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

- 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.

- 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

		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.

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

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

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**

   ☐

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.

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

- 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.
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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

- 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

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.

[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

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.