Obes Sci Pract. 2017;3:434–445. [PubMed: 29259802]
6. Farr OM, Sofopoulos M, Tsoukas MA, Dincer F, Thakkar B, Sahin-Efe A, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. Diabetologia 2016;59:954–965. [PubMed: 26831302]
7. Ten Kulve JS, Veltman DJ, van Bloemendaal L, Groot PFC, Ruhé HG, Barkhof F, et al. Endogenous GLP1 and GLP1 analogue alter CNS responses to palatable food consumption. J Endocrinol. 2016;229:1–12. [PubMed: 26769912]
8. Farr OM, Upadhyay J, Rutagengwa C, DiPrisco B, Ranta Z, Adra A, et al. Longer-term liraglutide administration at the highest dose approved for obesity increases reward-related orbitofrontal cortex activation in response to food cues: Implications for plateauing weight loss in response to anti-obesity therapies. Diabetes Obes Metab. 2019;21:2459–2464. [PubMed: 31282006]
9. Vosoughi K*, Atieh J*, Khanna L, Khoshbin K, Prokop LJ, Davitkov P, et al. (* joint 1st authors). Association of glucagon-like peptide 1 analogs and agonists administered for obesity with weight loss and adverse events: A systematic review and network meta-analysis. EClinicalMedicine 2021 Nov 27;42:101213. [PubMed: 34877513]
10. Halawi H*, Khemani D*, Eckert D, O'Neill J, Kadouh H, Grothe K, et al. (*joint first authors). Effects of liraglutide on weight, satiation and gastric functions in obesity: randomized, placebo-controlled pilot trial. Lancet Gastroenterol Hepatol. 2017;2:890–899. [PubMed: 28958851]
11. Deane AM, Nguyen NQ, Stevens JE, Fraser RJ, Holloway RH, Besanko LK, et al. Endogenous glucagon-like peptide-1 slows gastric emptying in healthy subjects, attenuating postprandial glycemia. J Clin Endocrinol Metab. 2010;95:215–221. [PubMed: 19892837]
12. Delgado-Aros S, Kim DY, Burton DD, Thomforde GM, Stephens D, Brinkmann BH, et al. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. Am J Physiol Gastrointest Liver Physiol. 2002;282:G424–G431. [PubMed: 11841992]
13. Sathananthan A, Dalla Man C, Micheletto F, Zinsmeister AR, Camilleri M, Giesler PD, et al. Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. Diabetes Care 2010;33:2074–2076. [PubMed: 20805279]
14. de Luis DA, Diaz Soto G, Izaola O, Romero E. Evaluation of weight loss and metabolic changes in diabetic patients treated with liraglutide, effect of RS6923761 gene variant of glucagon-like peptide 1 receptor. J Diabetes Complications 2015;29:595–598. [PubMed: 25825013]
15. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PIW, Shuldiner AR, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med. 2006;355:241–250. [PubMed: 16855264]
16. Vazquez-Roque MI, Camilleri M, Vella A, Carlson P, Laugen J, Zinsmeister AR. Association of TCF7L2 allelic variations with gastric function, satiation, and GLP-1 levels. Clin Transl Sci. 2011;4:183–187. [PubMed: 21707949]
17. Camilleri M, Iturrino J, Bharucha AE, Burton D, Shin A, Jeong I-D, et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. Neurogastroenterol Motil. 2012;24:1076–e562. [PubMed: 22747676]
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psych Scand. 1983;67:361–370.
19. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998;158:1789–1795. [PubMed: 9738608]
20. Yanovski SZ, Marcus MD, Wadden TA, Walsh BT. The Questionnaire on Eating and Weight Patterns-5: an updated screening instrument for binge eating disorder. Intl J Eating Disord. 2015;48:259–261.

21. Sachdeva P, Malhotra N, Pathikonda M, Khayyam U, Fisher RS, Maurer AH, et al. Gastric emptying of solids and liquids for evaluation for gastroparesis. Dig Dis Sci. 2011;56:1138–1146. [PubMed: 21365240]
22. Bouras EP, Delgado-Aros S, Camilleri M, Castillo EJ, Burton DD, Thomforde GM, et al. SPECT imaging of the stomach: comparison with barostat and effects of sex, age, body mass index, and fundoplication. Gut 2002;51:781–786. [PubMed: 12427776]
23. Chial HJ, Camilleri C, Delgado-Aros S, Burton D, Thomforde G, Ferber I, et al. A nutrient drink test to assess maximum tolerated volume and postprandial symptoms: effects of gender, body mass index and age in health. Neurogastroenterol Motil. 2002;14:249–253. [PubMed: 12061909]
24. Kadouh H, Chedid V, Halawi H, Burton DD, Clark MM, Khemani D, et al. GLP-1 analog modulates appetite, taste preference, gut hormones and regional body fat stores in adults with obesity. J Clin Endocrinol Metab. 2020;105:1552–1563.
25. Chedid V, Vijayvargiya P, Carlson P, Van Malderen K, Acosta A, Zinsmeister A, et al. Allelic variant in the glucagon-like peptide 1 receptor gene associated with greater effect of liraglutide and exenatide on gastric emptying: a pilot pharmacogenetics study. Neurogastroenterol Motil. 2018;30:e13313. [PubMed: 29488276]
26. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Intl J Obes. 2014;38:784–793.
27. Frandsen CS, Dejgaard TF, Andersen HU, Holst JJ, Hartmann B, Thorsteinsson B, et al. Liraglutide as adjunct to insulin treatment in type 1 diabetes does not interfere with glycaemic recovery or gastric emptying rate during hypoglycaemia: a randomised, placebo-controlled, double-blind, parallel-group study. Diabetes Obes Metab. 2017;19:773–782. [PubMed: 27868372]
28. Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying -- long lasting effects on body weight. Diabetes Obes Metab. 2012;14:531–538. [PubMed: 22226053]
29. Nagai Y, Hashimoto E, Oikawa R, Asai S, Terashima Y, Nakamura Y, et al. Differing effects of liraglutide on gastric emptying in Japanese patients with type 2 diabetes. Diabetes Obes Metab. 2014;16:573–576. [PubMed: 24320758]
30. Horowitz M, Aroda VR, Han J, Hardy E, Rayner CK. Upper and/or lower gastrointestinal adverse events with glucagon-like peptide-1 receptor agonists: Incidence and consequences. Diabetes Obes Metab. 2017;19:672–681. [PubMed: 28058769]
31. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373:11–22. [PubMed: 26132939]
32. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. Three years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–1409. [PubMed: 28237263]
33. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. Diabetes 2011;60:1561–1565. [PubMed: 21430088]
34. Dahl K, Brooks A, Almazedi F, Hoff ST, Boschini C, Baekdal TA. Oral semaglutide improves postprandial glucose and lipid metabolism, and delays gastric emptying, in subjects with type 2 diabetes. Diabetes Obes Metab. 2021;23:1594–1603. [PubMed: 33710717]
35. Jones KL, Rigda RS, Buttfield MDM, Hatzinikolas S, Pham HT, Marathe CS, et al. Effects of lixisenatide on postprandial blood pressure, gastric emptying and glycaemia in healthy people and people with type 2 diabetes. Diabetes Obes. Metab. 2019;21:1158–1167. [PubMed: 30623563]
36. Jalleh R, Pham H, Marathe CS, Wu T, Buttfield MD, Hatzinikolas S, et al. , Acute effects of lixisenatide on energy intake in healthy subjects and patients with type 2 diabetes: relationship to gastric emptying and intragastric distribution. Nutrients. 2020;12:1962.
37. Marathe CS, Pham H, Wu T, Trahair LG, Rigda RS, Buttfield MDM, et al. Acute administration of the GLP-1 receptor agonist lixisenatide diminishes postprandial insulin secretion in healthy

subjects but not in type 2 diabetes, associated with slowing of gastric emptying. Diabetes Ther. 2022 Apr 22. doi: 10.1007/s13300-022-01258-4.

38. Urva S, Coskun T, Loghin C, Cui X, Beebe E, O'Farrell L, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists Diabetes Obes Metab. 2020;22:1886–1891. [PubMed: 32519795]
39. Kuwata H, Yabe D, Murotani K, Fujiwara Y, Haraguchi T, Kubota S, et al. Effects of glucagon-like peptide-1 receptor agonists on secretions of insulin and glucagon and gastric emptying in Japanese individuals with type 2 diabetes: A prospective, observational study. J Diabetes Investi. 2021;12:2162–2171.
40. https://www.ema.europa.eu/en/documents/scientific-conclusion/saxenda-h-c-psusa-00001892-201812-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf (accessed April 26, 2022)
41. Yi F, Brubaker PL, Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-3beta. J Biol Chem. 2005;280:1457–1464. [PubMed: 15525634]
42. Grant SFA, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38:320–323. [PubMed: 16415884]
43. Shu L, Matveyenko AV, Kerr-Conte J, Cho J-H, McIntosh CHS, Maedler K. Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP-1 receptors and impaired beta-cell function. Hum Mol Genet. 2009;18:2388–2399. [PubMed: 19386626]
44. Le Bacquer O, Shu L, Marchand M, Neve B, Paroni F, Kerr Conte J, et al. TCF7L2 splice variants have distinct effects on beta-cell turnover and function. Hum Mol Genet. 2011;20:1906–1915. [PubMed: 21357677]
45. Halawi H, Camilleri M, Acosta A, Vazquez-Roque M, Oduyebo I, Burton D, et al. Relationship of gastric emptying or accommodation with satiation, satiety and postprandial symptoms in health. Am J Physiol Gastrointest Liver Physiol. 2017;313:G442–G447. [PubMed: 28774870]

STUDY IMPORTANT QUESTIONS

What is already known about this subject?

- Liraglutide, a subcutaneous long-acting GLP-1 receptor agonist, is approved for treatment of obesity.
- Factors associated with greater weight loss with liraglutide are unknown.
- Thus, we conducted a randomized, parallel-group, placebo-controlled, 16-week trial of liraglutide, escalated to 3mg subcutaneously daily, with standardized dietetic and behavioral counseling in 136 adults with obesity to determine the effects of liraglutide on weight and gastric functions and to evaluate effects of gastric emptying of solids and single nucleotide polymorphisms (SNPs) in *GLP-1R* (rs6923761) and *TCF7L2* (rs7903146) on responses to liraglutide.

What are the new findings in your manuscript?

- Liraglutide increased weight loss at 5 weeks and 16 weeks, slowed gastric emptying of solids $T_{1/2}$ at 5 and 16 weeks, increased fasting gastric volume, and increased satiation at 16 weeks.
- The severity of the slowing of gastric emptying and *TCF7L2* variant were associated with greater weight loss and *GLP1R* variant with greater reduction in total body fat with liraglutide treatment.

How might your results change the direction of research or the focus of clinical practice?

Individuals who develop substantial gastric emptying delay or carry a variant in a gene that drives transcription of pre-proglucagon are more likely to achieve weight loss with liraglutide treatment.

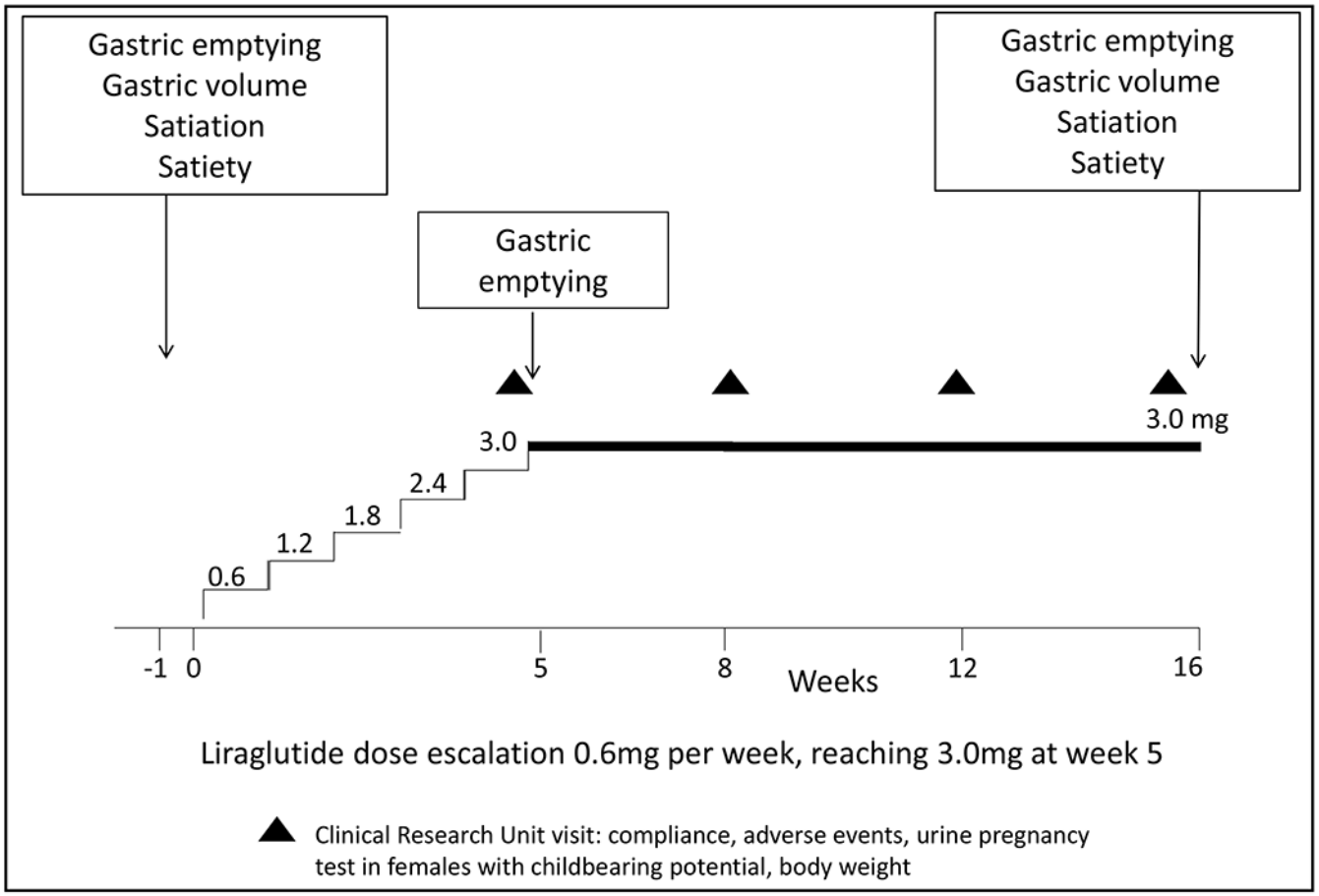


Figure 1.
Study design and gastric function testing in 136 participants over a 16-week period

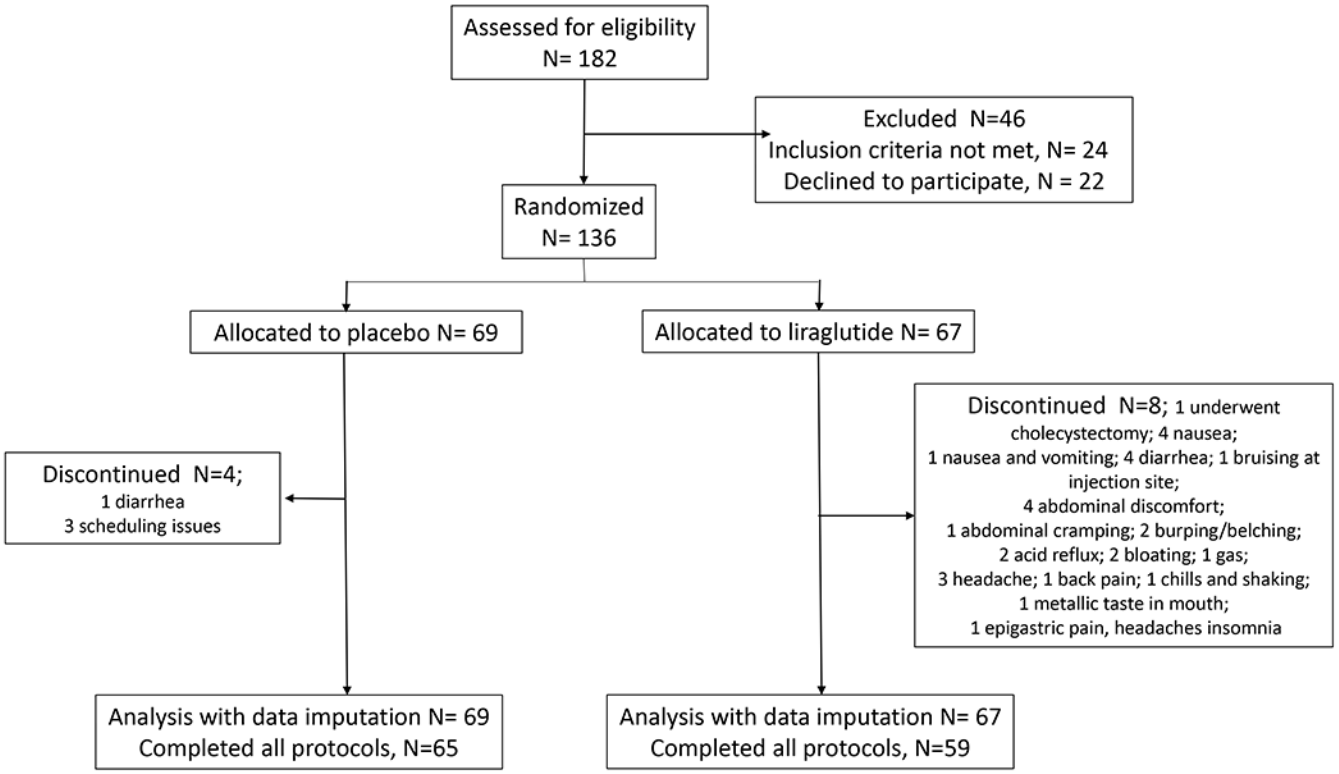


Figure 2.

CONSORT flow chart of participants; note discontinuation may have been recorded for more than one reason per withdrawal

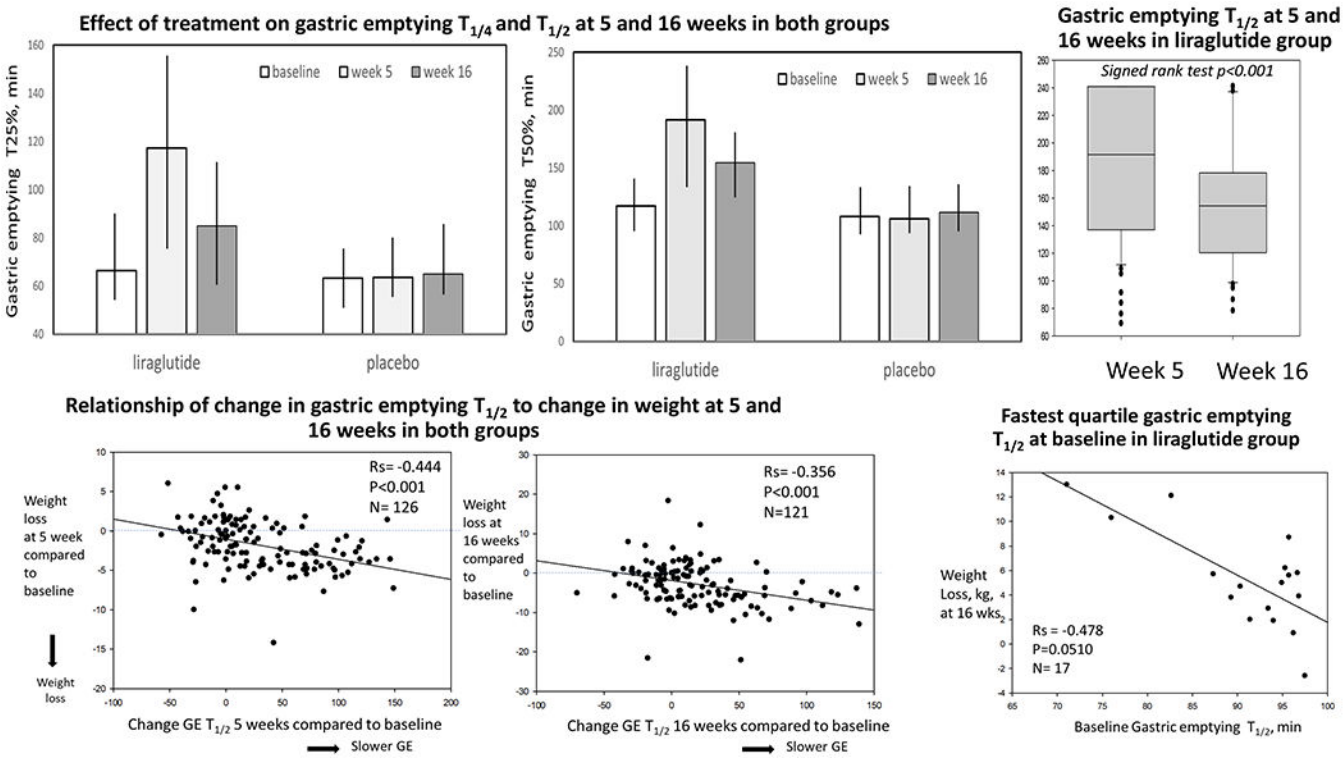


Figure 3.

Effects of liraglutide vs. placebo on gastric emptying $T_{1/4}$ (upper left panel) and $T_{1/2}$ (upper middle panel) at baseline, 5 weeks and 16 weeks of treatment showing group data (data show median, IQR); gastric emptying $T_{1/2}$ in liraglutide group showing faster gastric emptying at 16 weeks compared to 5 weeks (upper right panel). Lower left panel shows relationship of change in gastric emptying $T_{1/2}$ to change in weight at 5 and 16 weeks in both treatment groups. Lower right panel shows relationship of fastest quartile gastric emptying $T_{1/2}$ at baseline to weight loss at 16 weeks in liraglutide group.

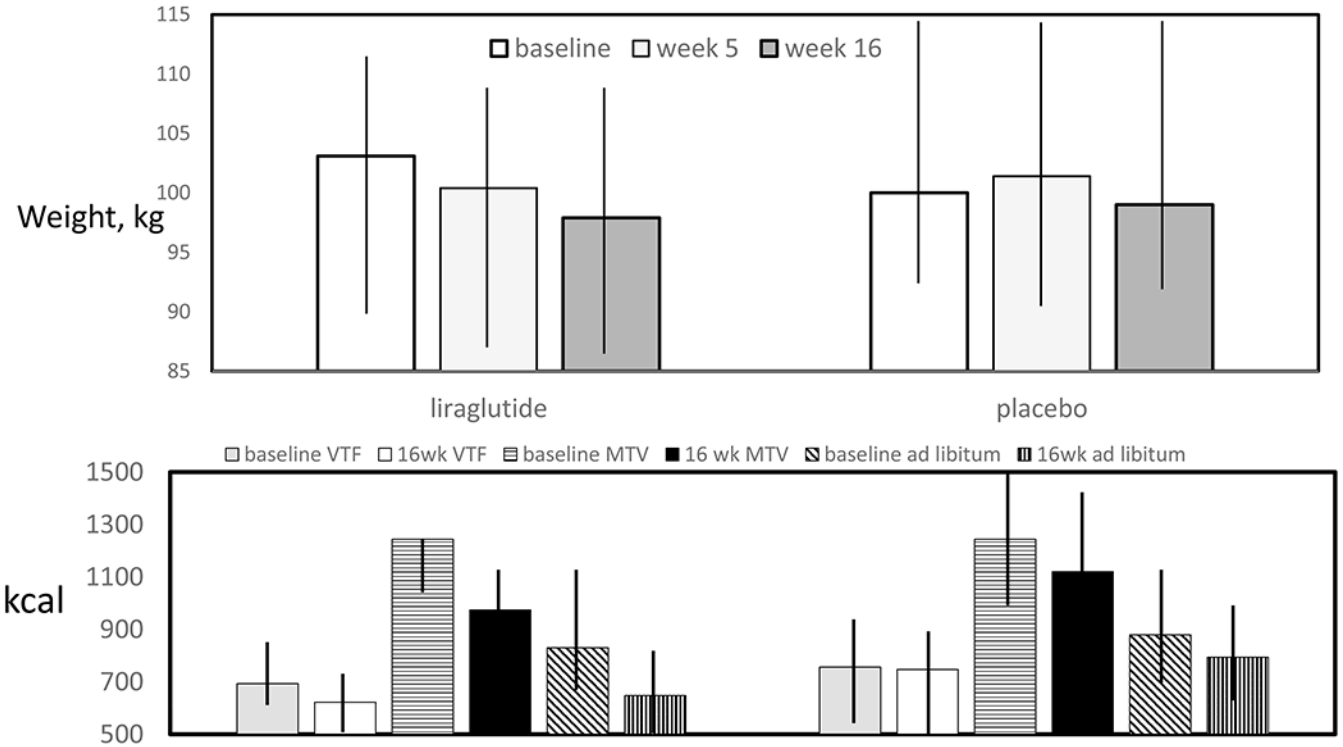
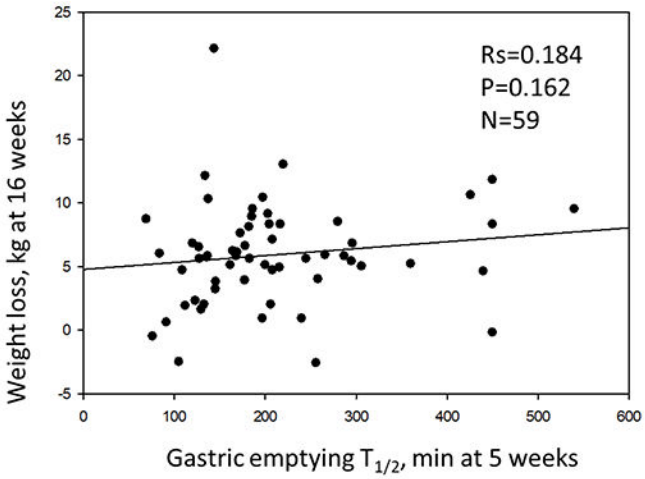


Figure 4.

Effects of liraglutide vs. placebo on body weight at baseline, 5 weeks and 16 weeks of treatment (upper panel), and on kcal intake during nutrient drink test (VTF, volume to fullness and MTV, maximum tolerated volume) and ad libitum meal at baseline and 16 weeks (lower panel) showing group data (data show median, IQR).



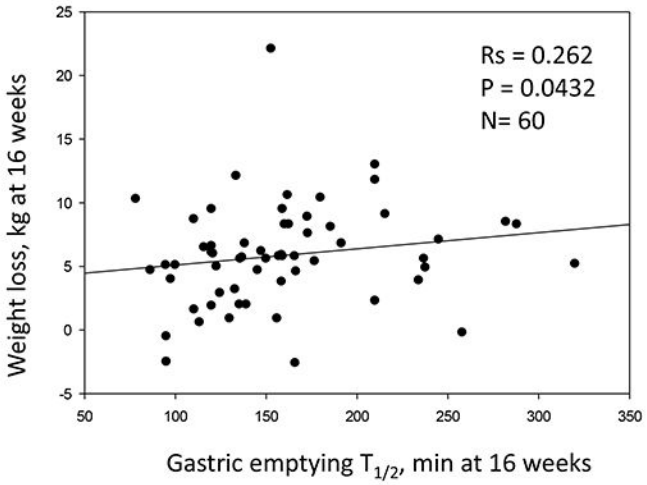


Figure 5.

Correlation of gastric emptying $T_{1/2}$ at 5 weeks and 16 weeks and weight loss at 16 weeks in the liraglutide treatment group

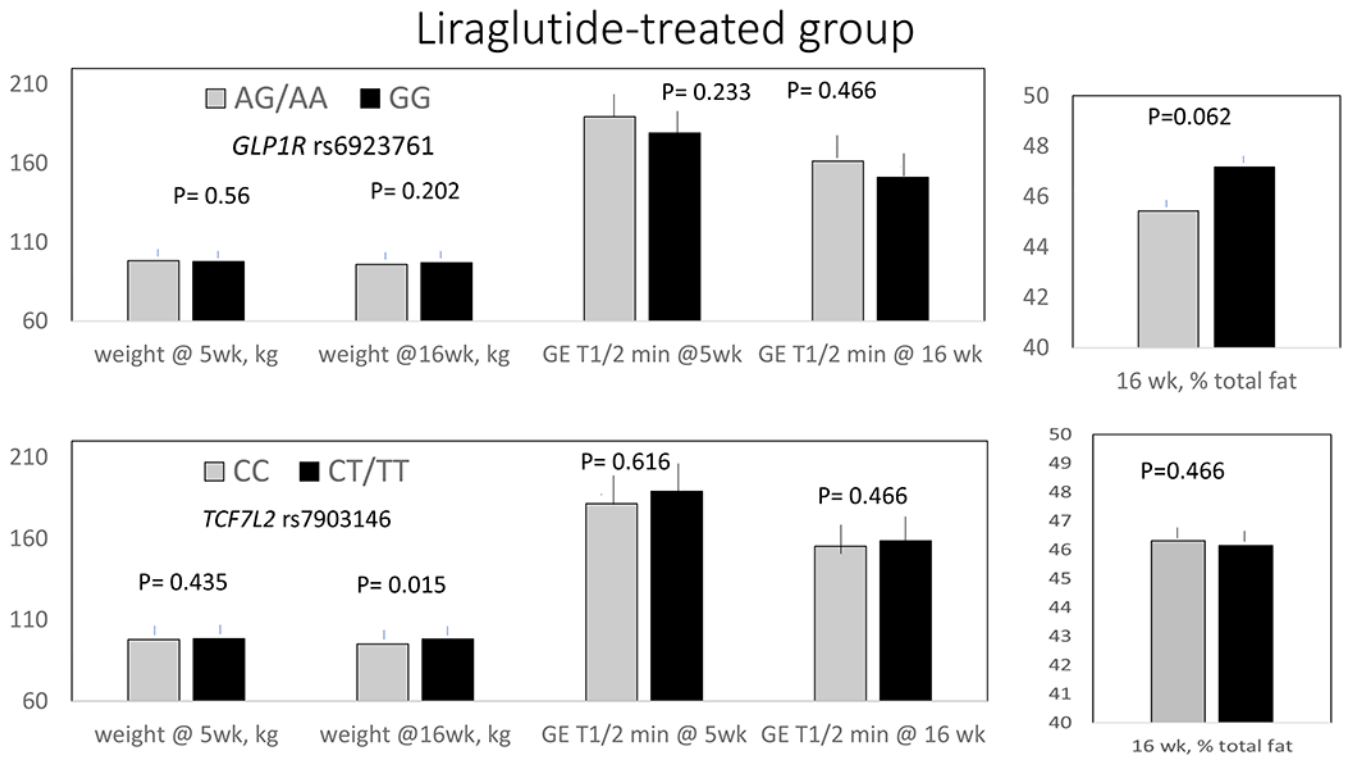


Figure 6.

Pharmacogenomics: effect of SNP variants in GLP1R and TCF7L2 on responses to liraglutide of phenotypes related to obesity

Table 1.

Effects of liraglutide, 3.0mg, on gastric emptying and weight after 5 weeks' and 16 weeks' treatment (based on ITT population and P values based on rank sum test). Data show absolute values and delta variables which were calculated as Week 5 or Week 16, minus baseline.

Data show median and IQR	Placebo, n=69	Liraglutide, n=67	Overall p*
Demographic features at baseline			
N randomized	69	67	
Age, y	37.2 (29.3, 45.2)	42 (32, 51)	
Sex (% female)	85.5%	88.1%	
Race, % white	94.2%	89.6%	
BMI, kg/m^2	35.6 (33.1, 39.7)	35.9 (32.6, 40.2)	
Body weight (kg) and percent fat			
Baseline weight, kg	100.0 (92.4, 114.9)	103.1 (89.1, 111.9)	
Weight @ 5 weeks, kg	101.4 (90.5, 114.2)	100.4 (87.0, 108.6)	
Weight @ 16 weeks. kg	99.0 (90.8, 114.6)	97.9 (85.9, 108.3)	
Delta Weight @ 5 weeks vs. baseline	0.1(−1.5, 1.4)	−3.8 (−4.8, −2.5)	0.004
Delta Weight @ 16 weeks vs. baseline	0.0 (−3.1, 2.1)	−5.8 (−8.3, −3.9)	0.033
Baseline total percent fat (%)	47.9 (43.5, 51.8)	48.6 (45.4, 51.1)	
16 weeks % total fat	47.6 (42.6, 52.0)	47.3 (43.7, 49.1)	
Delta % total fat @ 16 weeks vs. baseline	−0.5 (0.9, −1.3)	−2.0 (−0.9, −3.1)	0.008
Baseline % trunk fat	51.5(46.6,56.0)	52.7(49.0, 54.9)	
16 weeks % trunk fat	50.8(45.6, 55.7)	49.7(46.3, 53.8)	
Delta % trunk fat @ 16 weeks vs. baseline	−0.9(−1.8, 0.9)	−2.5(−4.0, −1.0)	0.004
Gastric emptying, min			
Baseline GES T25%, min	63.2 (48.5, 75.0)	66,4 (55.7, 87.5)	
GES T25% @ 5weeks, min	63.6 (56.0, 80.0)	117.2 (75.0, 156.1)	
GES T25%, @ 16weeks, min	65.0 (52.5, 83.1)	85 (59.7, 114.3)	
Delta GES T25% @ 5weeks vs. baseline, min	1 (−10.2, 14.2)	44.8 (4.1, 94.1)	<0.001
Delta GES T25% @ 16weeks vs. baseline, min	0.7 (13.3, −10.0)	13.2 (48.4, −7.2)	0.011
Baseline GES $T_{1/2}$, min	108.0 (93.1, 128.6)	117.2 (97.5, 140.0)	
GES $T_{1/2}$ @ 5weeks, min	105.9 (92.6, 127.8)	191.6 (137.0, 241.0)	
GES $T_{1/2}$ @ 16weeks, min	111.4 (97.3, 132.9)	154.4 (120.4, 178.3)	
Delta GES $T_{1/2}$ @ 5weeks vs. baseline, min	−0.1 (−14.4, 16.4)	69.7 (32.3, 97.1)	<0.001
Delta GES $T_{1/2}$ @ 16weeks vs. baseline, min	1.8 (−11.2, 14.1)	33.8 (3.7, 63.4)	<0.001

Table 2.

Effects of liraglutide, 3.0mg, on gastric accommodation, satiation, and satiety (B) after 5 weeks' and 16 weeks' treatment (based on ITT population and P values based on rank sum test). Data show absolute values and delta variables which were calculated as Week 5 or Week 16, minus baseline.

Data show median and IQR	Placebo, n=69	Liraglutide, n=67	Overall p[#]
Gastric emptying volume, mL			
Baseline gastric fasting volume, mL	200.8 (179.3, 231.2)	200.4 (179.3, 231.2)	
Baseline gastric postprandial vol., mL	587.0 (525.4, 678.0)	593.5 (489.3, 648.6)	
Baseline gastric accommodation vol, mL	378.5 (322.5, 455.9)	377.1 (322.6, 445.3)	
Gastric fasting volume @16 weeks, mL	191.5 (176.5, 231.5)	221.2 (187.7, 269.8)	
Gastric postprandial vol @16 weeks, mL	583.8 (549.8, 667.7)	629.1 (538.9, 705.1)	
Gastric accommodation (accomm.) vol. @16 weeks, mL	391.8 (348.6, 433.5)	385.4 (332.6, 445.2)	
Delta Gastric fasting volume @ 16 weeks vs. baseline	−5.9 (−39.9, 24.7)	30.0 (−24.1, 77.6)	0.010
Delta Gastric postprandial vol @ 16 weeks vs. baseline	−6.7 (−67.0, 78.6)	50.1 (−45.2, 126.8)	0.14
Delta Gastric accomm. vol @ 16 weeks vs. baseline	4.7 (−54.7, 86.2)	9.2 (−58.7, 87.7)	0.73
Satiation volume (mL) and symptoms (VAS, mm)			
Baseline satiation volume to fullness (VTF), mL	756 (535.5, 945.0)	693 (567.0, 871.0)	
Baseline satiation maximum tolerated (MTV), mL	1244.3 (995.4, 1493.1)	1244.3 (995.4, 1244.3)	
Satiation VTF @16 weeks, mL	746.6 (497.7, 871.0)	622.1 (496.7, 746.6)	
Satiation MTV @16 weeks, mL	1119.8 (995.4, 1430.9)	974.4 (746.6, 1156.3)	
Delta, satiation VTF (mL), @16 weeks vs. baseline	0.0 (−126.0, 124.4)	−124.4 (−248.9, 41.0)	0.006
Delta, Satiation MTV (mL) @16 weeks vs. baseline	−124.4 (−248.9, 85.3)	−248.9 (−497.7, 0.0)	<0.001
Baseline VAS aggregate score	206.0 (151.5, 256.5)	204.0 (156.0. 253.0)	
Baseline VAS nausea score	33.5 (19, 64)	43 (12, 62)	
Baseline VAS fullness score	77.5 (72.5, 83)	74 (66, 84)	
Baseline VAS bloating score	66.5 (49, 78.5)	67 (52, 79)	
Baseline VAS pain score	27.5 (7.5, 50)	27 (10, 55)	
VAS aggregate score @16 weeks	219.5 (179.5, 258.5)	236.0 (188, 277)	
VAS nausea score @16 weeks	37.0 (23.5, 61)	48 (21, 66)	
VAS fullness score @16 weeks	75 (70, 82.5)	74 (68, 81)	
VAS bloating score @16 weeks	71 (53, 82.5)	74 (55, 81)	
VAS pain score @16 weeks	29 (14.5, 59.5)	51 (21, 63)	
Delta, VAS aggregate score @16 weeks vs. baseline	6.0 (−20.0, 53.0)	24.0 (−34.0, 67.0)	0.28
Satiety (appetite), kcal ingested			
Baseline ad libitum meal total calories	878.6 (708.2, 1151.1)	829.5 (665.7, 1088.5)	
ad libitum meal total calories at 16 weeks	793.7 (624.6, 1019.3)	647.5 (472.4, 826.4)	
Delta ad libitum meal total calories at 16 weeks vs. baseline	−129.2 (−197.6, −23.2)	−184.8 (−322.3, −69.4)	0.004

[#]Analyses run using analysis of covariance (ANCOVA) model of rank transformed data; model covariates include baseline of dependent variable in the model, sex, and treatment arm. Maximum tolerated volume (MTV); aggregate symptom score maximum is 400; individual symptom scores maximum 100.