Protocol Title: Clinical Efficacy and Safety of Using 3.0mg Liraglutide to Treat Weight Regain After Roux-en-Y Gastric Bypass Surgery

INVESTIGATOR-INITIATED STUDY PROTOCOL

Universal Trial Number: U1111-1178-7319

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Study Product: Liraglutide (rDNA origin) injection, Saxenda®

Protocol Number: NYULWMP-01, 16-01527

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Version 7: 10/11/2019

Table of Contents

List of Abbreviations/Formula

Term/Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
BMP	Basic Metabolic Panel
BMR	Basal Metabolic Rate
BP	Blood pressure
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IC	Informed Consent
ICH	International Conference on Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intention-To-Treat
LAGB	Laparoscopic Adjustable Gastric Banding
MEN	Multiple Endocrine Neoplasia
MTC	Medullary Thyroid Carcinoma
NYULMC	New York University Langone Medical Center
OSA	Obstructive Sleep Apnea
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PP	Per-Protocol
RD	Registered Dietician
RYGB	Roux-en-Y Gastric Bypass
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBWL	Total body weight loss
UAE	Unexpected Adverse Event
WL	Weight loss (Baseline weight – Follow-up visit weight)

151 **Study Summary**

<table>
<tr><td>Title</td><td>Clinical Efficacy and Safety of Using 3.0mg Liraglutide to Treat Weight Regain After -Roux-en-Y Gastric Bypass Surgery</td></tr>
<tr><td>Short Title</td><td>Liraglutide after RYGB Weight Regain</td></tr>
<tr><td>Protocol Number</td><td>NYULWMP-01</td></tr>
<tr><td>Phase</td><td>Phase 4</td></tr>
<tr><td>Methodology</td><td>Randomized, double-blind, placebo controlled study</td></tr>
<tr><td>Study Duration</td><td>Mar. 2017 to Dec. 2020</td></tr>
<tr><td>Study Center(s)</td><td>Single-center</td></tr>
<tr><td>Objectives</td><td>The primary objective of this study is to assess the utility of 3.0mg liraglutide to reverse weight regain versus placebo in patients at least 18 months following RYGB who at the time of enrollment have regained of ≥10% of maximum TBWL (total body weight loss) after surgery.</td></tr>
<tr><td>Number of Subjects</td><td>132</td></tr>
<tr><td>Diagnosis and Main Inclusion Criteria</td><td>• ≥18 years who are deemed medically stable
• ≥18 months status-post RYGB
• BMI 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition
• BMI 30 kg/m^2 or greater
• Regain of ≥10% of maximum TBWL post-RYGB
• Ability to provide informed consent before any trial-related activities
• Express willingness to follow protocol requirements</td></tr>
<tr><td>Study Product, Dose, Route, Regimen</td><td>• Saxenda® (Liraglutide (rDNA origin)) injection, pre-dose pen
• Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers dose of 0.6mg,1.2mg, 1.8mg, 2.4mg or 3.0mg (6mg/mL, 3 mL)
• The recommended dosage of Saxenda® is 3.0mg daily.
• The dose escalation below will be used.
<table>
<tr><th>Week</th><th>Daily Dose</th></tr>
<tr><td>1</td><td>0.6 mg</td></tr>
<tr><td>2</td><td>1.2 mg</td></tr>
<tr><td>3</td><td>1.8 mg</td></tr>
<tr><td>4</td><td>2.4 mg</td></tr>
<tr><td>5 and onward</td><td>3.0 mg</td></tr>
</table></td></tr>
<tr><td>Duration of administration</td><td>12 months</td></tr>
<tr><td>Reference therapy</td><td>A placebo</td></tr>
<tr><td>Statistical Methodology</td><td>Data will be analyzed on an intention-to-treat basis. Our primary outcome (proportion of subjects losing at least 5% enrollment body weight) will be assessed using Cochran-Mantel-Haenszel test after accounting for stratification variables. The treatment groups will be further compared by secondary outcomes, using t-tests or Wilcoxon rank sum tests, (as appropriate) for continuous variables.</td></tr>
</table>

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1 Introduction

1.1 Background and Significance

Nearly 90 million Americans are obese. To combat obesity and its myriad comorbidities, annually almost 200,000 Americans undergo bariatric surgery, the most effective treatment for obesity. Of contemporary procedures, Roux-en-Y Gastric Bypass (RYGB) achieves the greatest weight loss - between one and two years following RYGB, patients tend to have lost over 30% total body weight. However, the majority of patients regain weight following a two-year nadir [1]. As time from surgery increases, so does the amount of weight regained. Some have reported that more than a third of patients no longer manifest loss of more than 50% pre-surgical excess body weight by ten years after surgery [2]. Weight regain after RYGB is associated with the return of obesity-related comorbidies initially resolved following surgery [3]. Many patients opt for revisional bariatric surgery to address weight regain, but these procedures are often the source of significant morbidity [4, 5]. There are currently few non-surgical therapies with which to address inadequate weight loss and weight regain after bariatric surgery, and these are of limited efficacy.

The use of GLP-1 agonists holds great promise for this population, which likely numbers in the hundreds of thousands in the United States alone. GLP-1 agonist use has been associated with weight loss in diabetic populations, with a meta-analysis finding an average loss of 3% total body weight with GLP-1 receptor agonists versus placebo [6]. Further, several recent randomized trials have demonstrated the efficacy of a specific GLP-1 receptor agonist, liraglutide 3.0mg daily, for the purpose of weight loss. In a study of overweight and obese subjects who first completed a low calorie diet, Wadden and colleagues reported 6.2% weight loss at 56 weeks versus 0.2% with placebo [7]. Another recent trial in over 3,500 overweight and obese patients randomized to liraglutide or placebo, in addition to lifestyle interventions, demonstrated 8.0% weight loss in the liraglutide arm versus 2.6% in the placebo group [8]. Neither of the above randomized trials included overweight or obese patients who had previously undergone bariatric surgery. Although the use of a GLP-1 receptor agonist as an adjuvant to bariatric surgery for weight loss has shown promise in animal models, this therapy has yet to be tested in humans [9].

The use of GLP-1 receptor agonists to augment weight loss and combat weight regain could provide a sorely needed adjunctive therapy to prevent remission following bariatric surgery. With nearly 200,000 bariatric surgical procedures performed annually in the United States, a sizable population of patients experiencing post-surgical weight regain stands to potentially benefit from therapy with liraglutide. The safety and efficacy of the medication in this population must first be assessed, however. The purpose of the present study is to investigate the safety and efficacy of 3.0mg liraglutide to achieve weight loss in patients at least 18 months status-post RYGB who are experiencing weight regain at the time of enrollment.

1.2 Investigational Agent

1.2.1 Name: Saxenda® (liraglutide (rDNA origin)) or matching placebo

Saxenda® is a clear, colorless solution. Each 1 mL of Saxenda® solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of Saxenda® equivalent to 18 mg liraglutide (free-base, anhydrous).

Matching placebo will have the same ingredients without the active ingredient (6 mg of liraglutide).

1.2.2 **Class**: Glucagon-like peptide-1 (GLP-1) receptor agonist

1.2.3 Indications

Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30kg/m^2 (obese), or ≥27kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition (eg, HTN, type 2 diabetes mellitus [DM], dyslipidemia)

1.2.4 Adult dosage

Usual: 3.0mg daily; dose escalation should be used to reduce the likelihood of GI symptoms

Dose Escalation:
Week 1: 0.6mg/day
Week 2: 1.2mg/day
Week 3: 1.8mg/day
Week 4: 2.4mg/day
Week 5 and Onward: 3.0mg/day
May delay dose escalation for 1 additional week if unable to tolerate increased dose

Missed Dose

If a dose is missed, resume once-daily regimen with next scheduled dose; do not take an extra dose or increase dose to make up for missed dose

If >3 days have elapsed since last dose, reinitiate at 0.6mg/day and retitrate following dose escalation schedule

1.2.5 Administration

Subcutaneous route
Administer daily at any time of day, without regard to timing of meals
May inject in the abdomen, thigh, or upper arm; injection site/timing can be changed without dose adjustment

1.2.6 Pharmacokinetics

Absorption

- Bioavailability: subcutaneous: 55%
- Tmax, subcutaneous: 8 to 12 hours; 11 hours (Saxenda®)

Distribution

- Vd, subcutaneous: 13 L; 20 to 25 L (patients weighing 100 kg)
- Vd, IV: 0.07 L/kg
- Protein binding: Greater than 98%

Metabolism

- Metabolism: not significant

Excretion

- Fecal: 0% unchanged; 5% changed
- Renal excretion: 0% unchanged; 6% changed
- Total body clearance: 1.2 L/hr; 0.9 to 1.4 L/hr

Elimination Half Life

- 13 hours

1.2.7 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist that acts to increase insulin release in the presence of elevated glucose concentrations, decrease glucagon secretion in a glucose-dependent manner, and delay gastric emptying, thereby reducing the rate at which postprandial glucose appears in circulation. GLP-1 regulates appetite and calorie intake, including via receptors that are present in the brain. The weight reduction effect of liraglutide is due to decreased calorie intake

1.2.8 Contraindications

- Hypersensitivity to liraglutide or any product component
- Personal or family history of medullary thyroid carcinoma
- Personal or family history of multiple endocrine neoplasia syndrome type 2
- Pregnancy

1.2.9 Limitations of Use

- Saxenda® is not indicated for the treatment of type 2 diabetes mellitus
- Saxenda® and Victoza® both contain the same active ingredient, liraglutide, and therefore should not be used together. Saxenda® should not be used in combination with any other GLP-1 receptor agonist.
- Saxenda® has not been studied in patients taking insulin. Saxenda® and insulin should not be used together.
- The effects of Saxenda® on cardiovascular morbidity and mortality have not established.
- The safety and effectiveness of Saxenda® in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.
- Saxenda® has not been studied in patients with a history of pancreatitis.

1.2.10 Precautions

- **Black Box Warning**
  - **Risk of Thyroid C-cell Tumors**
    - 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 Saxenda® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance has not been determined.
    - Saxenda® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the risk of MTC with use of Saxenda® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using

thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Saxenda®.

- Warnings and Precautions
  - Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected since it may be life-threatening. Do not restart if pancreatitis is confirmed.
  - Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated.
  - Serious hypoglycemia: Can occur when Saxenda® is used with an insulin secretagogue (eg, sulfonylureas). Consider lowering the dose of anti-diabetic drugs to reduce the risk of hypoglycemia.
  - Heart rate increase: Monitor heart rate at regular intervals. Discontinue Saxenda® if patients experience a sustained increase in resting heart rate.
  - Renal impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may require hemodialysis. Use caution when initiating or escalating doses of Saxenda® in patients with renal impairment.
  - Hypersensitivity reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue Saxenda® and other suspect medications and promptly seek medical advice.
  - Angioedema has been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Saxenda®.
  - Suicidal behavior and Ideation: monitor for depression or suicidal thoughts. Discontinue Saxenda® if symptoms develop.

- Adverse Reaction
  - Most common adverse reactions, reported in greater than or equal to 5% are: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsis, fatigue, dizziness, abdominal pain, and increased lipase.

Pregnancy & Lactation

U.S. Food and Drug Administration's Pregnancy Category: Category X (All Trimesters)

Crosses Placenta: Unknown

Clinical Management
The brand name Saxenda®, which is indicated as an adjunct to diet and exercise for chronic weight management in overweight or obese patients, has a pregnancy category of X. Saxenda® is contraindicated in all pregnant women, including those who are already overweight or obese, because weight loss may result in fetal harm. If a woman becomes or wishes to become pregnant while on Saxenda®, discontinue treatment.

Literature Reports
There are no adequate and well-controlled studies of liraglutide in pregnant women. In animal studies, teratogenicity occurred when female rats were given SC doses of 0.1, 0.25, and 1 mg/kg/day (0.8, 3, and 11 times the human exposure at the maximum recommended human dose (MRHD) based on plasma AUC) starting 2 weeks before mating through gestation day 17. Fetal abnormalities, kidney and blood vessel variations,

irregular skull ossification, and ossification were observed at all doses. In pregnant rats given the same doses from gestation day 6 through weaning or termination of nursing on lactation day 24, the majority had a slight delay in parturition. Group mean body weight of neonatal rats from the liraglutide-treated group was lower compared with controls. Male offspring had bloody scabs and agitated behavior following maternal exposure to 1 mg/kg/day. In pregnant rabbits, teratogenicity was seen following SC doses of 0.01, 0.025, and 0.05 mg/kg/day (less than the exposure at the MRHD at all doses) from gestation day 6 through day 18. Reduced fetal weight and dose-dependent major fetal abnormalities were reported at all doses. Malformations at the various doses included kidney and scapula (0.01 mg/kg), the eyes and forelimbs (0.01 mg/kg or greater), the brain, sacral vertebrae, major blood vessels, heart, and umbilicus (0.025 mg/kg), the sternum (0.025 mg/kg and greater), and parietal bones and major blood vessels (0.05 mg/kg). Ossification, skeletal abnormalities, and dose-dependent minor skeletal variations were observed. Visceral abnormalities and bilobed or bifurcated gallbladder were seen in all dose groups.

Breastfeeding
Micromedex Lactation Rating: Infant risk cannot be ruled out.

Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Clinical Management
It is not known whether liraglutide is excreted in human breast milk. In animal studies, liraglutide was excreted unchanged in the milk of lactating rats at concentrations approximately 50% of maternal plasma concentrations. Because data are limited and because of the tumorigenicity potential evident in animal studies, either discontinue nursing or discontinue liraglutide considering the importance of the drug to the mother.

1.2.11 Storage & Stability

Preparation for administration

- Inject liraglutide SC in the abdomen, thigh, or upper arm. Liraglutide may be administered any time of the day, independent of meals. Do not share pens with other patients.
- To reduce the risk of IM injections and for better tolerance, use 4, 5, or 6 mm needles in all patients regardless of BMI or age. Injections should be given at a 90 degree angle to the skin surface. When injecting into limbs or a slim abdomen, use a lifted skin fold (4 and 5 mm needles) or 45 degree angle (6 mm needle).

Storage

- Store unopened prefilled pens refrigerated, between 2 and 8 degrees C (36 and 46 degrees F).
- Store opened pens up to 30 days at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F), or refrigerated, between 2 and 8 degrees C (36 and 46 degrees F).
- Protect from excessive heat and sunlight.
- Avoid storing directly adjacent to cooling compartment in refrigerator.
- Do not freeze or use a pen that has been frozen.

1.3 Preclinical Data

GLP-1 agonists such as liraglutide have been noted to induce satiety and weight loss in multiple animal models. When given to both normal and obese rats, a significant reduction in food and water intake was noted in both groups, leading to significant weight loss of up to 15% of initial body weight [10]. A similar study in obese mini-pigs also noted substantial weight loss due to its suppressive effect on food intake [11]. Candy-fed rats were also found to have normalized weight and fat levels after administration of liraglutide, reversing the effects of their diets [12].

1.4 Clinical Data to Date

(Please see ***Background and Significance*** for additional relevant clinical data)

Initial clinical data regarding the use of liraglutide in the treatment of obesity is from the NN8022-1807 study conducted by Astrup et al [13]. This was a double-blinded, placebo-controlled trial comparing liraglutide to Orlistat. Liraglutide was administered at 4 different doses – 1.2 mg, 1.8 mg, 2.4 mg, and 3 mg daily. Patients taking liraglutide lost significantly more weight than both the placebo and Orlistat groups. Based on the success of this trial, participation in the study was extended to two years. Subjects receiving the 2.4 mg/3.0 mg liraglutide doses for two years lost on average 7.8 kg [14]. 67% of patients completed two year follow-up. The most common reasons for discontinuing the study were poor results (placebo arm) and nausea/vomiting (liraglutide arms).

Further studies were then conducted in obese, non-diabetic subjects. Van Can et al. showed increased satiety, fullness, and decreased gastric emptying using both liraglutide 1.8 mg and 3.0 mg dosing compared to placebo [15]. This suggested that liraglutide-induced weight loss was secondary to reduced appetite and intake rather than increased energy expenditure. Pi-Sunyer et al. conducted a recent trial in which over 3,500 overweight and obese patients were randomized to liraglutide or placebo, in addition to lifestyle interventions. These authors demonstrated 8.0% total body weight loss in the liraglutide arm, versus 2.6% in the placebo group [8].

None of the above randomized trials included overweight or obese patients who had previously undergone bariatric surgery. Although the use of a GLP-1 receptor agonist as an adjuvant to bariatric surgery for weight loss has shown promise in animal models, this therapy has yet to be rigorously tested in humans [9].

1.5 Dose Rationale

The dosage chosen for this study is 3 mg daily, injected subcutaneously. Dosages are steadily escalated over a 5 week period, from 0.6 mg/day to 3.0 mg/day. Route of administration is subcutaneous injection, as this is the only current formulation of the drug. The dosage chosen is based on prior studies in obese patients. Astrup et al. demonstrated that the 3.0 mg daily dose showed the greatest percentage of weight loss in patients, compared to doses of 1.2, 1.8, and 2.4 mg, without increased adverse events [13]. Subsequent studies have also used the 3.0 mg dosing and shown comparable weight loss effects [7, 8]. The 3.0 mg dosing is currently approved by the FDA for the indication of weight loss in overweight and obese individuals. The dosage regimen and period in this study are also based on these prior studies. Liraglutide is a once-daily dosed medicine, with a half-life of 11-12 hours [16].

1.6 Research Risks & Benefits

1.6.1 Risk of Study Drug

- Nausea (39.3%)

- Diarrhea (20.9%)
- Hypoglycemia in Type 2 DM (23.0%)
- Constipation (19.4%)
- Vomiting (15.7%)
- Headache (13.6%)
- Decreased appetite (10.0%)
- Dyspepsia (9.6%)
- Fatigue (7.5%)
- Dizziness (6.9%)
- Abdominal pain (5.4%)
- Increased lipase (5.3%)
- Upper abdominal pain (5.1%)
- Gastroesophageal reflux disease (4.7%)
- Gastroenteritis (4.7%)
- Abdominal distension (4.5%)
- Eructation (4.5%)
- Urinary tract infection (4.3%)
- Flatulence (4.0%)
- Viral gastroenteritis (2.8%)
- Injection site erythema (2.5%)
- Injection site reaction (2.5%)
- Insomnia (2.4%)
- Dry mouth (2.3%)
- Asthenia (2.1%)
- Anxiety (1.6%)
- Cholelithiasis (1.5%)
- Hypotension (1.1%)
- Urticaria (0.7%)
- Breast cancer (0.6%)
- Cholecystitis (0.6%)
- Colorectal neoplasms (0.5%)
- Pancreatitis (0.3%)
- Cardiac conduction disorder (0.3%)
- Suicidal thoughts (0.2%)
- Papillary thyroid carcinoma (0.2%)
- Angioedema and anaphylactic reaction (reported, but percentage unknown)
- C-cell hyperplasia of thyroid (potential risk)
- Medullary thyroid carcinoma (potential risk)

Measures to minimize the risks

- Dose escalation is used to reduce the likelihood of GI symptoms
- All contraindications included in exclusion criteria
- Lipase and Amylase included in study blood work
- Monitor heart rate during study visits
- Monitor depression during study visits
- Monitor fasting glucose at each study visit for hypoglycemia and lower the dose of anti-diabetic drugs for patients taking an insulin secretagogue (eg, sulfonylureas) if fasting glucose is ≤70 m/dL. If hypoglycemia continues, the insulin secretagogue

will be discontinued after consulting with the subject's primary physician/endocrinologist.

- Patients taking an insulin secretagogue (eg, sulfonylureas) will be informed of the increased risk of hypoglycemia associated with co-administration of the study drug and instructed to notify the investigators of any symptoms of hypoglycemia.
- If the subject is a female of childbearing potential (sexually active and not sterile nor postmenopausal for at least 1 year), have a negative pregnancy test within 4 weeks prior to study commencement, and then at 3, 6, and 9 months.
- Use of reliable contraception will be assessed during the study period.
- DSMB reviews all AEs including SAEs and provides the appropriate recommendations

1.6.2 Potential benefits

It is hypothesized that this study drug will help the subject lose weight and decrease the incidence or severity of weight related co-morbidities. In addition, the medical community and society stand to benefit from a better understanding of the efficacy and safety of the study drug post-RYGB.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to assess the utility of liraglutide to reverse weight regain versus placebo in patients at least 18 months following RYGB who are experiencing weight regain.

2.2 Secondary Objective

The secondary objectives of this study are to assess the efficacy of liraglutide in improving cardiometabolic risk profile (as indicated by serum lipids, HbA1c, and waist circumference) and quality of life (as assessed by PHQ-9 (Patient Health Questionnaire), versus placebo in patients at least 18 months following RYGB who are experiencing weight regain. as well as the safety of liraglutide in this patient population.

3 Study Design

3.1 Research Design and Methods

The specific aims of this proposal are:

- To evaluate the effects of liraglutide on body weight loss in patients who are experiencing weight regain following RYGB.
    - We will perform a randomized, double-blinded, placebo-controlled trial of liraglutide versus placebo over a follow-up period of 12 months.
        - *We hypothesize that the liraglutide group will contain a significantly greater proportion of patients achieving at least 5% loss of pre-randomization body weight at 12 months, than the placebo group.*
- To evaluate the effects of liraglutide on cardiometabolic risk and quality of life in patients who are experiencing weight regain following RYGB.
    - We will perform a randomized, double-blinded, placebo-controlled trial of liraglutide versus placebo over a follow-up period of 12 months.
        - *We hypothesize that the liraglutide group will demonstrate greater improvement in cardiovascular risk profile (as assessed by serum lipids, HbA1c, and waist*

circumference) and quality of life (as assessed by the PHQ-9) at 12 months, than the placebo group.

- To evaluate the safety of liraglutide in post-RYGB subjects.
  - We will monitor adverse events, blood counts and serum chemistries in subjects receiving liraglutide or placebo over a period of 12 months.
    - *We hypothesize that the liraglutide group will exhibit more frequent hypoglycemia and elevations in lipase and amylase, but that these episodes will be clinically insignificant.*
- To evaluate the changes in obesity-related comorbid conditions in patients who are experiencing weight regain following RYGB.
  - We will monitor obesity-related comorbid conditions in subjects receiving liraglutide or placebo over a period of 12 months.
    - *We hypothesize that the liraglutide group will exhibit improvements in obesity-related comorbid conditions (*hyperglycemia, hyperlipidemia, blood pressure, and obstructive sleep apnea) *at 12 months, than the placebo group.*

3.2 Endpoints

- Primary Endpoint: Proportion of subjects losing at least 5% of enrollment body weight at 12 months.
- Secondary Endpoints: Fasting serum glucose, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides, waist circumference, blood pressure, STOP-BANG score, PHQ-9
- Primary and secondary endpoints will be assessed at clinic visits prior to randomization and at 3, 6, 9 and 12 months post-first study drug administration**.**

3.3 Study Type

Randomized, single-center, double-blind, placebo-controlled study with two arms. Randomization will be 2:1 (drug:placebo) with stratification by gender and percent post-operative TBWL (25%, 25 – 49.9%).

3.4 Rationale for study Design

A randomized, placebo-controlled study design was chosen as this is the methodology that will best assess the efficacy of liraglutide for weight loss in the post-RYGB population. 2:1 randomization was chosen with the intention of increasing potential participant interest given better than even odds of randomization to liraglutide.

A single-center study was chosen given that the NYU Langone weight management program has a pool of 700 post-RYGB patients in our retrospective database, and that recent data from our program suggests that 80 % of patients at least 18 months status-post RYGB exhibit regain of ≥10% of maximum post-surgical TBWL – our program has a potential subject pool of 560. We estimate that at least 50% of 560 will be eligible for and agree to participate in the study, which will allow us to be able to enroll adequate subjects from our program alone. In addition, approximately five post-RYGB patients are referred to our program monthly for evaluation of weight regain. In the case that subject recruitment falls short of goals, we would expand recruitment using advertisements.

3.5 Primary Study Endpoints

Proportion of subjects losing at least 5% of enrollment body weight at 12 months.

3.6 Secondary Study Endpoints

Fasting serum glucose, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides, waist circumference, blood pressure, STOP-BANG score, PHQ-9, Obesity-related co-morbidities assessment

Primary and secondary endpoints will be assessed prior to randomization and at clinic visits at 3, 6, 9 and 12 months post-first treatment administration.

3.7 Primary Safety Endpoints

The primary safety endpoint is the percentage of patients who are experiencing AEs during 12 months of the trial.

3.7.1 Assessments for Safety

- BMP (Fasting glucose)
- Amylase
- Lipase
- Pregnancy Test (Only applicable for women of childbearing potential)
- Heart Rate
- PHQ-9
- Current medication list review
- Adverse event assessment including symptomatic hypoglycaemia for Type 2 DM patients

4 Subject Selection and Withdrawal

4.1 Number of the subjects: 132

Subjects will not be replaced if they withdraw or become ineligible.

4.2 Rationale for study population

The Roux-en-Y gastric bypass (RYGB) is not only the most common bariatric procedure, but also the gold standard to which all others are compared. The average weight loss after RYGB is approximately 35% total body weight.. However, the majority of patients who undergo this procedure experience weight regain and thus are at risk of, or re-acquire co-morbid conditions, such as Type 2 diabetes mellitus or hypertension. Revisional surgery, which is the most common treatment for weight regain after bariatric surgery, is often thwarted by resistance from insurance companies, leaving patients with only diet and behavioral change as an option. Due to the fact the GLP-1 agonism plays a significant role in weight loss after RYGB, liraglutide is thought to be a promising adjunct to the long-term treatment plan in patients who experience weight regain after RYGB.

4.3 Inclusion Criteria

- >18 years who are deemed medically stable
- ≥18 months status-post RYGB at time of enrollment
- BMI of ≥30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one weight-related comorbid condition
- Regain of ≥10% of maximum TBWL post-RYGB
- Ability to provide informed consent before any trial-related activities
- Express willingness to provide signed informed consent and follow protocol requirements

4.4 Exclusion Criteria

- BMI of >45 kg/m^2

- Pregnancy at time of enrollment
- Intention of becoming pregnant or breast feeding in the next 12 months
- Females of childbearing potential who are not using adequate contraceptive methods
- Presence of acute psychiatric problems or immaturity which would compromise cooperation with the study protocol
- Presence of biliary disease
- Known or suspected allergy to liraglutide or any product components
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- History of pancreatitis
- History of alcoholism
- History of Type 1 DM (Diabetes Mellitus)
- History of previous bariatric surgery other than RYGB except h/o LAGB and band removal.
- >10 years status-post RYGB
- < 25% TBWL at post-RYGB weight nadir
- >50% post-operative TBWL at time of screening
- Simultaneous use of any weight loss medications
- Use of insulin at the time of enrollment
- Current use of any GLP-1 agonist medication
- History of taking any GLP-1 agonist medication
- Participation in another ongoing clinical study
- Conditions that, in the opinion of the principal investigator, may jeopardize the patient's well-being and/or the soundness of this clinical study

4.5 Subject Recruitment and Screening

4.5.1 Recruitment and Screening

Subject recruitment and screening will be conducted by members of the research team.

- Potentially eligible patients will be identified from the investigators' confidential clinical registry and referring physicians including self-referring patients
- If necessary, potential eligible patients will be recruited via online platform (i.e. Obesity Help, Bariatric Pal, Facebook), newspaper advertisements, study fliers, or study brochures
- In addition to these methods, subjects may be recruited through MyChart (if indicated they are willing to be contacted regarding research), DataCore, i2b2 or iConnect.
- DataCore may be used as a recruitment method to request reports from Epic, NYU's electronic medical record system. The following data points will be requested: medical record number (MRN), DOB (to assess current age), diagnosis, gender, and living status (alive). Patients will be contacted either by phone or e-mail by members of the research team using an IRB approved script. SendSafe Secure email will be used when sending these recruitment e-mails. Once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. If the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation. If a subject is ineligible or chooses not to participate their information will be deleted from the list immediately. PHI, including name, MRN, and DOB of patients who schedule an appointment will be kept on secure NYU servers. This information will be deleted if patients do not sign an informed consent form during their first visit. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858. The amount of times EPIC will be searched over the

course of the study will be dependent on the success of the results. We prefer to contact patients who are open for recruitment (based on their choice listed in Epic) directly.

- Due to the time-sensitive inclusion criteria for this study (surgery between 18 months and 10 years), eligible participants may not have a treating physician on record in Epic as they may not have continued their care at NYUMC during this time. If they do have a primary care physician listed, the study team will notify the provider through their NYUMC email address using an IRB approved script stating that they are planning to contact this patient as indicated through a DataCore search and provide the PI and study team contact information if there are any concerns. If there is no primary care physician listed, this will be noted in the patient's research record; however they still may be contacted for research purposes.
- The following roles will have access to the EPIC search results: Principle Investigator, Research Coordinator and Study Team Member.
- The research staff will contact the potential patients via email or telephone if the contact information was sent to us via recruiting websites or the patients will contact the research staff directly using the contact information on the online websites.
- Study eligibility will be determined by assessing evidence that the patient meets all inclusion and exclusion criteria
- Patients will be offered the opportunity to participate in this study via telephone, email, mail or/and in-person conversation in a private room to protect patient's privacy. More privacy will be provided if required or demanded
- A verbal explanation of the study will be given followed by a written consent form
- For any patient who might be illiterate, consent forms will be read to him or her and witnessed by an impartial third party Patients will be provided with ample time and opportunity to ask about the details of the study, and decide whether or not they want to participate, and patient informed consent will be obtained, prior to any study specific procedures
- No screening tests/procedures will be performed before a subject signs the consent form

4.5.2 Informed Consent

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. The subject must also give Authorization for Use and Release of Health and Research Study Information and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

The Investigator or his/her authorized designee conducts the informed consent (IC) discussion and will document in the subject's medical records the acquisition of IC and the subject's agreement. The IC shall include all aspects of the study that are relevant to the subject's decision to participate throughout the study. The IC process should avoid any coercion or undue influence on, or inducement of, the subject to participate. The subject should personally sign and date the IC form. The Investigator will retain the original copy of the signed form, and the subject will receive a copy. Upon signing the IC form, the subject is considered to be enrolled in the study and receives a subject number that will be used on all documentation for the subject throughout the study. The Investigator will ensure that important new information is provided to new or existing subjects throughout the study.

4.6 Early Withdrawal of Subjects

4.6.1 When and How to Withdraw Subjects

- If a subject is not able to tolerate the study drug, the subject will be removed from the study.
- If a subject decides to withdraw from the study, the subject will be removed from the study.

- If the PI believes that it is in a subject's best interest to discontinue participation, the subject will be removed from all remaining study requirements.
- A subject may be withdrawn from the study at the discretion of the PI due to a safety concern or if judged non-compliant with trial procedures.

If a subject fails to return for one scheduled study visits, the Investigator will attempt to contact the subject to determine and document the reason the subject has failed to return and to encourage compliance with the study visit schedule. Before a subject can be considered lost to follow-up, a minimum of 2 phone calls at different times of the day and a certified letter are required. All of these contact attempts will be documented in the source documents.

In case of withdrawal from the study, the appropriate follow-up care will be provided for those cases, including hospital and clinic follow-up when necessary.

4.6.2 Data Collection and Follow-up for Withdrawn Subjects

Follow-up data will be collected at 12 months on the subjects who withdraw from the study after obtaining the subject's permission to record this information.

Lost-to-follow-up

- A minimum of 2 phone calls and 1 certified letter contact attempts will be made before a patient is considered as a lost-to-follow-up.

5 Study Drug

5.1 Description

Saxenda® or matching placebo

- Subcutaneous Solution: 6 mg/ml
- Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg (6mg/mL, 3mL)

5.2 Treatment Regimen

Dose:

- Recommended dose of Saxenda® or matching placebo is 3.0 mg daily
- Administer at any time of the day, without regard to the timing of meals

Dose escalation should be used to reduce the likelihood of GI symptoms

- **Week 1:** 0.6mg/day
  Week 2: 1.2mg/day
  Week 3: 1.8mg/day
  Week 4: 2.4mg/day
  Week 5 and Onward: 3.0mg/day
- May delay dose escalation for 1 additional week if unable to tolerate increased dose
- Discontinue if patient is unable to tolerate the study drug for any reason

Route:

- Inject subcutaneously in the abdomen, thigh or upper arm.
- The injection site and timing can be changed without dose adjustment.

5.3 Subject Compliance Monitoring

- The study drug will be dispensed to each subject at study visits (baseline, 3, 6, 9 months) and will be recorded by the investigational pharmacy and study team.
- The subjects are required to return used pens when receiving new drug and the number of used pens returned will be recorded by the investigational pharmacy.
- Subjects are required to bring a daily study drug administration log to 3, 6, 9, and 12 months study visits.
- Subjects who are not compliant with administrating the study drug ≥ 30 days will be withdrawn from the study.

5.4 Concomitant Therapy

- Avoid use with insulin
- Avoid use with other glucagon-like peptide-1 receptor agonists
- Advise to take daily post RYGB supplements which include multivitamin with copper, calcium, vitamin D, iron, and vitamin B12.

5.5 Receiving, Storage, Dispensing and Return

5.5.1 Receipt of Drug Supplies

- Upon receipt of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment.
- The designated study staff will counts and verifies that the shipment contains all the items noted in the shipment inventory.
- Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.
- The investigator will notify Novo Nordisk of any damaged or unusable study drug that was supplied to the investigator's site.

5.5.2 Storage

- All study drugs will be stored at the NYULMC investigational pharmacy and distributed by the NYULMC investigational pharmacist.
- Store unopened prefilled pens refrigerated, between 2 and 8 degrees C (36 and 46 degrees F).
- Store opened pens up to 30 days at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F), or refrigerated, between 2 and 8 degrees C (36 and 46 degrees F) and protect from excessive heat and sunlight.
- Avoid storing directly adjacent to cooling compartment in refrigerator.
- Do not freeze or use a pen that has been frozen.

5.6 Method for Assigning Subjects to Treatment Groups and Dispensing of Study Drug

5.6.1 Randomization Process

Eligible subjects will be randomized to one of the two treatment groups in a 2:1 ratio to receive either study drug (Liraglutide (rDNA origin) injection, 3 x Saxenda® pen, NDC 0169-2800-13) or matching placebo, with stratification by gender and percent post-operative TBWL (<25%, 25 – 49.9%). Stratified block randomization will be employed. Randomization lists will be sent to the pharmacist who will then be able to distribute the study drug/placebo as patients are enrolled, and the remainder of the study staff will be blinded.

5.6.2 Dispensing of Study Drug

The study drug will be dispensed to each subject at study visits (baseline, 3, 6, 9 months) upon returning the used pens and the compliance with study drug administration will be recorded by the investigational pharmacy and study team.

Study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.6.3 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

Visit Number	**1**			**2**			**3**			**4**			**5**
	Baseline	**1M**	**2M**	**3 months**	**4M**	**5M**	**6 months**	**7M**	**8M**	**9 months**	**10M**	**11M**	**12 months**
Visit window	0-4 wks prior to the treatment			± 4 wks			± 4 wks			± 4 wks			± 4 wks
Informed consent	X												
Screening	X												
Demographics	X												
Medical History	X												
Weight, BP, HR, Waist & Neck Circumference	X			X			X			X			X
Height	X												
Medications	X			X			X			X			X
Blood Pregnancy Test (Beta Quantitative HCG) (Only applicable for women of childbearing potential)	X			X			X			X			X
[1]BMP, HbA1c, [1]Lipid profile, Amylase, Lipase	X			X			X			X			X
Additional plasma and	X						X						X

serum for future analyses													
PHQ-9, IPAQ, 24 hr diet recall	X			X			X			X			X
Diet and Physical Activity Counseling by RD	X			X			X			X			X
Body Composition	X			X			X			X			X
Comorbidities: Diabetes, Hypertension, STOP-BANG	X			X			X			X			X
[2]AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Compliance Phone call		X	X		X	X		X	X		X	X	

1. Fasting is required
2. Ask about hypoglycemia symptoms for patients with Type 2 DM

6.1 Visit 1 (Baseline/Pre-Treatment)

6.1.1 Screening and Enrollment

Patients meeting all inclusion and no exclusion criteria will be offered the opportunity to participate in this study. Patient informed consent will be obtained prior to any study specific procedures and patients will be provided with ample time and opportunity to ask about the details of the study, and decide whether or not to participate.

6.1.2 Medical History

A full medical history will be taken during the baseline visit. Medical history includes previous bariatric and non-bariatric surgeries, and recent & lifetime health history.

6.1.3 Demographics

At baseline, the following demographic data will be collected and recorded: gender, date of birth, and race/ethnicity.

6.1.4 Physical Examination / Clinical Assessment

During the baseline and all in-office follow-up visits, a physical examination will be performed and the following data will be collected and recorded:

- Blood pressure
- Heart rate
- Height (only at baseline)
- Weight
- Waist and neck circumference
- Medications

6.1.5 Diet and Physical Activity Counseling

- Initial nutritional assessment by RD (Registered Dietician)
- 24 hr diet recall (see attachment)
- Body composition (Basic metabolic rate, % total body fat, % body water weight, muscle mass weight)

6.1.6 Comorbidities Assessment

Comorbidity status will be assessed at baseline. The following co-morbid conditions will be assessed: diabetes, hypertension, and STOP-BANG score.

Diabetes Scale

Score	Description
0	Fasting blood glucose (<100 mg/dL)
1	Fasting blood glucose ≥100-125 mg/dL or diabetes, no medications
2	Fasting blood glucose ≥126 mg/dL or diabetes treated with medication (oral and/or injectable)

Number of medications: _____

Hypertension Scale

	Description
0	Normal BP, no indication of hypertension (BP below 120/80 mmHg), no medication
1	Prehypertension (systolic BP 120-139 or diastolic BP 80-89 mmHg), no medication
2	Stage 1 hypertension (systolic BP 140-159 or diastolic BP 90-99 mmHg) or hypertension controlled with single medication
3	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥ 100 mmHg) or hypertension controlled with multiple medications
4	Hypertension poorly controlled despite multiple medications

STOP-BANG score: _____

1. Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
2. Do you often feel tired, fatigued, or sleepy during daytime?	Yes	No
3. Has anyone observed you stop breathing during your sleep?	Yes	No
4. Do you have or are you being treated for high blood pressure?	Yes	No
5. BMI >30kg/m2	Yes	No
6. Age >50	Yes	No
7. Neck circumference >16 inches	Yes	No
8. Male	Yes	No

6.1.7 Blood work (total 25 ml blood collection)

- Blood Pregnancy (Total Beta Quantitative HCG) (Only applicable for women of childbearing potential)
- Fasting BMP
- HbA1c
- Lipid profile
- Amylase
- Lipase

- Additional 15 ml blood for future analyses - Banking of additional plasma and serum for future markers of caridometabolic risk in post-RYGB patients.
    - Collecting additional blood for future analysis is mandatory because it is imperative that the stored sample be used for continued analyses as new scientific discoveries are available and for retesting during the course of the study if necessary.
    - Samples will be stored in the Bell Vascular Biology Research Program (NYU Smilow 7th floor) and accessed only by the study team members. The unique code number that is used to label the samples will not be based on any subject's identifiers. The master list linking names to code numbers will be kept into the password-protected REDCap data management system.
    - Results from these analyses will be preliminary, and the clinical implications of any findings may not be understood for years. Therefore, individual study results will not be shared with the subjects.
    - No genetic testing will be done on the stored samples.
    - Some of the stored de-identified samples may be sent to other places to study the related diseases and conditions.
    - All samples will be destroyed no more than twenty years from the end of the study. However, if the subject requests to destroy the stored samples, the study team will destroy the samples upon receiving your written request.

6.1.8 Questionnaires

- PHQ-9 (see attachment)
- IPAQ (see attachment)

6.2 Visit 2, 3, 4 (Post-treatment)

6.2.1 Physical Examination / Clinical Assessment

During the baseline and all in-office follow-up visits, a physical examination will be performed and the following data will be collected and recorded:

- Blood pressure
- Heart Rate
- Weight
- Waist and neck circumference
- Medications

6.2.2 Diet and Physical Activity Counseling

- Follow up diet and physical activity counseling by RD
- Collection of diet and exercise diaries (see attachment)
- Body composition (Basic metabolic rate, % total body fat, % body water weight, muscle mass weight)

6.2.3 Comorbidities Assessment

The following co-morbid conditions will be assessed: diabetes, hypertension, and STOP-BANG score at the 3, 6, 9 and 12 month visits.

6.2.4 Blood work

Total 10 ml blood collection for visit 2 and 4
Total 25 ml blood collection for visit 3 and 5

- Blood Pregnancy (Total Beta Quantitative HCG) (Only applicable for women of childbearing potential)

- BMP
- HbA1c
- Lipid profile
- Amylase
- Lipase
- Additional 15 ml blood for future analyses - Banking of additional plasma and serum for future markers of caridometabolic risk in post-RYGB patients (6 and 12 months only).

6.2.5 Questionnaires

- PHQ-9
- IPAQ

6.2.6 Adverse Events Assessment

Through-out the study the occurrence of drug-related AEs and pregnancies will be monitored, recorded, and reported to IRB and Novo Nordisk.

6.2.7 Monthly Contact

Study staff will call or email each subject at 1, 2, 4, 5, 7, 8, 10, and 11 months to review medication compliance and adverse events.

7 Statistical Plan

7.1 Sample Size Determination

We intend to recruit 132 subjects. A recent study of liraglutide versus placebo in subjects weighing 106.2 +/- 21.1 kg (BMI 38.2 ± 6.4) at baseline demonstrated that nearly 2/3 of subjects treated with liraglutide for 56 weeks lost at least 5% of enrollment body weight, vs. approximately 1/4 with placebo. We expect to see similar results in our subjects. In order to detect an absolute difference of 36.1% in the proportion of subjects losing at least 5% of enrollment body weight in the liraglutide (expected proportion 63.2%) and placebo arms (expected proportion 27.1%), with an alpha of 0.05 and beta of 0.1, we will require a sample size of 99 (2x liraglutide:1x placebo). In order to account for an estimated loss-to-follow-up of 25%, we increase the sample size to 132.

7.2 Statistical Methods

Data will be analysed on an intention-to-treat basis. Missing values will be assessed for patterns and imputed using a multiple imputation method for measurements made after baseline. Patient demographics will be summarized by treatment group. Categorical variables will be presented as proportions, normally distributed continuous variables will be presented as mean ± standard deviation, and skewed continuous variables will be presented as median [interquartile range]. Our primary outcome (proportion of subjects losing at least 5% enrollment body weight) will be assessed using Cochran-Mantel-Haenszel test after accounting for stratification variables. The treatment groups will be further compared by secondary outcomes, using t-tests or Wilcoxon rank sum tests, (as appropriate) for continuous variables. Prior to analysis, non-normally distributed continuous data will be categorized using quartiles or using an appropriate transformation method (e.g. log-transformed).

Paired sample t-tests assessing change at 6 months and 12 months will be used to test, separately for each treatment group, whether each of the post-intervention measurements differs from the baseline measurement. Change in continuous secondary outcome variables will be compared between treatment groups using independent samples t-tests. An ANCOVA model including stratification variables (gender, percent post-operative weight loss) will be used to assess changes in these secondary outcomes. These

results will provide information to inform further studies, but will remain descriptive given our limited power.

7.3 Subject Population(s) for Analysis

Primary and secondary analyses will be performed in the all-treated population.

7.4 Interim Analysis

Given the limited duration of the study, we do not plan interim analyses of efficacy parameters.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.1.2 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2.1 Expected Adverse Events related to study drug

- Nausea (39.3%)
- Diarrhea (20.9%)
- Hypoglycemia in Type 2 DM (23.0%)
- Constipation (19.4%)
- Vomiting (15.7%)
- Headache (13.6%)
- Decreased appetite (10.0%)
- Dyspepsia (9.6%)
- Fatigue (7.5%)
- Dizziness (6.9%)
- Abdominal pain (5.4%)
- Increased lipase (5.3%)
- Upper abdominal pain (5.1%)
- Gastroesophageal reflux disease (4.7%)
- Gastroenteritis (4.7%)

- Abdominal distension (4.5%)
- Eructation (4.5%)
- Urinary tract infection (4.3%)
- Flatulence (4.0%)
- Viral gastroenteritis (2.8%)
- Injection site erythema (2.5%)
- Injection site reaction (2.5%)
- Insomnia (2.4%)
- Dry mouth (2.3%)
- Asthenia (2.1%)
- Anxiety (1.6%)
- Cholelithiasis (1.5%)
- Hypotension (1.1%)
- Urticaria (0.7%)
- Breast cancer (0.6%)
- Cholecystitis (0.6%)
- Colorectal neoplasms (0.5%)
- Pancreatitis (0.3%)
- Cardiac conduction disorder (0.3%)
- Suicidal thoughts (0.2%)
- Papillary thyroid carcinoma (0.2%)
- Angioedema and anaphylactic reaction (reported, but percentage unknown)
- C-cell hyperplasia of thyroid (potential risk)
- Medullary thyroid carcinoma (potential risk)

8.1.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- suspicion of transmission of infectious agents
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

8.1.4 Serious Adverse Drug Reaction (SADR)

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study 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.

8.1.4.1 Reported serious adverse events/reactions related to study drug

- Potential Risk of Thyroid C-Cell Tumors
- Acute Pancreatitis
- Acute Gallbladder Disease
- Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy
- Heart Rate Increase
- Renal Impairment
- Hypersensitivity Reactions
- Suicidal Behavior and Ideation

8.1.5 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

8.1.6 Relationship to Study Drug 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

8.1.7 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, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

8.2 Collection, Recording and Reporting of Adverse Events

8.2.1 Collection and Recording of Adverse Events

All events meeting the definition of an adverse event must 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.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.2.1.1 Preexisting Condition

A preexisting condition is one that is present at the screening of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.2.1.2 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.2.1.3 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.2.1.4 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for any adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2.1.5 Pregnancy

If a female becomes pregnant during the study, the Investigator should stop the study drug. The Investigator shall instruct the subject to notify her physician of the study drug. Best practices should be followed in order to ensure the welfare of the subject and the fetus. The subject will continue to be followed as part of the ITT population, but the pregnancy will be documented as a protocol deviation. The subject will not be evaluated as part of the PP population for timepoints after the pregnancy is confirmed.

Pregnancy by itself will not be considered an AE or serious adverse event (SAE). Hospitalization for a normal delivery does not constitute an SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these should be reported as AE. Reporting of all pregnancies to Novo Nordisk should occur within 5 working days from the time the investigator becomes aware of the event.

8.2.2 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities including Novo Nordisk, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected,
- serious or involve risks to subjects or others, and
- serious adverse events

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.2.2.1 Investigator reporting: notifying the IRB

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

Unanticipated problems including adverse events that are unexpected and related

- Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
- Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.
- Harmful: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:

The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again

- the deviation was necessary to protect a subject from immediate harm

- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.2.2.2 AE Reporting to Novo Nordisk

The investigator will report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the investigator becoming aware of such adverse events, whichever comes first.

The investigator will collect the following information at minimum for each of these events:

- Study name
- Patient identification (e.g. initials, sex, age)
- Event (preferably a diagnosis)
- Drug
- Reporter identification (e.g. Name, or initials)
- Causality
- Outcome

8.2.3 Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. State that this medical care for study subjects will be provided regardless of their insurance status.

All adverse events classified as serious or severe or possibly/probably related to the trial product must be followed until the subject has recovered and all queries have been resolved. For cases of chronic conditions follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered".

All other adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

8.3 Liability

The sponsor-investigator will be responsible for the conduct of the study and agrees to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of sponsor-investigator's obligations or representations; or (b) sponsor-investigator's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities

8.4 Unblinding Procedures

The randomization information will be revealed to the investigator only in a medical emergency, i.e. when this appears necessary to ensure the subject's safety and would be instrumental in further treatment decisions.

If a subject's treatment is unblinded, details of the time and reason for revealing must be documented in the subject's medical records and in the CRF and should be reported to DSMB in 48 hours.

8.5 Stopping Rules

- The trial will be terminated if two or more patients die within the 30 days of study drug administration.
- The trial will be terminated if during the follow-up period five or more of the first 50 patients developed gastrointestinal or endocrine disorder leading to inpatient admission.
- The trial will be terminated if the DSMB determine that the study should be terminated.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan.

8.6.1 Data Monitoring Committee

Data Safety and Monitoring Board (DSMB)

8.6.1.1 DSMB Responsibilities

- Review the research protocol, informed consent documents, and plans for data safety;
- Review the following blinded data;
  - baseline data
  - safety data (mortality and morbidity)
  - efficacy data
  - study withdrawal due to non-compliance and AEs
  - major protocol violation
- Review external data to the study when relevant information that may have an impact on subject safety becomes available;
- Review and evaluate ad hoc safety issues concerning the study at the request by study team; and

- Make recommendations to the investigators concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the study.

All DSMB members will disclose their conflicts of interests before the study initiation and any updates during the study period.

8.6.1.2 DSMB membership

The data safety monitoring board will be composed of several physicians at least one independent physician whose expertise is in the treatment of obesity, clinical trials, and statistical knowledge. One DSMB member will serve as chair. The DSMB chair must have served as a member and chair of this study and be willing to make firm commitment to participate as chair for the duration of the study.

Members

Medical monitor (Chair): an independent endocrinologist or gastroenterologist whose expertise is in the treatment of obesity, clinical trials, and statistical knowledge
Jose O Aleman, M.D.
Department of Medicine, NYUSOM, 212-501-0585, jose.aleman@nyumc.org

Physicians: an independent endocrinologist or gastroenterologist
Elizabeth Weinshel, M.D.
Department of Medicine, NYUSOM, 212-686-7500, elizabeth.weinshel@nyumc.org

Holly Lofton, M.D.
Department of Surgery, Medical Weight Loss Physician, NYUSOM, 212-263-0883, holly.lofton@nyumc.org

Christine Ren-Fielding, M.D.
Department of Surgery, Bariatric Surgeon, 212-263-2174, christine.ren-fielding@nyumc.org

Sean Heffron, M.D., M.S., M.Sc.
Department of Medicine, Leon H. Charney Division of Cardiology, 212-263-0855, sean.heffron@nyumc.org

8.6.1.3 Projected Schedule of Meetings

Initial Meeting: An initial meeting of the DSMB will be held prior to any subject enrollment in order to review the protocol, establish a distribution and meeting schedules, the study modification, termination guidelines, and reports formats. This meeting will be done via e-mail or telephone conference.

Regular DSMB Meetings: Subsequent DSMB meetings will be held to review and discuss study data according to the schedule as described in the table below. This meeting will be done via telephone conference or in-person meeting after distributing the data/reports via e-mail.

Timeline	Data Review by	Type of Data
When the first 25 patients were enrolled.	Entire DSMB	baseline data safety data (mortality and morbidity) efficacy data study withdrawal due to non-compliance and AEs accrual and withdrawal rates major protocol violation

		external data to the study if available
When the first 50 patients were completed.	Entire DSMB	baseline data safety data (mortality and morbidity) efficacy data study withdrawal due to non-compliance and AEs accrual and withdrawal rates major protocol violation external data to the study if available
When the first 100 patients were completed.	Entire DSMB	safety data (mortality and morbidity) efficacy data study withdrawal due to non-compliance and AEs accrual and withdrawal rates major protocol violation study conduct issues external data to the study if available
Upon completion (132 patients) or termination of study	Entire DSMB	safety data (mortality and morbidity) efficacy data study withdrawal due to non-compliance and AEs accrual and withdrawal rates major protocol violation study conduct issues external data to the study if available

Ad Hoc meetings: An ad hoc meeting will be called at any time by the investigator and DSMB member if immanent study subject safety issues arise. If a significant safety concern arises during the study, the DSMB chair or PI may convene a meeting to review safety and any other aspects of the study.

Significant safety events may include, but are not limited to the followings:

- A death or life-threatening condition sustained by a study subject, regardless of causality
- An unexpected serious safety issue newly identified that could expose participants to unnecessary risks.

The above case may require suspension or termination of study if DSMB review confirms that the risks are too high to continue the study enrollment

Proposed study amendments that significantly alter the treatment plan and /or deal with subject safety concerns will prompt an ad hoc meeting for review prior to implementation of changes. This may require suspension of enrollment pending DSMB review.

8.6.1.4 Meeting Format

DSMB meetings will generally be conducted by face to face or teleconference and facilitated by the DSMB chair. The investigator and study coordinator will attend the meeting with DSMB members to provide additional information requested or answer the questions raised during the review of the data.

All Adverse Events Report including expected and unexpected will be recorded and reported to DSMB using Excel and SPSS program. The AE reports will not contain any information that can potentially disclose any subject's treatment group. AE reports will include the followings.

- Name of event
- Onset and end date
- UAE
- Severity (mild, moderate, severe)
- Seriousness
- Relationship to the study drug/procedure
- Action taken
- Outcomes

All reports will be submitted by the study coordinator.

Meeting Minutes: Minutes of DSMB meetings will be distributed to members, all investigators, and study personnel within 4 weeks and also to IRB annually if available.
Minutes include at a minimum:

- Protocol number and study title
- DSMB meeting date
- Copy of agenda
- A list of attendances, including DSMB members and any other people present, listing their professional title and role at the meeting
- Information reviewed and related discussion during the meeting
- DSMB recommendations including clear and concise rationale

Communications
The DSMB chair communicates directly with the investigators to allow them the opportunity to ask questions and discuss any recommendations. If the investigator(s) accepts the recommendations of the DSMB, the investigator(s) will be responsible for implementing the actions in response. In the event the study must be amended, the investigator will prepare and submit the amendment to the DSMB for approval prior to implementing amendment changes.

8.6.1.5 Reportable Adverse Events

All SAEs will be reported to all DSMB member and all investigators via e-mail within one or two working day of learning of the event. A summary of all adverse events, (previously reported or not, serious or not) will be submitted to the DSMB as described in this plan.

All unexpected serious adverse events will be reported to IRB, DSMB, and Novo Nordisk regardless the relationship to the study drug.

8.6.1.6 DSMB Considerations and Policies

Stopping Rules: After reviewing/considering the information, the DSMB will determine whether the study should continue as planned, proceed with modifications, or be terminated. The justification to terminate the study may be due to the DSMB's analysis that there is overwhelming safety issue.

9 Data Handling and Record Keeping

9.1 Confidentiality

To safeguard against the loss of confidentiality, all study information will be stored using REDCap (Research Electronic Date Capture) database, which is a commonly used, secure, web-based system that is compliant with HIPAA standards. Access to the database will be restricted to the members of the research staff for this project. The unique study ID will be used to link the subject's identifiers. No

names or other identifying information will be used in publications which stem from this research. Only research staff will have the linking key. Subjects will be informed of these exceptions in the informed consent document.

Only consent forms signed by study subjects will be stored in a locked cabinet inside a locked office on NYULMC property.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

All research data will be collected in Case Report Forms (CRFs). Clinical safety data, labs, screening information, questionnaires, informed consent, and progress notes will also be collected in Source Documents.

CRFs of all research data will be entered into a password protected electronic database using a secure server at NYU Langone School of Medicine. The computer used for this study will be password protected and kept locked in a locked office at NYU Langone Weight Management Program. Only designated study staff will have access to patient data and these include: the PI of the study, sub-investigators, the research

coordinator and the research assistant. Though the information collected in this study may be published, no patient will be identified by name or other personal information.

9.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after completion of the study. These documents will be retained for a longer period if required by an agreement with Novo Nordisk. In such an instance, it is the responsibility of Novo Nordisk to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

A contracted CRA will conduct monitoring visit after the first 10 enrollments and every 30 enrollments after the initial monitoring to review subject and drug accountability records for compliance with the protocol. Any protocol deviations will be discussed with the Investigator upon identification. All protocol deviations will be reported to the Institutional Review Board (IRB) according to the IRB's reporting requirements. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, Novo Nordisk, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations, Internaltional Conference on Harmonisation Good Clinical Practice guidelines, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to before commencement of this study.

The study team will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting the informed consent. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study will be financed by Novo Nordisk.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

12.3 Costs to the Subject

There is no cost for the research related components (study drugs, visits, tests, procedures).

12.4 Subject Stipends or Payments

For their participation in each aspect of the study, patients will be paid in gift cards up to $500 for their time and travel expenses. The subjects will receive a gift card for each completed visit according to the below schedule. The subjects will receive a matching gift card if the visit is completed within the time below.

- $50 - Visit 2 (3 month +/- 4 weeks from the first day of study drug)
- $50 - Visit 3 (6 months +/- 4 weeks from the first day of study drug)
- $50 - Visit 4 (9 months +/- 4 weeks from the first day of study drug)
- $100 - Visit 5 (12 months +/- 4 weeks from the first day of study drug)

13 Publication Plan

Once the data analysis is complete the data will then be prepared for publication in a peer reviewed journal deemed appropriate by Novo Nordisk and PI or otherwise disclose publicly the data or results of this study. The study information will be registered at clinicaltrials.gov.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by Novo Nordisk for the purposes of performing the study, will be published or passed on to any third party without the consent of Novo Nordisk. Any investigator involved with this study is obligated to provide Novo Nordisk with complete test results and all data derived from the study.

PI will provide Novo Nordisk with a manuscript of submission(s) for review and comment. PI will not publish any manuscript without Novo Nordisk's prior approval.

14 References

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15 Attachments

15.1 ***Attachment 1- Study Procedures***

15.2 ***Attachment 2- PHQ (Patient Health Questionnaire)***

15.3 ***Attachment 3- International Physical Activity Questionnaire (IPAQ)***

15.4 ***Attachment 4- 24 hours Food Recall***

15.5 Attachment 5- Diet and Exercise Diary with Preferred Starches List

ATTACHMENT 1

Visit Number	1			2			3			4			5
	Baseline	1M	2M	3 months	4M	5M	6 months	7M	8M	9 months	10M	11M	12 months
Visit window	0-4 wks prior to the treatment			± 4 wks			± 4 wks			± 4 wks			± 4 wks
Informed consent	X												
Screening	X												
Demographics	X												
Medical History	X												
Weight, BP, HR, Waist & Neck Circumference	X			X			X			X			X
Height	X												
Medications	X			X			X			X			X
Blood Pregnancy Test (Beta Quantitative HCG) (Only applicable for women of childbearing potential)	X			X			X			X			X
[1]BMP, HbA1c, [1]Lipid profile, Amylase, Lipase	X			X			X			X			X
Additional plasma and serum for future analyses	X						X						X
PHQ-9, IPAQ, 24 hr diet recall	X			X			X			X			X
Diet and Physical Activity Counseling by RD	X			X			X			X			X
Body Composition	X			X			X			X			X
Comorbidities: Diabetes, Hypertension, STOP-BANG	X			X			X			X			X

[2]AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Compliance Phone call		X	X		X	X		X	X		X	X	

1. Fasting is required
2. Ask about hypoglycemia symptoms for patients with Type 2 DM

ATTACHMENT 2:

15.4.1.1 PHQ-9 (Patient Health Questionnaire Nine Symptom Checklist)

Name _____ Date _____				
Over the *last 2 weeks*, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
(For office coding: Total Score ____ = ____ + ____ + ____)				

If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
□	□	□	□

ATTACHMENT 3

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

(AUGUST 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRES (IPAQ) COMPRISES A SET OF 4 QUESTIONNAIRES. LONG (5 ACTIVITY DOMAINS ASKED INDEPENDENTLY) AND SHORT (4 GENERIC ITEMS) VERSIONS FOR USE BY EITHER TELEPHONE OR SELF-ADMINISTERED METHODS ARE AVAILABLE. THE PURPOSE OF THE QUESTIONNAIRES IS TO PROVIDE COMMON INSTRUMENTS THAT CAN BE USED TO OBTAIN INTERNATIONALLY COMPARABLE DATA ON HEALTH–RELATED PHYSICAL ACTIVITY.

BACKGROUND ON IPAQ

THE DEVELOPMENT OF AN INTERNATIONAL MEASURE FOR PHYSICAL ACTIVITY COMMENCED IN GENEVA IN 1998 AND WAS FOLLOWED BY EXTENSIVE RELIABILITY AND VALIDITY TESTING UNDERTAKEN ACROSS 12 COUNTRIES (14 SITES) DURING 2000. THE FINAL RESULTS SUGGEST THAT THESE MEASURES HAVE ACCEPTABLE MEASUREMENT PROPERTIES FOR USE IN MANY SETTINGS AND IN DIFFERENT LANGUAGES, AND ARE SUITABLE FOR NATIONAL POPULATION-BASED PREVALENCE STUDIES OF PARTICIPATION IN PHYSICAL ACTIVITY.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

16 Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7**

days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?
   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?
   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?
   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?
   _____ **days per week**

   ☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?
   _____ **hours per day**

   _____ **minutes per day**

   ☐

Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Attachment 4

24 Hour Food/Drink Recall

Breakfast

Food/Drinks Item	Amount consumed	Serving unit (i.e. slice, cup, tablespoon, ounce)

Lunch

Food/Drinks Item	Amount consumed	Serving unit (i.e. slice, cup, tablespoon, ounce)

Dinner

Food/Drinks Item	Amount consumed	Serving unit (i.e. slice, cup, tablespoon, ounce)

Snacks

Food/Drinks Item	Amount consumed	Serving unit (i.e. slice, cup, tablespoon, ounce)

Desserts

Food/Drinks Item	Amount consumed	Serving unit (i.e. slice, cup, tablespoon, ounce)

ATTACHMENT 5

1640 Diet and Exercise Diary with Preferred Starches List

Name: Date:

Goal of this diet is to eat protein with every meal and snack and decrease carbohydrate intake as the day progresses- No fried food							
	Portion mate cylinder color	**Red**	**Orange**	**Green**	**Yellow**	**Purple**	**Water**
Meal Type	**Recommendations**	**All meats, poultry, fish, seafood, tofu, eggs, egg whites**	**All carbohydrate Non-preferred fruits**	**All vegetables**	**Preferred fruits List (Apple, pear, raspberry, blackberry, blueberry)**	**Fat, cheese, oils, nuts, seeds**	**Drink 48-64 oz. (1.5 to 2 liters)**
			Refer to starch list (avoid after 6 pm)	**Not including veggies in the starch list**	**Up to 1 serving each day (avoid after 6 pm)**	**Up to 2 serving each day**	**Avoid soda and juice**
		Write down number of portions you ate (i.e. 1, 2,3)	Write down number of portions you ate (i.e. 1, 2,3)	Write down number of portions you ate (i.e. 1, 2,3)	Write down number of portions you ate (i.e. 1, 2,3)	Write down number of portion you ate (i.e. 1, 2,3)	Write down number of oz. you drank
Breakfast Eat calories within 1-2 hours of waking up	**Up to 1 Red Up to 1 Orange Up to 1 Green**						
Lunch	**Up to 1 Red Up to 1 Orange Up to 1 Green**						
Dinner Eat veggies first, then protein	**Up to 1 Red Up to 1 Green (No Orange)**						
Snack 1							
Snack 2							
Other food							
Exercise	**Number of Steps: _____**				**Other exercise:_____minutes**		

IDEAL SNACKS - 6 OZ NONFAT OR LOW FAT GREEK YOGURT (MUST HAVE MORE PROTEIN GRAMS THAN CARB GRAMS) , 1-2 LOW FAT MOZZARELLA STRING CHEESE STICKS OR MINI BABYBEL LIGHT CHEESE ROUNDS, 4 OZ SLICED DELI TURKEY, HAM, LEAN ROAST BEEF (NO MARBLED MEATS: PEPPERONI, SALAMI, ETC.), 1/2 CUP LOW FAT COTTAGE CHEESE, OTHER FOODS FROM THE PROTEIN LIST ABOVE

Activity

- **Goal of 150 minutes of exercise weekly** - You can split this up however you would like
- You may want to use a Pedometer – Ultimate goal of **at least 10,000 steps daily**

Behavioral - Chew each bite at least 20 times before swallowing

PREFERRED STARCHES	NON-PREFERRED STARCHES
BREAD	**BREAD**
Bread, pumpernickel	Bagel
Bread, rye	Biscuit
Bread, whole wheat	Bread, white
Bread, reduced calorie	English Muffin
English muffin, whole wheat	Hot dog bun or Hamburger bun
Pancake, whole wheat	Naan
Pita, whole wheat	Pancake
Tortilla, wheat	Pita
	Roll
	Raisin bread
	Stuffing
	Taco shell
	Tortilla, corn or flour
	Waffle
CEREAL AND GRAINS	**CEREAL AND GRAINS**
Bran cereals	Cornmeal
Bulgar	Granola
Cereals, cooked	Grits
Cereals, unsweetened	Pasta, white
Couscous	Puffed cereal
Kasha	Rice, white
Millet	Sugar-frosted cereal
Muesli	
Oats	
Pasta, whole wheat	
Rice, brown	
Shredded wheat	
Wheat germ	
STARCHY VEGETABLES	**STARCHY VEGETABLES**
Corn	Baked beans
Corn on the cob	French-fried potatoes
Mixed vegetables with corn and peas	Potato, boiled
Peas, green	Potato, mashed
Plantain	
Potato, baked with skin	
Squash, winter (acorn, butternut, pumpkin)	
Yam, sweet potato, plain with skin	
CRACKERS AND SNACKS	**CRACKERS AND SNACKS**
Popcorn (no fat or low-fat microwave)	Animal crackers
Rice cakes	Chow mein noodles
Snack chips, fat free or baked (tortilla, potato)	Crackers, round butter type

PREFERRED STARCHES	NON-PREFERRED STARCHES
Whole wheat crackers, no fat added	Graham cracker
	Matzoh
	Oyster crackers
	Pretzels
	Saltine-type crackers
	Sandwich crackers, cheese or peanut filling
BEANS, PEAS AND LENTILS	**BEANS, PEAS AND LENTILS**
Beans/peas (garbanzo, pinto, kidney, white)	
Hummus	
Lima beans	
Lentils	
Miso	
FRUIT	**FRUIT**
Apple, unpeeled, small	Apples, dried
Applesauce, unsweetened	Apricots, fresh
Blackberries	Apricots, dried
Blueberries	Banana
Pear, fresh	Cantaloupe
Raspberries	Cherries, fresh
	Cherries, sweet, canned
	Dates
	Figs, dried
	Fruit cocktail
	Grapefruit
	Grapes
	Honeydew melon
	Kiwi
	Mandarin oranges, canned
	Mango
	Nectarine
	Orange
	Papaya
	Peach, fresh
	Peaches, canned
	Pears, canned
	Pineapple, fresh
	Pineapple, canned
	Plums
	Raisins
	Tangerines
	Strawberries
	Watermelon