Official title: **Impact of Liraglutide 3.0 on Body Fat Distribution, Visceral Adiposity, and Cardiometabolic Risk Markers In Overweight and Obese Adults at High Risk for Cardiovascular Disease**

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Impact of Liraglutide 3.0 on Body Fat Distribution, Visceral Adiposity, and Cardiometabolic Risk Markers In Overweight and Obese Adults at High Risk for Cardiovascular Disease

A Phase 4 randomized, double blinded, placebo controlled 46-week clinical trial

INVESTIGATOR-INITIATED TRIAL PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1171-4812

CLINICALTRIALS.GOV REGISTRATION: PENDING

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Abbreviations:

ASCVD = atherosclerotic cardiovascular disease

BMI = body mass index

H^1 MRS = proton magnetic resonance spectroscopy

SAT = subcutaneous adipose tissue

VAT = visceral adipose tissue

CLINCAL TRIAL EXECUTIVE SUMMARY:

Primary Objective:
To investigate the efficacy of liraglutide compared to placebo in reducing visceral adiposity measured by MRI in overweight or obese subjects at high risk for cardiovascular disease after 40 weeks on-treatment.

Secondary Objectives:
To compare liraglutide and placebo regarding the effect on:

- Changes in abdominal subcutaneous adipose tissue by MRI
- Changes in total fat mass by MRI
- Changes in fat-free mass by MRI
- Changes in lower body adipose tissue mass by MRI
- Changes in hepatic fat content by MRI
- Changes in circulating blood biomarkers of cardiometabolic risk including markers of insulin resistance, inflammation, lipids, and natriuretic peptides.

Trial Design:

This is a randomized, double-blind, parallel-group, placebo controlled, prospective clinical trial to be conducted at a single center over 46 weeks (40 weeks on-treatment). There are two treatment arms. Patients will be randomized to liraglutide 3.0 administered once a day by subcutaneous injection or matching placebo, in addition to a reduced-calorie diet and increased physical activity. All participants will be prescribed a 500 kcal per day deficit diet, based on estimated 24-h energy expenditure.[1] All participants will be instructed to maintain physical activity at the recommended level of 150 minutes of moderate activity per week.

Trial Population:

Planned number of subjects to be screened: 356 (2:1 screen to randomization ratio)
Planned number of subjects to be treated in run-in period: 214
Planned number of subjects to be randomized/started on trial medication(s):178
Anticipated number of subjects to be studied: At least 128 completers
Number of trial sites: Single center

Sample Size:

This trial is powered to detect a clinically meaningful difference in the percent relative reduction in VAT. The estimates used in the sample size calculations below are derived from prior data from the SCALE program. Assuming a mean 8% relative reduction of VAT among placebo treated subjects and an expected 16% relative reduction of VAT among liraglutide treated subjects (with a standard deviation of 16%, based on data from [2]), we expect to require 128 total subjects (in a 1:1 trial drug:placebo randomization scheme) to achieve 80% power to detect an 8% difference between groups at an alpha level of 0.05. Assuming an estimated 28% of subjects may withdraw trial medication during the trial, we expect a planned total of 178 patients will be randomized in order to achieve at least 128 completers of the full trial protocol.

Inclusion Criteria:

1. Age ≥ 35 years
2. Able to provide informed consent
3. BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with metabolic syndrome
4. Metabolic syndrome as defined by at least three of the following:[3]
    1) waist circumference > 102 cm (40 in) in men and 88 cm (35 in) in women
    2) triglycerides $\geq$ 150 mg/dL or on treatment for hypertriglyceridemia
    3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women
    4) blood pressure $\geq$ 130/85 mmHg or on treatment for hypertension
    5) fasting glucose $\geq$ 100 mg/dL

Exclusion Criteria:

1. Treatment with GLP-1 receptor agonists (including liraglutide, exenatide or others as become available for use), DPP-4 inhibitors or insulin within the last 3 months.
2. Receipt of any anti-obesity drug or supplement within 1 month prior to screening for this trial.
3. Self-reported or clinically documented history of significant fluctuations (>5% change) in weight within 3 months prior to screening for this trial.
4. History of diabetes mellitus (type 1 or 2) or on treatment with anti-diabetes medication.
5. History of chronic pancreatitis or idiopathic acute pancreatitis (current or prior history).
6. History of gallbladder disease (cholelithiasis or cholecystitis).
7. Chronic kidney disease stage III or greater (eGFR<60 mL/min).
8. Obesity induced by other endocrinologic disorders (e.g. Cushing Syndrome).

9. Current or history of treatment with medications that may cause significant weight gain, within 1 month prior to screening for this trial, including systemic corticosteroids (except for a short course of treatment, i.e., 7- 10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g., imipramine, amitryptiline, mirtazapine, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium).
10. Diet attempts using herbal supplements or over-the-counter medications within 1 month prior to screening for this trial.
11. Current participation in an organized weight reduction program or within the last 1 month prior to screening for this trial.
12. Participation in a clinical trial within the last 3 months prior to screening for this trial.
13. Familial or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma.
14. Personal history of non-familial medullary thyroid carcinoma.
15. History of Major Depressive Disorder within the last 2 years.
16. History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder.
17. Any lifetime history of a suicide attempt.
18. A history of any suicidal behavior in the last month prior to randomization.
19. Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the Investigator.
20. Known or suspected hypersensitivity to trial product(s) or related product(s).
21. Known or suspected abuse of alcohol or narcotics.
22. Language barrier, mental incapacity, unwillingness or inability to understand.
23. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods. These include abstinence and the following methods: diaphragm with spermacide, condom with spermacide (by male partner), intrauterine device, sponge, spermacide, Norplant®, Depo-Provera® or oral contraceptives.

Assessment of Efficacy Endpoints:
The following endpoints will be assessed at the end of 40 weeks of treatment:

Primary Endpoint:
- The liraglutide treatment effect on relative percent change from baseline in visceral adipose tissue mass measured by MRI

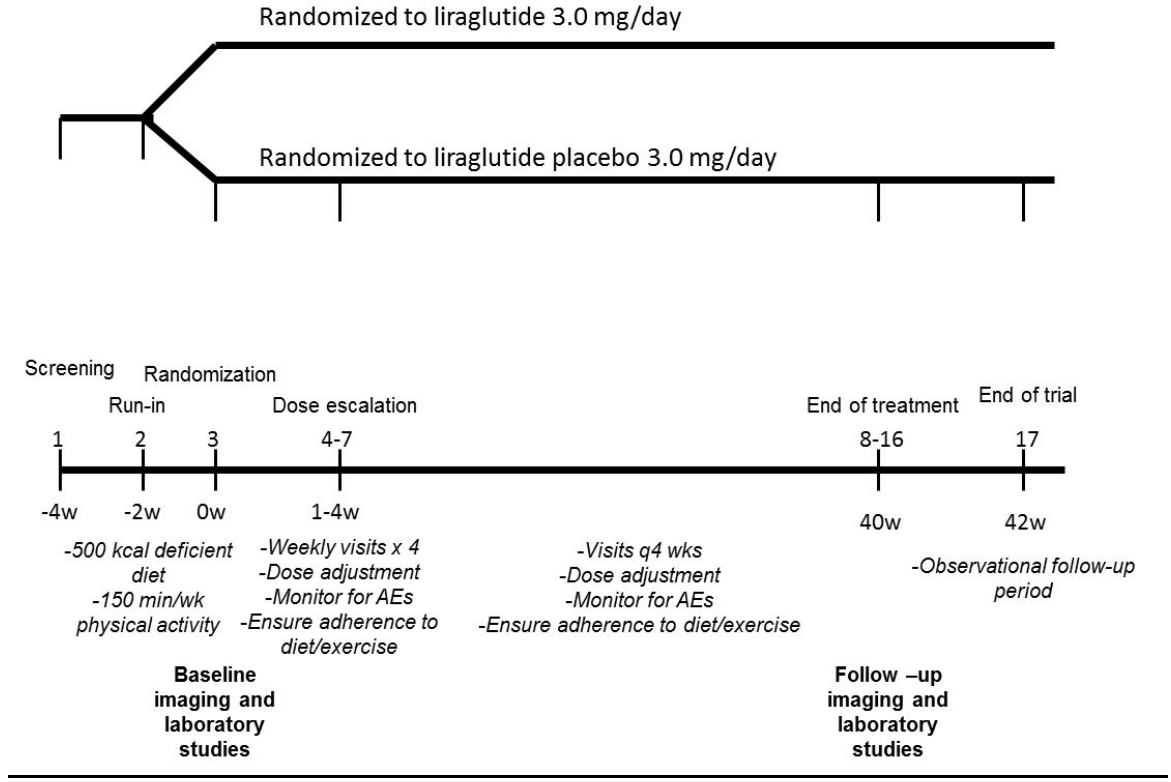
Secondary Endpoints: Liraglutide treatment effect on:
- Relative percent change from baseline in body weight
- Absolute change from baseline in body weight
- Absolute change from baseline in visceral adipose tissue mass
- Relative percent change from baseline in abdominal subcutaneous adipose tissue mass
- Absolute change from baseline in abdominal subcutaneous adipose tissue mass
- Change from baseline in VAT/SAT ratio
- Relative percent change from baseline in total fat mass
- Absolute change from baseline in total fat mass
- Relative percent change from baseline in fat-free mass
- Absolute change from baseline in fat-free mass
- Relative percent change from baseline in lower body adipose tissue mass
- Absolute change from baseline in lower body adipose tissue mass

- Change from baseline in total fat/fat-free mass ratio
- Relative percent change from baseline in hepatic fat content
- Absolute change from baseline in hepatic fat content
- Relative percent change from baseline in biomarkers of cardiometabolic risk
  - Markers of insulin resistance: fasting blood glucose, insulin, HOMA-IR
  - Markers of inflammation: CRP
  - Lipids: TG/HDL-C ratio
  - Natriuretic peptides: NT-proBNP
- Absolute change from baseline in biomarkers of cardiometabolic risk
- Change from baseline in heart rate and blood pressure
- Change in waist circumference

Trial Products:

Liraglutide will be administered at a concentration of 6.0 mg/mL. Liraglutide and placebo will be supplied in a 3 mL pen-injector. Subjects will follow a fixed dose escalation and in order to reduce the level of side effects, liraglutide is gradually escalated up to the maintenance dose. Subjects will be instructed to escalate the liraglutide (active or placebo) dose to 3.0 mg/day over a 4 week period following an initial dose of 0.6 mg/day and weekly dose escalation steps of 0.6 mg/day. If subjects do not tolerate an increase in dose during dose-escalation, the Investigator will have the option to delay the next dose escalation for approximately one week.

Trial Design Diagram



Trial Chart

BACKGROUND AND SIGNIFICANCE:

Section 1: Obesity and Cardiovascular Risk

Obesity has long been recognized as a risk factor for all-cause mortality[4] and morbidity, including the development of cardiovascular and metabolic diseases such as coronary artery disease, hypertension, insulin resistance, diabetes, and dyslipidemia.[5] Obesity has recently been formally defined as a chronic disease characterized by pathophysiological processes that result in increased adipose tissue mass and can result in increased morbidity and mortality.[6] Although the health risks associated with obesity are clear, there is an emerging appreciation that obesity *per se*, as defined by simple anthropometric measures such as waist circumference or body mass index (BMI), is neither necessary nor sufficient to promote cardiometabolic disease and atherosclerotic cardiovascular disease (ASCVD) risk. As a result, BMI alone is an insufficient marker of risk and may not accurately identify individuals at elevated risk for ASCVD.[7] There is a pressing need to more accurately phenotype obesity to identify individuals at elevated risk for ASCVD that may benefit from more intensive preventive and therapeutic strategies.

Section 2: Visceral adipose tissue as a key marker of CV Risk

It appears that risk for ASCVD and metabolic diseases varies substantially by distribution of body fat, as well as by adipocyte size and function. Excess intra-abdominal (i.e. visceral) adipose tissue (VAT) may be a primary driver of the cardiometabolic complications of obesity[8], and ectopic fat linked to VAT may itself play a key contributory role. An increase in VAT is thought to reflect the relative inability of the subcutaneous adipose tissue depot to sufficiently expand its clearance and storage capacity in response to caloric excess.[9] Defects in adipocyte maturation and differentiation[10] cause adipocyte dysfunction, resulting in spillover of excess triglycerides and promotion of ectopic fat deposition in the viscera, liver, heart, and skeletal muscle. The ensuing milieu of overactive lipolysis, altered glucose homeostasis, pro-inflammatory adipocytokine release, and endothelial dysfunction appears to be a primary cause of the pathophysiological alterations observed in obesity related cardiometabolic disease.

Trial periods	**Screening**	**Run-In**	**Randomization**	**Dose escalation period/ Maintenance**			**Maintenance/ End of treatment**	**Follow-up**
Weeks in relation to Visit 2 (randomization)	-4	-2	0	1	2	3	4-40	42
Visit number	1	2	3	4	5	6	7-16	17
Liraglutide	Screening	Run-In	0.6 mg	1.2 mg	1.8 mg	2.4 mg	3.0 mg	No treatment
Placebo			Placebo	Placebo	Placebo	Placebo	Placebo	

Although more simplistic anthropomorphic measures of abdominal obesity, such an increased waist circumference, identify individuals at increased risk for atherosclerosis[11] and mortality

across different levels of BMI[12], it is an imprecise surrogate for the VAT phenotype. First, the correlation between BMI, waist circumference, and VAT is highly variable among different racial groups, prompting the American Diabetes Association and the International Diabetes Federation to define different cutoffs for abnormal BMI and waist circumference, respectively, in Asian populations.[13,14] Second, waist circumference measurement includes both VAT and abdominal subcutaneous adipose tissue (SAT) compartments. These two depots are anatomically and physiologically distinct, especially within the obese population, and are differentially associated with markers of cardiometabolic risk.[15] VAT, but not abdominal subcutaneous fat, has been shown to associate with incident T2D and pre-T2D[16], incident hypertension[17], and alterations in left ventricular structure and function[18], and has also been linked to increased risk of developing ASCVD and cancer.[19] Medical treatments that reduce VAT mass may translate into improved major adverse cardiac event (MACE)-free survival.

Section 3: Liraglutide 3.0

GLP-1: Physiology and current literature

In response to a meal, GLP-1, an incretin hormone secreted from the L-cells in the lower gut, stimulates endogenous insulin secretion in a glucose-dependent manner, decreases blood glucagon levels, reduces gastric emptying and increases satiety. GLP-1 reduces appetite in lean and normal weight individuals, as well as in obese individuals, and has been shown to reduce body weight. The combination of these mechanisms makes GLP-1 receptor stimulation an attractive mechanism to investigate for weight management.

Liraglutide

Liraglutide 3.0 mg (Saxenda®, Novo Nordisk, Bagsvaerd, Denmark) is a glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of ≥30 kg/m^2 (obese) or in patients with a BMI of ≥27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition such as hypertension, type 2 diabetes mellitus, or dyslipidemia.

Compared to human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at position 26 (lysine) of the peptide, and has lysine at position 34 replaced by arginine. When administered subcutaneously, these structural modifications result in a compound with protracted kinetic properties suitable for once daily injection. The dose approved for use in the United States for the chronic treatment of obesity is 3.0 mg injection once daily. This dose was approved for use by the FDA based upon the results of a clinical trial which evaluated weight change after 20 weeks using liraglutide 1.2, 1.8, 2.4 and 3.0 mg compared to placebo and open-label orlistat (Trial 1807).[1] Those trials (a dose-ranging phase 2 and four phase 3 trials) included 5922 patients and demonstrated a consistent and clinically meaningful reduction in weight. Liraglutide met the 5% mean placebo-corrected difference in weight loss as described in the FDA draft weight management guidance (http://www.fda.gov/downloads/Drugs/Guidances/ucm071612.pdf, accessed June 3, 2015). The safety and efficacy of Liraglutide was established in three 56-week, randomized, double blind, placebo-controlled trials. In all studies, liraglutide was titrated to 3.0 mg daily during a 4-week period. All patients received instruction for a reduced calorie diet (approximately 500 kcal/day deficit) and exercise counseling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication and continued throughout the trial. Study patients were either overweight defined as a BMI of 27 kg/m^2 or greater in the presence

of at least one obesity related comorbidity or were obese defined as a BMI of 30 kg/m^2 or greater.

These 3 trials included 4788 patients, of these 3122 were treated with liraglutide. Study 1 included 3,371 obese or overweight patients; study 2 included 635 patients with type 2 diabetes mellitus with obesity or overweight; and study 3 included 422 obese and overweight patients who also lost at least 5% of body weight with diet and exercise alone. The primary efficacy endpoint in trials 1 and 2 was the mean percent change in body weight and the percentages of patients achieving greater than or equal to 5% of weight loss from baseline through 56 weeks. In study 3 there was an additional efficacy measure which was the percentage of patients not gaining more than 0.5% of body weight from randomization. Patients treated with liraglutide experienced a significant decrease in percent change (from baseline) in total body weight ranging from -4.9 to -7.4% (least square mean). Over 50% of patients lost greater than 5% of their baseline body weight and approximately 30% lost greater than 10% of their body weight. These changes were significantly greater than weight loss seen in the placebo arms of these three trials. In study 3 there were a statistically greater number of patients randomized to placebo that gained at least 0.5% of their body weight at week 56. Liraglutide use was also associated with a reduction in waist circumference, blood pressure and modest reductions in total cholesterol, LDL and increase in HDL. Liraglutide was associated with an increase in heart rate of approximately 2 beats per minute.

Tolerability and Adverse Events

Treatment with liraglutide in prior obesity trials was generally well tolerated. Approximately 70% of patients randomized to liraglutide completed the trials on medication. The withdrawal rate was approximately 8.5% in the liraglutide arms and 8.6% in the placebo treated patients. Serious adverse events were relatively uncommon, but were more frequent in liraglutide-treated subjects compared with placebo (4.2 vs. 2.4%). GI side effects seen in the SCALE Maintenance trial were common in patients taking liraglutide 3.0 mg. The frequency of nausea was 47.6%, of diarrhea was 17.9%, of constipation was 26.9% and of vomiting was 16.5%. Other less common AEs included dyspepsia (9.4%), abdominal pain (6.6%), abdominal distension (6.1%), eructation (5.2%), and flatulence (5.2%).[20]

There have been rare, spontaneous post-marketing reports of acute pancreatitis in patients without a history of pancreatitis being treated with liraglutide. In the obesity clinical trials, acute pancreatitis was confirmed in 9 of 3291 liraglutide treated patients and 1 of 1843 placebo treated patients. There were 3 additional cases of pancreatitis occurring in liraglutide treated patients ranging 14 to 124 days after study discontinuation. A history of pancreatitis was an exclusion criterion in clinical trials performed to date. If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory tests have been conducted and appropriate treatment initiated.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may

have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors.

Liraglutide and Body Composition

Body composition was measured in a sub-study of Trial 1807 which included 113 patients (92 completers) from 7 European centers using dual energy x-ray absorptiometry (DXA) and computerized axial tomography (CT) scans. Trial 1807[2] was a placebo-controlled 20 week trial with open label orlistat, placebo and once daily injection of liraglutide. At 1 year liraglutide 3.0 mg recipients lost 5.8 kg (95% CI 3.7–8.0) more body weight than those on placebo and 3.8 kg (1.6–6.0) more than those on orlistat (P<0.0001). In this body composition sub-study at week 20, mean total body fat mass was reduced between 5.0-6.9 kg with liraglutide, 4.4 kg with placebo and 4.9 with orlistat. The percentage of body weight lost due to fat was 80-90% of the total weight lost in the liraglutide treated group and 63% in the placebo group. The weight loss and reduction in waist circumference with liraglutide was primarily due to reduction in fat mass rather than lean body mass. This sub-study also quantified the VAT and abdominal SAT mass lost. Summary data from this body composition sub-study are presented in Table 1 and Figure 1 below:

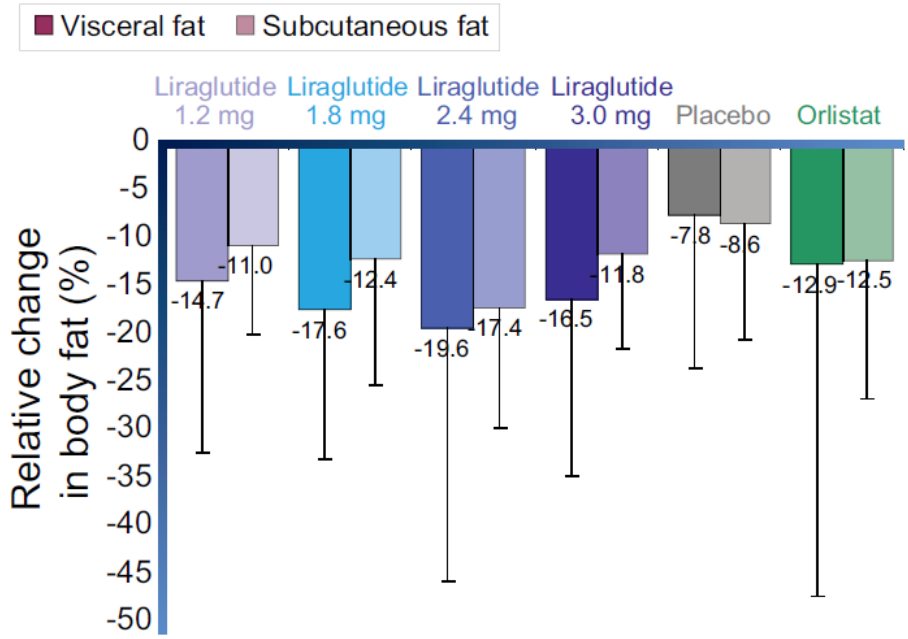
<u>While there was a numerical trend for greater VAT mass loss in the liraglutide 3.0 mg group, this study was underpowered to detect between group differences in absolute or relative VAT mean mass lost.</u> This initial work is a fundamental first step but has important limitations, including: 1) lack of study subjects in the United States; patients enrolled in this study were exclusively recruited from European centers including Belgium, Czech Republic, Denmark, Finland, Netherlands, Spain, and Sweden; 2) there were very few subjects treated with 3.0 mg of liraglutide (N=15); therefore this study was not only underpowered to detect clinically meaningful differences in abdominal fat distribution, but also systematically underdosed; 3) the use of ionizing radiation (with CT scans) limits the generalizability to other research projects that will likely be conducted over long-term follow-up with repeat imaging; and 4) this study did not directly quantify hepatic fat, a known correlate of insulin resistance and cardiometabolic risk. We will address these limitations in the research proposed below.

<u>Table 1. Body composition assessed by DXA and CT in a subgroup of participants at 20 weeks</u>

	Placebo n = 14	Liraglutide 1.2 mg n = 15	Liraglutide 1.8 mg n = 13	Liraglutide 2.4 mg n = 15	Liraglutide 3.0 mg n = 15	Orlistat n = 12
Dual-energy X-ray absorptiometry measurements: body composition at randomization (kg)[a]						
Fat tissue	45.8 (10.5)	43.5 (7.6)	45.0 (8.8)	42.6 (6.1)	43.9 (8.4)	41.3 (6.7)
Lean tissue	51.0 (11.0)	55.0 (8.9)	51.7 (11.3)	50.6 (11.9)	53.1 (10.3)	47.4 (6.4)
Relative change at week 20 (%)						
Fat tissue[b]	−11.9 (2.5)	−13.9 (2.7)	−13.0 (2.6)	−16.5 (2.5)	−15.4 (2.6)	−13.3 (2.9)
Change vs placebo[c]	—	−2.0 (−8.9 to 4.9); P = 0.57	−1.1 (−8.0 to 5.9); P = 0.76	−4.6 (−11.2 to 2.1); P = 0.18	−3.5 (−10.3 to 3.4); P = 0.32	—
Lean tissue[b]	−1.3 (1.0)	−0.9 (1.1)	−2.9 (1.1)	−2.6 (1.0)	−2.0 (1.1)	0.9 (1.2)
Change vs placebo[c]	—	0.4 (−2.4 to 3.3); P = 0.77	−1.6 (−4.4 to 1.3); P = 0.28	−1.3 (−4.1 to 1.4); P = 0.33	−0.7 (−3.6 to 2.1); P = 0.61	—
Computerized axial tomography measurements: body composition at randomization (cm^2)[a]						
Visceral fat	136 (38)	172 (77)	121 (39)	149 (76)	145 (69)	101 (40)
Subcutaneous fat	474 (107)	453 (68)	476 (71)	426 (75)	434 (116)	459 (113)
Relative change at week 20 (%)						
Visceral fat[b]	−13.8 (5.7)	−19.0 (6.3)	−19.4 (6.0)	−23.0 (5.7)	−20.3 (6.0)	−20.2 (6.7)
Change vs placebo[c]	—	−5.1 (−21.2 to 11.0); P = 0.53	−5.6 (−21.8 to 10.6); P = 0.49	−9.2 (−24.7 to 6.4); P = 0.25	−6.4 (−22.1 to 9.2); P = 0.42	—
Subcutaneous fat[b]	−12.1 (3.0)	−15.6 (3.3)	−15.9 (3.6)	−19.3 (3.0)	−15.3 (3.3)	−17.9 (3.6)
Change vs placebo[c]	—	−3.5 (−11.8 to 4.9); P = 0.41	−3.8 (−12.6 to 5.1); P = 0.40	−7.1 (−15.2 to 1.0); P = 0.09	−3.1 (−11.5 to 5.2); P = 0.45	—

[a]Mean (s.d.). [b]Estimated mean (s.e.). [c]Estimated mean (95% CI); *P*-value. Values are for participants who completed the substudy according to the protocol (PP completers).

Figure 1. Relative changes in Visceral and Abdominal Subcutaneous Fat Mass Assessed by CT



Therefore, we believe there is an important and pressing need for extensive and detailed phenotyping to further elucidate the impact of Liraglutide 3.0 mg on markers of body fat distribution, visceral adiposity, and adverse cardiometabolic risk and its potential benefits on long-term cardiovascular disease outcomes. Our long term goal is to understand how VAT contributes to cardiometabolic disease risk and to identify strategies to reduce the cardiometabolic consequences of excess VAT. Our objectives here are to elucidate the effect of Liraglutide 3.0 on body fat distribution, visceral adiposity, and markers of cardiometabolic

disease risk among overweight and obese adults at high risk for cardiovascular disease using detailed circulating blood biomarker and imaging phenotyping.

TRIAL RATIONALE:

The rationale of this project is to utilize adipose tissue imaging with minimal or no ionizing radiation to investigate the potential beneficial effects of Liraglutide 3.0 mg on pathways underlying excess cardiovascular disease risk related to visceral adiposity and an adverse cardiometabolic phenotype. We will achieve the scientific objectives of this application by pursuing the following objectives with the following hypothesis:

OBJECTIVES AND ENDPOINTS:

Hypothesis:

Liraglutide will decrease visceral adiposity, favorably alter body fat distribution, and improve the cardiometabolic risk marker profile significantly better than placebo in overweight or obese subjects at high risk for cardiovascular disease.

Primary Objective:

To investigate the efficacy of liraglutide compared to placebo in reducing visceral adiposity in overweight or obese subjects at high risk for cardiovascular disease after 40 weeks on-treatment.

Secondary Objectives:

To compare liraglutide and placebo regarding the effect on:

- Changes in abdominal subcutaneous adipose tissue by MRI
- Changes in total fat mass by MRI
- Changes in fat-free mass by MRI
- Changes in lower body adipose tissue mass by MRI
- Changes in hepatic fat content by MRI
- Changes in circulating blood biomarkers of cardiometabolic risk including markers of insulin resistance, inflammation, lipids, and natriuretic peptides.

Endpoints: The following endpoints will be assessed at the end of 40 weeks of treatment:

Primary Endpoint:

- The liraglutide treatment effect on relative percent change from baseline in visceral adipose tissue mass measured by MRI.

Secondary Endpoints: Liraglutide treatment effect on:

- Relative percent change from baseline in body weight
- Absolute change from baseline in body weight
- Absolute change from baseline in visceral adipose tissue mass
- Relative percent change from baseline in abdominal subcutaneous adipose tissue mass
- Absolute change from baseline in abdominal subcutaneous adipose tissue mass
- Change from baseline in VAT/SAT ratio
- Relative percent change from baseline in total fat mass
- Absolute change from baseline in total fat mass
- Relative percent change from baseline in fat-free mass
- Absolute change from baseline in fat-free mass

- Relative percent change from baseline in lower body adipose tissue mass
- Absolute change from baseline in lower body adipose tissue mass
- Change from baseline in total fat/fat-free mass ratio
- Relative percent change from baseline in hepatic fat content
- Absolute change from baseline in hepatic fat content
- Relative percent change from baseline in biomarkers of cardiometabolic risk
    - Markers of insulin resistance: fasting blood glucose, insulin, HOMA-IR
    - Markers of inflammation: CRP
    - Lipids: TG/HDL-C ratio
    - Natriuretic peptides: NT-proBNP
- Absolute change from baseline in biomarkers of cardiometabolic risk
- Change from baseline in heart rate and blood pressure
- Change in waist circumference

TRIAL DESIGN AND METHODS:

Trial type:

This is a randomized, double-blind, parallel-group, placebo controlled, prospective clinical trial to be conducted at a single center over 46 weeks (40 weeks on-treatment). There are two treatment arms. Patients will be randomized to liraglutide 3.0 administered once a day by subcutaneous injection or matching placebo, in addition to a reduced-calorie diet and increased physical activity. All participants will be prescribed a 500 kcal per day deficit diet, based on estimated 24-h energy expenditure.[1] All participants will be instructed to maintain physical activity at the recommended level of 150 minutes of moderate activity per week.

Rationale for trial design:

This trial design will directly address the trial objectives by allowing determination of the effects of Liraglutide on body fat distribution, visceral adiposity, and cardiometabolic risk markers independent of a reduced calorie diet and increased physical activity among overweight and obese adults at high cardiovascular disease risk.

Trial population:

Planned number of subjects to be screened: 356 (2:1 screen to randomization ratio)
Planned number of subjects to be treated in run-in period: 214
Planned number of subjects to be randomized/started on trial medication(s):178
Anticipated number of subjects to be studied: At least 128 completers
Number of trial sites: Single center

The anticipated screening failure rate of 40% and the anticipated drop-out rate at 40 weeks of 28% are based on reported rates from obesity and diabetes trials.

Inclusion criteria:

1. Age ≥ 35 years
2. Able to provide informed consent
3. BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with metabolic syndrome
4. Metabolic syndrome is defined as at least three of the following:[3]
    1) waist circumference > 102 cm (40 in) in men and 88 cm (35 in) in women
    2) triglycerides ≥ 150 mg/dL or on treatment for hypertriglyceridemia
    3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women

4) blood pressure ≥ 130/85 mmHg or on treatment for hypertension
5) fasting glucose ≥ 100 mg/dL

Exclusion criteria:

1. Treatment with GLP-1 receptor agonists (including liraglutide, exenatide or others as they become available), DPP-4 inhibitors or insulin within the last 3 months.
2. Receipt of any anti-obesity drug or supplement within 1 month prior to screening for this trial.
3. Self-reported or clinically documented history of significant fluctuations (>5% change) in weight within 3 months prior to screening for this trial.
4. History of diabetes mellitus (type 1 or 2) or on treatment with anti-diabetes medication.
5. History of chronic pancreatitis or idiopathic acute pancreatitis (current or prior history).
6. History of gallbladder disease (cholelithiasis or cholecystitis).
7. Chronic kidney disease stage III or greater (eGFR<60 mL/min).
8. Obesity induced by other endocrinologic disorders (e.g. Cushing Syndrome).
9. Current or history of treatment with medications that may cause significant weight gain, within 1 month prior to screening for this trial, including systemic corticosteroids (except for a short course of treatment, i.e., 7- 10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g., imipramine, amitryptiline, mirtazapine, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium).
10. Diet attempts using herbal supplements or over-the-counter medications within 1 month prior to screening for this trial.
11. Current participation in an organized weight reduction program or within the last 1 month prior to screening for this trial.
12. Participation in a clinical trial within the last 3 months prior to screening for this trial.
13. Familial or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma.
14. Personal history of non-familial medullary thyroid carcinoma.
15. History of Major Depressive Disorder within the last 2 years.
16. History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder.
17. Any lifetime history of a suicide attempt.
18. A history of any suicidal behavior in the last month prior to randomization.
19. Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the Investigator.
20. Known or suspected hypersensitivity to trial product(s) or related product(s).
21. Known or suspected abuse of alcohol or narcotics.
22. Language barrier, mental incapacity, unwillingness or inability to understand.
23. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods. These include abstinence and the following methods: diaphragm with spermacide, condom with spermacide (by male partner), intrauterine device, sponge, spermacide, Norplant®, Depo-Provera® or oral contraceptives.

Withdrawal Criteria:

1. Participants may withdraw at will at any time.
   - Informed consent may be withdrawn at any time.

- Permission to follow up for endpoint determination may be withdrawn at any time
- This is distinguished from withdrawal of trial medication.

2. Participants can be withdrawn from the trial at the discretion of the Investigator due to safety concerns of if judged to be non-compliant with the trial protocol.
3. Pregnancy or intention of becoming pregnant
4. If target treatment dose of the randomized product is not tolerated by the subject.
5. If the trial investigator suspects acute pancreatitis, the trial drug will be discontinued until the confirmatory tests (clinically indicated laboratory and imaging) have been conducted and appropriate treatment has been administered. We anticipate confirmation within 72 hours. If acute pancreatitis is confirmed, the participant will be withdrawn from the trial. If acute pancreatitis is not confirmed, the participant will resume the trial drug at the same dose previously used before temporary discontinuation.
6. Temporary trial drug discontinuation criteria:
   - Side effects to trial medication (until such side effects have resolved or have been otherwise addressed)
   - Acute illness requiring treatment or hospitalization
   - The longest time that the subject can be off trial drug and still continue in the trial is 4 weeks. If the trial drug is discontinued for >72 hours, then the dosing escalation regimen will be restarted at 0.6 mg daily and titrated up according to prescribing information recommendations.

Subject Replacement

Participants will not be replaced if they withdraw or become ineligible but they will be asked to return at the end of the trial period to complete the follow-up imaging/laboratory testing and analyzed in an intention to treat analysis. As up to a 28% drop-out rate is anticipated, enrolment will account for expected drop-out to minimize loss to follow-up given that subjects will not be replaced.

Rationale for Trial Population

The trial population represents the target population for which liraglutide is approved for chronic weight management in adult patients, with the additional inclusion criterion of a diagnosis of metabolic syndrome. This important criterion has been selected to enrich the trial population with participants with a high visceral adipose tissue burden in order to improve the statistical power to observe a meaningful effect on visceral adipose mass and enrich the trial population with individuals at high risk for cardiovascular disease.

Imaging Assessments

The primary and secondary endpoints of visceral fat, abdominal subcutaneous fat, lower body fat, liver fat, and total body fat and fat-free (lean) mass will be assessed using a Phillips 3T MRI system utilizing a two point Dixon fat-water segmentation technique (Advanced MR Analytics, Sweden).[21] This MRI system has been extensively studied and validated in multiple cohorts,[21-23] has excellent test/retest precision and reliability,[24] and is rapid (<6 minutes) and therefore cost effective.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation:

This trial is powered to detect a clinically meaningful difference in the placebo-corrected relative reduction in VAT. The estimates used in the sample size calculations below are derived from

prior data from the SCALE program. Assuming a mean 8% relative reduction of VAT among placebo treated subjects and an expected 16% relative reduction of VAT among liraglutide treated subjects (with a standard deviation of 16%, based on data from [2]), we expect to require 128 total subjects (in a 1:1 trial drug:placebo randomization scheme) to achieve 80% power to detect an 8% difference between groups at an alpha level of 0.05. Assuming an estimated 28% of subjects may withdraw trial medication during the trial, we expect a planned total of 178 patients will be randomized in order to achieve at least 128 completers of the full trial protocol.

Placebo-corrected Effect Size	**Power**		
	80%	*85%*	*90%*
	Sample Size (Total N, 1:1 randomization)		
5%	322	368	432
8%	128	146	170
10%	82	92	108

Statistical Methods: A formal statistical analysis plan will follow. Briefly, baseline characteristics between liraglutide and placebo treated groups will be compared using appropriate parametric or non-parametric tests depending on the distribution of the data. The primary outcome will be analyzed using an intention to treat analysis. Mean change in outcome measurements will be compared between groups using the appropriate statistical test. Outcomes will also be analyzed by subgroups including age (above/below median), sex, race (non-Hispanic black, non-Hispanic white, and Hispanic), BMI category (overweight, class I obese, class II/III obese), and prediabetes status (yes/no). In order to minimize type II error in subgroup analyses by race, we will attempt to ensure Hispanics comprise at least 25% of the trial population. A pre-specified analysis stratified by those who did vs. did not lose ≥4% body weight at 16 weeks of treatment will be performed prior to unblinding to determine differential outcomes among "responders" vs. "non-responders" as outlined in the package insert. All statistical tests are two-sided at a 5% significance level.

Interim Analysis: No interim analysis will be performed.

Missing Data: The preferred approach to missing data is to incorporate proactive standard operating procedures to mitigate the likelihood of missingness. We will implement measures to reduce missing data (both baseline and endpoint). The statistical analysis plan will describe analytical approaches to address missingness of data, including multiple imputation including the last observation carried forward (LOCF) and mixed-effects model repeated measure approaches. Sensitivity analyses will also be performed to determine the effect of missingness on the primary and secondary outcomes.

DATA HANDLING AND RECORD KEEPING:

Subjects will be assigned an identification code. A subject's name and code will be contained within a small notebook and will be kept in a locked cabinet in the research coordinator's locked office. The research chart will contain personal health information and will be kept in locked file cabinet in the research coordinator's locked office. All other data on a computer will be de-identified with the subject's identification code. Blood samples waiting for analysis will not be labeled with the subject's name, but with the assigned identification code. The trial database will be password protected. No data will be sent over the internet unless it is encrypted. All email with subject-identifiable information will be password protected. Only key personnel will have access to the information in the trial database on an as-needed basis. Key personnel may not

alter the data in the database or directly view all of it without specific cause and approval of the PI.

ETHICS:

Informed Consent

Before screening takes place subjects will be provided with written and verbal information about the trial and the procedures involved. Qualified site will ensure that subjects are fully informed both verbally and in writing about the practical consequences of participating, of their rights and responsibilities while participating in the trial as well as any possible advantages and disadvantages in being treated with the trial products. Subjects will have the opportunity to ask questions to a medically qualified person and have ample time to consider participation. Subjects who wish to participate must give signed and dated informed consent. This must be done prior to any trial related activities, i.e. procedures that would not have been performed during normal management of the subject. It must be stated in the medical record that the subject is participating in the current trial.

Written informed consent will be obtained from each subject at entry into the trial. Informed consent is obtained by the following process:

- Subject reviews the trial consent form.
- PI or trial coordinator meets with the subject to review the consent, confirm subject's understanding, and answer any questions.
- Once the investigator is convinced that the subject verbally demonstrates understanding and agrees to the process, the consent is signed. Individuals authorized to obtain written consent are the principal investigator, co-investigators, and assigned medical staff specifically designated by the principal investigator to work on this project.

The trial protocol will be submitted to the local IRB for approval before any trial activities will be initiated. The trial protocol will be conducted and maintain compliance with appropriate ethical responsibility standards according to the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice guidelines, as well as local institutional review board standards and approval. The investigators will comply with all applicable regulatory and legal requirements, ICH-GCP guidelines, and the Declaration of Helsinki in obtaining and documenting the informed consent.

The trial investigators take full responsibility to ensure quality assurance and proper maintenance of all trial materials by periodic (biweekly) quality control checks of trial drug storage and handling, electronic database materials, and measurement devices.

Confidentiality

- Protection of subject privacy. All materials will be obtained for research purposes only, and data will be kept in strict confidence. Subjects will be assigned an identification code. A subject's name and code will be contained within a small notebook and will be kept in a locked cabinet in the research coordinator's locked office. The research chart will contain personal health information and will be kept in locked file cabinet in the research coordinator's locked office. All other data on a computer will be de-identified with the subject's identification code. Blood samples waiting for analysis will not be labeled with the subject's name, but with the assigned identification code.

- Database protection. The trial database will be password protected. No data will be sent over the internet unless it is encrypted. All email with subject-identifiable information will be password protected. Only key personnel will have access to the information in the trial database on an as-needed basis. Key personnel may not alter the data in the database or directly view all of it without specific cause and approval of the PI.
- Confidentiality during adverse event reporting. Adverse event reports and annual summaries will not include subject-identifiable material. Each will include the identification code only.

Potential Benefits of the Proposed Research to Human Subjects and Others and Importance of Knowledge to be Gained

- There is a potential direct benefit of the proposed research to trial participants.
- Knowledge gained from this project will likely lead to better understanding of obesity and visceral adiposity in the general population and across ethnic minorities and women as well as potentially lead to improved targets of therapies aimed at reducing cardiovascular disease risk.
- The risks outlined in this proposal are reasonable for this societal benefit as it may lead to improved care to reduce cardiovascular disease risk, the leading cause of morbidity and mortality in the U.S.

TRIAL SCHEDULE:

Planned duration of recruitment period: 2.5 years

Planned date for first subject (FPFV): January 2017

Planned completion of the last subject (LPLV): 30 months from FPFV

Planned completion of clinical trial report: 36 months from FPFV

The end of the clinical trial is defined as the last visit of the last subject (LPLV).

Trial Sites:

The trial will be conducted at three sites in Dallas, TX:

1. University Hospital Ambulatory Clinics (at Aston and St. Paul Professional Office Buildings)
2. Clements University Hospital
3. Parkland Hospital and Ambulatory Clinics

Visit Procedures:

Prior to the first trial visit, potential subjects will be identified by physician referral or media advertisement and will be introduced to participation in the trial by one of the trial staff. If the patient meets potential inclusion criteria, written informed consent will be obtained and the subject will be scheduled for Visit 1.

Subjects enrolled in the trial will be provided with a subject ID card, stating that they are participating in a trial and whom to contact (site address, Investigator's name and telephone number) for further information, if necessary. The subjects will be reminded to show the card to other health care providers, as applicable. The subjects will be instructed to return the card to the Investigator at the last visit of the subject or destroy the card after the last visit

The Investigator will keep a subject screening log and a subject enrolment log. For screening failures (subjects who have given informed consent but who do not meet the inclusion, exclusion and/or randomization criteria and hence are not randomized), all data for completed trial procedures will be recorded in the case record form (CRF), and the reason for exclusion from the trial will be recorded on the screening failure form. The screening failure form will be entered into the clinical database.

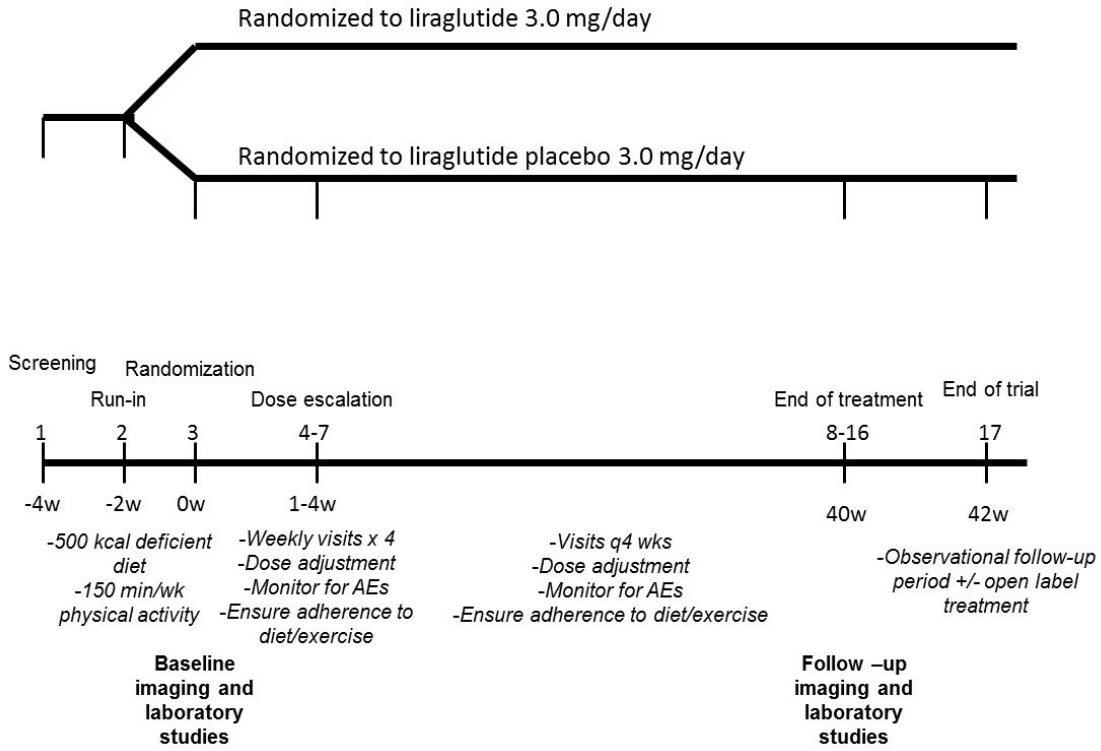


Table: Visit Schedule

Visit no.	Time of Visit	Visit Type
1	-4 weeks ± 5 days	Screening
2	-2 weeks ± 3 days	Run-In
3	Day 0, baseline	Randomization
4	1 week ± 3 days	Dose escalation
5	2 weeks ± 3 days	Dose escalation

6	3 weeks ± 3 days	Dose escalation
7	4 weeks ± 3 days	Dose escalation/maintenance
8	8 weeks ± 3 days	Maintenance
9	12 weeks ± 3 days	Maintenance
10	16 weeks ± 3 days	Maintenance
11	20 weeks ± 3 days	Maintenance
12	24 weeks ± 3 days	Maintenance
13	28 weeks ± 3 days	Maintenance
14	32 weeks ± 3 days	Maintenance
15	36 weeks ± 3 days	Maintenance
16	40 weeks ± 3 days	End of treatment
17	42 weeks ± 3 days	Observational Follow-up/End of trial

The total duration of the trial (for a subject completing the trial) will be up to 46 weeks and will comprise a total of 17 visits.

Table: Treatment of subjects

Trial periods	**Screening**	**Run-In**	**Randomization**	**Dose escalation period/ Maintenance**			**Maintenance / End of treatment**	**Follow-up**
Weeks in relation to Visit 2 (randomization)	-4	-2	0	1	2	3	4-40	42
Visit number	1	2	3	4	5	6	7-16	17
Liraglutide	Screening	Run-In	0.6 mg	1.2 mg	1.8 mg	2.4 mg	3.0 mg	No treatment
Placebo			Placebo	Placebo	Placebo	Placebo	Placebo	

Table: Visit schedule with assessments

	Prior to Screening Visit	**Screening**	**Run-In**	**Randomization**	**Dose Escalation**				**Maintenance Period**								**End of Treatment**	**Observational Follow-up**
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Informed consent	X	X (review)																
In/exclus		X																

ion criteria																		
Randomization criteria				X														
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics																		
Age		X		X														
Sex		X		X														
Race		X		X														
Concomitant illnesses/ Medical history		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Measurements																		
Height		X		X													X	
Weight		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Heart rate		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood glucose		X		X													X	
Triglycerides		X		X													X	
HDL-cholesterol		X		X													X	
Pregnancy test (if female)		X		X													X	
Waist circumference				X													X	
Hip circumference				X													X	
Visceral AT (MRI)				X													X	
Abd subcutaneous AT (MRI)				X													X	
Total fat				X													X	

mass (MRI)																		
Total fat-free mass (MRI)				X													X	
Lower body AT (MRI)				X													X	
Hepatic fat (MRI)				X													X	
Laboratory tests																		
Fasting insulin				X													X	
CRP				X													X	
NT-proBNP				X													X	
Trial Related																		
Diet and physical activity counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability					X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

At Visits 1, 3, and 16 the subject must attend the clinic in a fasting condition in the morning (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). Background medication should be withheld on the day of the fasting Visits 1, 3, and 16 until blood sampling has been done. At all other visits the background medication and trial product should be taken as usual during the conduct of the trial.

Trial product will be dispensed at visits 3 through 15. Subjects will be asked to bring all empty, partly used and unused trial product at visits 4 through 16 for drug accountability. The computerized randomization system should be contacted for trial product dispensing. If the subject attends the clinic for a visit not described in the protocol, then an Unscheduled Visit Form must be completed. The Unscheduled Visit Form should not be completed if the sole purpose of the visit is trial product dispensing. If an unscheduled visit is made for the purpose of dispensing trial products to the subjects then an unscheduled dispensing session must be completed in the computerized randomization system. If it is not possible to attend the visit within the visit window, the subjects should be called in for an Unscheduled Visit.

In case a subject is being prematurely withdrawn from the trial before or at visit 16, the Investigator will ensure that the procedures for the End of Treatment visit (Visit 16) are

undertaken, if possible. The primary reason (adverse event, non-compliance with protocol or other) for discontinuation will be specified in the CRF and a computerized randomization system withdrawal session should be completed. Even if the subject is not able to attend a final visit, the End of Trial Form (EOT) must be completed.

Subjects that have discontinued the trial prematurely before Visit 16 will be asked to attend a visit (Visit 16x) taking place 40 weeks after the randomization date. The purpose of this visit will be recording of all outcome assessments if possible. If the subject is not willing to attend Visit 16x, it should be documented in the patient medical record that the subject has refused to attend the visit.

Visit 1

At Visit 1, the informed consent will be reviewed again for signature and participants will be screened for eligibility in the trial. This will include interview assessment for inclusion and any exclusion criteria and laboratory components of the metabolic syndrome. Subjects that meet all eligibility requirements to participate in the trial will then return for a Run-In visit (Visit 2).

Subjects must give signed and dated informed consent prior to any trial-related activities (including Visit 1). All subjects will be provided with a copy of the subject information and a copy of their own signed and dated Informed Consent Form.

The subjects will be allocated the unique lowest consecutive 6 digit subject number available from the range of subject numbers. The subject number is composed of three digits unique for each trial site and three digits for each enrolled subject at the trial site. The subject number is maintained throughout the trial. The computerized randomization system will be activated to register the subject as screened and the subject will be provided with a trial card indicating that the subject is participating in a trial.

The following will be recorded in the case record form (CRF). Expanded list of comorbidities will be developed prior to FPFV:

- Age
- Sex
- Race/ethnicity
- Height
- Weight
- Waist Circumference
- Blood Pressure
- Medical history
- Concomitant medications
- Informed consent, signed and dated

The following laboratory studies will be performed and recorded in the CRF when resulted:

- Fasting blood glucose
- Fasting triglycerides
- Fasting HDL-cholesterol
- For females of childbearing potential, urine pregnancy test

Visit 2

Visit 2 will be the start of the 2-week Run-In phase during which time eligible participants will be counseled on diet and physical activity to determine adherence to lifestyle recommendations. A dietary diary will be recorded by the participants and returned to the trial coordinator at Visit 3. Pedometers will be given to the participants to encourage adherence to physical activity guidelines and will be returned at Visit 3.

Counseling on Diet and Physical Activity

At Visit 2 subjects will receive dietary counseling by trial staff according to local standard and placed on a hypo-caloric diet containing approximately 30% of energy from fat, approximately 20% of energy from protein, approximately 50% of energy from carbohydrates and an energy deficit of approximately 500 kcal/day compared to the subjects' estimated total energy expenditure (TEE) (See Table below). The hypo-caloric diet will be continued from randomization through the treatment period. Counseling on diet and physical activity will be provided at every trial visit. All subjects will be instructed by trial staff to keep a 3-day diary of food intake between Visits 2 and 3. The 3-day food diaries will be used for counseling at each trial visit. The subject's dietary compliance and the average daily level of physical activity will be recorded at each visit. The subject will be questioned whether they performed less than half an hour, between half an hour and one hour or more than 1 hour of physical activity per day. An increase in physical activity (recommended minimum 150 minutes/week) will be encouraged. Subject compliance with the prescribed diet will be determined at the discretion of trial staff after review of the 3-day food diaries.

Calculation of estimated total energy expenditure

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (see Table) with a Physical Activity Level (PAL) value of 1.3[25]

Total Energy Expenditure (TEE) (kcal/day) = BMR x 1.3

Table _ Equations for estimating basal metabolic rate (BMR) in kcal/day*

Sex	Age	BMR (kcal/day)
Men	18-30 years	15.057 x actual weight in kg + 692.2
	31-60 years	11.472 x actual weight in kg + 873.1
	≥60 years	11.711 x actual weight in kg + 587.7
Women	18-30 years	14.818 x actual weight in kg + 486.6
	31-60 years	8.126 x actual weight in kg + 845.6
	≥60 years	9.082 x actual weight in kg + 658.5

Revised WHO equations[25]

Visit 3

At Visit 3, participants will be randomized to liraglutide or placebo injection in a 1:1 fashion. Randomization will be implemented using a computerized randomization system by an independent party at UT Southwestern. Subjects will have trial products supplied according to randomization and will be instructed in administration of daily injections of liraglutide/ placebo. Injections can be done at any time of day irrespective of meals. However, it is preferable that liraglutide/ placebo be injected during the same overall time period on a day to day basis. The injection site does not have to be kept consistent throughout the trial. The trial products dispensed will cover the dose escalation period. Subjects will follow a fixed dose escalation. The dose will be gradually escalated to 3.0 mg starting with 0.6 mg and with a dose level increment of 0.6 mg every 7 days.

If the subject is not eligible for randomization, the subject is considered a screening failure and the the subject will be registered as a screening failure in the computerized randomization system.

At this visit, they will undergo all baseline anthropometric, imaging, and laboratory assessments.

The following will be recorded in the CRF:

- Age
- Sex
- Race/ethnicity
- Weight
- Height
- Concomitant medications
- Blood Pressure
- Pulse
- Waist Circumference
- Hip Circumference
- Visceral adipose tissue mass
- Abdominal subcutaneous adipose tissue mass
- Total fat mass
- Total fat-free mass
- Lower body adipose tissue mass
- Hepatic fat content
- Laboratory tests, including
    - Markers of insulin resistance: fasting blood glucose, insulin
    - Markers of inflammation: CRP
    - Lipids: TG/HDL-C ratio,
    - Natriuretic peptides: NT-proBNP

Visits 4-7

At Visits 4-7, subjects will follow a dose escalation regimen and trial staff will monitor for AEs and ensure adherence to diet and exercise recommendations. Subjects will follow a fixed dose escalation. The dose will be gradually escalated to 3.0 mg starting with 0.6 mg and with a dose level increment of 0.6 mg every 7 days.

Visits 8-15

Visits 8-15 are the maintenance phase of the trial. Subjects will attend visits with trial staff every 4 weeks to ensure adherence to the trial protocol, monitor for AEs, monitor for non-adherence to trial medication, and monitor adherence to diet and exercise recommendations.

Visit 16

Visit 16 is the final visit during the maintenance phase during which follow-up imaging and laboratory studies will be assessed in addition to assessments done during Visits 8-15. All remaining doses of trial medication will be collected at this visit and returned to Novo Nordisk. No further trial drug will be administered after this visit.

The following will be recorded in the CRF:

- Weight

- Height
- Concomitant medications
- Blood Pressure
- Pulse
- Waist Circumference
- Hip Circumference
- Visceral adipose tissue mass
- Abdominal subcutaneous adipose tissue mass
- Total fat mass
- Total fat-free mass
- Lower body adipose tissue mass
- Hepatic fat content
- Laboratory tests, including
    - Markers of insulin resistance: fasting blood glucose, insulin
    - Markers of inflammation: CRP
    - Lipids: TG/HDL-C ratio,
    - Natriuretic peptides: NT-proBNP

Visit 17

Visit 17 will be an observational follow-up visit during which subjects will be monitored for AEs. At the End of Trial visit (Visit 17) the Investigator or delegate will provide counseling on the management of weight control and follow-up medical care.

Assessments for efficacy

Weight will be recorded to the nearest 0.1 kg using calibrated scales. Weight will be measured in a fasting state with an empty bladder, without shoes and only wearing light clothing. Height without shoes will be recorded at Visit 1. BMI will be calculated as follows: BMI = weight (kg)/height (m^2)

Systolic and diastolic blood pressure will be measured at all visits

- The auscultatory method should be used to measure blood pressure.
- The patient should avoid caffeine, smoking, physical activity for 30 minutes prior to measurement.
- Remove all clothing over the covered arm.
- The same sphygmomanometer should be used throughout the trial.
- The measurement should be taken in the seated position with legs uncrossed, back and arm supported.
- Subject should rest in a sitting position for 5 minutes prior to the first blood pressure being taken.
- The measurement should be in the upper arm with a stethoscope at the elbow crease over the brachial artery.
- The same arm should be used for blood pressure measurements at all trial visits.
- The size of the cuff should be appropriate. The bladder of the cuff should encircle at least 80% of the arm circumference and the width of the cuff is at least 40% of the arm circumference.
- The cuff placement must be preceded with palpation of the brachial artery and the antecubital fossa. The midline of the cuff bladder must be placed over the location of the arterial pulsation. The lower edge of the cuff should be 2 to 3 cm above the antecubital fossa to allow for stethoscope placement.

- The cuff should be inflated to at least 30 mm above the point at which the radial pulse disappears. The pulse should be then reduced at 2 or 3 mm/sec.
- Korotkoff sounds should be used to measure blood pressure using standard techniques. The measurement should be taken with the precision to the nearest 2 mmHg.
- There should be no talking during the measurement.
- Two reliable measurements at intervals of at least 2 minutes should to be performed. In case there is a greater than 5 mmHg difference between the first and second reading of the diastolic blood pressure, one additional reading should be obtained.

The resting heart rate will be recorded at all trial visits using the following methodology:

- The pulse will be recorded after resting for five minutes in a sitting position.
- The pulse will be counted for 30 seconds and recorded as beats per minute. The pulse will be measured using direct palpation.
- Exercise, alcohol, nicotine, and coffee should be avoided 30 minutes preceding measurement.
- Heart rate will be measured while the patient is seated in a comfortable position with legs uncrossed.

The laboratory analyses for efficacy and safety will be outsourced to a Central Laboratory unless otherwise specified. Descriptions of assay methods, instrumentation and procedures for obtaining samples, handling and storage of samples will be described in a trial specific laboratory manual provided by the Central Laboratory.

Samples will be coded with the intention that the subject's identity will remain encrypted but information such as age, sex, race, health information and response to liraglutide will be correlated. The samples will only be used in relation to the present trial. Novo Nordisk and its representatives and/or regulatory authorities, may have access to this information. However, the subject's identity will not be revealed.

Laboratory analysis results will be sent to the Investigator after visits during which laboratory studies are obtained. All laboratory reports must be dated and signed by the Investigator on the day of evaluation. If a result is outside the normal range, the Investigator will judge whether the abnormality is clinically significant or not. The signed laboratory report is retained at the Investigator site as source documentation. Any abnormal, clinically significant result identified at screening visit 1 will be recorded as a concomitant illness.

Ascertainment of clinical safety endpoints

At each visit trial staff will review criteria for withdrawal and AEs/SAEs with the subject. There will not be external independent event adjudications for the adverse cardiovascular endpoints of death, MI or stroke. The Investigator will identify adverse cardiovascular events. These adverse events of interest include death, all cause and cardiovascular deaths, nonfatal myocardial infarction and nonfatal stroke. These will be defined prospectively and identified by the Investigator. These events will not undergo external independent event adjudication. These endpoints will be investigator identified using *a priori* criteria.

Ascertainment of diet/physical activity

At each visit the trial staff will review diet and physical activity compliance with the subject. Subjects not meeting trial standards will be encouraged to adjust their behavior to adhere to trial

requirements. Subjects not meeting requirements after 2 attempts at correction may be subject to withdrawal from the trial at the discretion of the Investigator.

Subject Compliance:

At each visit the trial staff will review trial medication compliance with the subject. At the prescribed visits, the subject will return used or partly used trial products including all empty packaging materials. The investigator will assess the amount of return trial product and compare it to what was dispensed to estimate the subject's compliance with trial medication. If noncompliance is identified, the investigator will counsel the patient on the importance of trial medication compliance. Consistent failure to be compliant with trial medication or other trial protocols could ultimately lead to subject withdrawal from the trial.

End of trial treatment strategy

Following the end of the treatment, all trial drug treatment will be discontinued and the trial drug collected. Subjects will be advised with regards to the best possible post-trial treatment options for their weight management and metabolic syndrome. These treatments will be at the discretion of the local Investigator. Unblinding will occur at LPLV and after ascertainment of primary and secondary endpoints.

Premature discontinuation

If the trial subject opts for early trial termination, he/she will be asked to attend a premature trial discontinuation visit at the time of discontinuation. The purpose of this visit will be to assess body weight, occurrence of AEs and discuss end of trial imaging studies. The PI will offer end of trial imaging to assess for the primary and secondary efficacy endpoints if the subject has completed at least 40 weeks of trial treatment. Every effort will be made to assess for AE and SAEs during the trial for all patients including those prematurely withdrawing from the trial.

TRIAL DRUGS AND MATERIALS:

Treatment with liraglutide or placebo will be blinded to the subjects and investigators throughout the trial.

Trial medication(s) / devices(s)

The administration of liraglutide/ placebo will be as outlined above.

The following trial products will be supplied by Novo Nordisk, Denmark.

- Liraglutide 6.0 mg/mL, 3 mL pen-injector for subcutaneous injection
- Placebo 3 mL pen-injector for subcutaneous injection

Liraglutide will be available at a concentration of 6.0 mg/mL. Liraglutide and placebo will be supplied in a 3 mL pen-injector . Correct dosing is achieved by using the dose counter and the dose pointer to see how many mg to select. The subject will hear a “click” every time they turn the dose selector. The dose will not be set by counting the number of clicks the subject hears. Dosing with the liraglutide/ placebo pen-injector is controlled by turning the dose selector until the dose indicator shows the relevant dose (0.6, 1.2, 1.8, 2.4 or 3.0 mg, respectively or placebo). Therefore, the dose level (injection volume) of liraglutide or placebo is open labeled.

Liraglutide or placebo is administered once daily by subcutaneous injections with the pen-injector, either in the abdomen, thigh or upper arm. Injections can be done at any time of day irrespective of meals. However, it is preferable that liraglutide be injected during the same

overall time period on a day to day basis. Subjects will be instructed to perform an air shot before the first injection with the pen-injector. For further information, please see the direction for use (DFU) for the liraglutide pen-injector. These DFUs will be provided together with the trial product. The Investigator or trial staff will instruct subjects in how to inject liraglutide or placebo, and will ensure that the subjects are familiar with the DFU. It will be documented in the subject's research record that the subject has been instructed in the use of the pen-injector.

Subjects will follow a fixed dose escalation and in order to reduce the level of side effects, liraglutide is gradually escalated up to the maintenance dose. Subjects will be instructed to escalate the liraglutide (active or placebo) dose to 3.0 mg/day over a 4 week period following an initial dose of 0.6 mg/day and weekly dose escalation steps of 0.6 mg/day.
If subjects do not tolerate an increase in dose during dose-escalation, the Investigator will have the option to delay the next dose escalation for approximately one week. All subjects must be at the target dose 3.0 mg or placebo at the latest 8 weeks after randomization.

Dose escalation schedule:

Week	Dose (mg)
0	0.6
1	1.2
2	1.8
3	2.4
4 and beyond	3.0

After reaching the target dose, 3.0 mg liraglutide or placebo dose and dosing frequency should not be changed at any time during the treatment period. If any dose is missed by the subject up to and including 3 consecutive days it will be documented in the research record and the Investigator will discuss the importance of treatment compliance with the subject. After a potential discontinuation up to 3 days the subject must be re-initiated on trial drug on target dose 3.0 mg liraglutide or placebo. Missed doses for more than 3 consecutive days will be discussed with the PI and it will be up to Investigator's judgment if the subject can continue on target dose or should be withdrawn.

It is always important that the Investigator emphasizes to subjects the necessity of compliance with regard to taking trial drug as described in the protocol. It is the responsibility of the Investigator to access the subject's overall compliance throughout the trial and subjects deemed to be non-compliant subjects may be withdrawn at the Investigator's discretion. If subjects do not tolerate the target dose, they will be withdrawn from the trial. If the Investigator suspects acute pancreatitis, all suspected drugs will be discontinued until confirmatory tests have been conducted. If tests reveal that a subject does not have acute pancreatitis, the subject can remain in the trial with re-initiation of titration until the target dose is reached.

Packaging and Labelling of Trial Medication(s)

All trial products will be packed and labeled by Novo Nordisk and provided in non-subject specific boxes. Labeling will be in accordance with local law and trial requirements.

Storage and Drug Accountability of Trial Medication(s)

The Investigator must keep track of all received, used, partly used and unused trial products by the use of the drug accountability module in the computerized randomization system.

Store in a refrigerator (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze liraglutide/ placebo and do not use liraglutide/ placebo if it has been frozen. Liraglutide/ placebo should not be used if it does not appear clear and colorless. After first use of the liraglutide/ placebo pen, the product can be stored for 30 days at room temperature (+15°C to +30°C)/(59°F to 86°F) or in a refrigerator (+2°C to +8°C)/(+36°F to +46°F). Keep the pen cap on when liraglutide/ placebo pen is not in use in order to protect from light. Liraglutide/ placebo should be protected from excessive heat and sunlight. Always remove the injection needle after each injection and store the liraglutide/ placebo pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate. No trial product which has exceeded the expiry date must be used.

The Investigator will ensure the availability of proper storage conditions and record and evaluate the temperature. The temperature will be recorded and evaluated on a daily basis (working days) using as a minimum a calibrated min/max thermometer. A log to document the temperature must be kept. Storage facilities will be checked frequently (at least once every working day).

No trial product(s) should be dispensed to any person not enrolled in the trial and the computerized randomization system should always be updated when dispensing trial product(s). Returned trial product(s) (partly used or unused including empty packaging material) must be stored separately from non-allocated trial product(s) until the monitor has performed drug accountability. The monitor will be responsible for retrieval of trial products from the site. Destruction of trial products will be done according to local laws and will be recorded on a Destruction Form, which will be signed by the person responsible for destruction, as agreed with the monitor.

Randomization and Blinding

Trial participants and investigators will be blinded to treatment allocation throughout the trial.

Randomization Scheme:

Participants will be randomly assigned using a computerized randomization code generated by UT Southwestern.

Breaking of Blinded Codes

Blinding codes will be broken at the end of the trial. Blinding codes will only be broken before the end of trial if a subject develops a serious adverse event requiring knowledge of the treatment allocation. At such time, the subject will be considered to have completed the trial and will not undergo any further trial treatment but may be asked to undergo assessment of trial endpoints when feasible. Whenever a code is broken, the person breaking the code must print the Code Break Confirmation generated by the computerized randomization system, record the reason, and sign and date the document. If the subject should be withdrawn following a code break, a withdrawal session should be completed in the computerized randomization system.

CONCOMITANT ILLNESSES AND MEDICATIONS

All concomitant illnesses and medications will be recorded in the CRF and assessed as AEs or not AEs. If a subject is prescribed a medication meeting criteria for withdrawal/exclusion, the subject will have the opportunity to decide whether to take such medication and withdraw from the trial or not take it and continue the trial.

SUBJECT SAFETY AND DATA MONITORING

ADVERSE EVENTS:

Definitions

Adverse Event (AE):

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):

A serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience (an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe)
- In-patient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Suspicion of transmission of infectious agents must always be considered an SAE

Note: The term life-threatening in the definition of serious refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it was more severe.

Serious Adverse Drug Reaction (SADR):

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the trial drug and the occurrence of the event is suspected. The ADR should be classified as serious if it meets one or more of the seriousness criteria.

Suspected Unexpected Serious Adverse Reaction (SUSAR):

An SAE which is unexpected and regarded as possibly or probably related to the trial product by the investigator.

Non-Serious Adverse Event:
A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:
• Mild: Transient symptoms, no interference with the subject's daily activities
• Moderate: Marked symptoms, moderate interference with the subject's daily activities
• Severe: Considerable interference with the subject's daily activities, unacceptable

Relationship to trial medication Assessment Definitions:
• Probable: Good reasons and sufficient documentation to assume a causal relationship
• Possible: A causal relationship is conceivable and cannot be dismissed
• Unlikely: The event is most likely related to an etiology other than the trial product
• Suggested to specify the reference document (eg: USPI, CCDS) in the protocol which is agreed upon with NN, for evaluation of expectedness

Outcome Categories and Definitions:
• Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
• Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
• Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be rated as an SAE
• Not recovered
• Fatal – this term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed according to the state of the event at the time of death. An AE with fatal outcome must be reported as an SAE.
• Unknown

Collection, Recording and Reporting of Adverse Events
All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.

Plan for reporting both anticipated and unanticipated adverse events:
Each subject will be evaluated for any adverse events. Any event that is reported to either the principal investigator or his designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented as such. Any event that is reported will then generate an adverse event report, which will be submitted to the safety officer, local IRB, Novo Nordisk, and FDA. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. All adverse events will be graded as mild, moderate, or severe. All unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and will be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information. Any severe and/or unanticipated adverse event will be reported to the safety officer, local IRB, Novo Nordisk, and FDA within 24 hours of knowledge of the event. At a minimum, the investigator will copy NN when expediting SARs or SUSARs to health authorities and will

report all SARs related to NN product to the local NN affiliate safety department. All other adverse events will be reported in a timely fashion to the safety officer, local IRB, Novo Nordisk, and FDA preferably within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the local IRB, Novo Nordisk, and FDA. Any action resulting in a temporary or permanent suspension of this trial (e.g. FDA actions, IRB actions, or actions by the investigators or co-investigators) will be reported to the appropriate Novo Nordisk program official.

Follow-up of Adverse Events

Periodic reviews of adverse events and safety issues will be performed during the trial as listed below:

Safety reviews. The principal investigators (SM, IN) will review the safety and progress of this trial on a weekly basis.

Annual review. The principal investigators (SM, IN) will review this protocol on a continuing basis for subject safety and include results of the review in the annual progress reports submitted to the safety officer, local IRB, and Novo Nordisk.

Pregnancy

Pregnant and breast-feeding females cannot participate in the trial because they may expose the unborn child to risks. If participants can become pregnant, a pregnancy test will be done from a urine sample, and it must be negative before they can be a part of this trial. If they do become pregnant during this trial, they must inform the researchers immediately and their participation in the trial will be discontinued. Novo Nordisk will receive a report of any pregnancy in the trial subject that occurs during the use of a NN product. The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age. The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

At a minimum the following details will be reported - Trial name - Patient identification (e.g. subject number, initials, sex, age) - Event (Preferably diagnosis) - Drug - Reporter - Causality – Outcome. These details will be reported to Novo Nordisk Inc. safety department.

Precautions/Over-dosage

Certain precautions will be taken by the PI and trial staff based on prior data and experience. These include:

1. Injection Site Reaction
   Approximately 1-10/100 subjects developed pain, bruising, irritation, itching and/or rash at the injection site in the previous LEAD and SCALE clinical trials. A similar incidence of these injection site reactions will be expected in this clinical trial. Safety text regarding these reactions and the possibility of anaphylactic shock will be included in the informed consent and as part of site and investigator training.

2. Calcitonin Monitoring
   Calcitonin levels will not be routinely monitored during the trial.

Possible Side-Effects

As with any drug, allergic reactions to the drug in this study are possible. Liraglutide may cause some, all or none of the side-effects listed below that have been reported in patients previously.

- More frequent (>10%): nausea, diarrhea, constipation, and vomiting;
- Less common (1-10%): dyspepsia, abdominal pain, abdominal distension, eructation, flatulence; and
- Rarely (<1%): gallbladder disease, acute pancreatitis

All adverse effects are reversible with discontinuation of the medication.

Data and Safety Monitoring Committee (DSMC):

1. Parag Joshi MD
2. Steven P. Marso MD
3. James de Lemos MD
4. Darren McGuire MD MHSc

The DSMC will meet biannually by telephone/teleconference and distribute a report to the IRB at the completion of each meeting.

LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in the trial, the primary investigators (IN and SM) and UT Southwestern Medical Center will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

Novo Nordisk carries product liability insurance for its products. Sponsor-investigator agrees to indemnify Novo Nordisk in accordance with the written contract executed between the parties for this study. Generally, however, Novo Nordisk assumes no liability in the event of negligence of the sponsor-investigator conducting the trial, or by persons for whom the sponsor-investigator is responsible.

EVALUABILITY OF SUBJECTS:

The following analysis sets are defined:

Full analysis set (FAS)

All randomized subjects exposed to at least one dose of the trial product and with at least one post-baseline assessment of any efficacy endpoint will be included. Subjects in the FAS will be analyzed according to intention to treat (primary) and per-protocol (secondary). The requirement of a post-baseline observation is in alignment with the FDA recommendations.

Safety analysis set

All randomized subjects who have been exposed to at least one dose of trial product. Subjects in the safety analysis set will be analyzed "as treated".

PREMATURE TERMINATION OF TRIAL:

The trial will be prematurely terminated for the following reasons only:

1. A serious threat to the safety of trial participants occurs that cannot be addressed in any other manner than trial termination.
2. Funding is withdrawn from the trial.
3. The local IRB withdraws approval for the trial.

PUBLICATION PLAN:

It is expected that this trial will generate 1 or more scientific abstracts that will be presented at scientific meetings and 1 or more manuscripts that will be published in peer review journals. For each publication there will be a first and senior author and a responsible writing group. This subgroup will be responsible for driving the publication process forward. The manuscript will be forwarded to Novo Nordisk for review prior to publication. Novo Nordisk will be allowed 10 working days to review the manuscript and provide feedback. The investigators retain the right to publish results independent of findings and will not need Novo Nordisk permission prior to publication and or presentation of data.

KEY PERSONNEL:

Sponsor: UT Southwestern Medical Center, Dallas, TX
Clinical sites: UT Southwestern Medical Center (Ambulatory and Inpatient sites) and Parkland Hospital (Ambulatory and Inpatient sites)

Primary Investigator:
Parag Joshi MD

Data and Safety Monitoring Committee (DSMC):

5. Parag Joshi MD
6. Steven P. Marso MD
7. James de Lemos MD
8. Darren McGuire MD MHSc

Trial coordinator: Bienka Milton MPH, BS

Statistician: Colby Ayers, MS

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