Effect of GLP-1 receptor agonism on weight and caloric intake in subjects after sleeve gastrectomy

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INVESTIGATOR-INITIATED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1186-7919

Endocrinology & Metabolism
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BACKGROUND AND SIGNIFICANCE:

1) Obesity is a public health problem. In the United States the prevalence of obesity is rapidly increasing with 65% of adults and 17% of adolescents and children classified as being overweight or obese [1]. This represents a doubling of obesity prevalence in adults, and a tripling in adolescents over the previous 25 years. Obesity is associated with multiple diseases, such as type 2 diabetes, non-alcoholic steatohepatitis and osteoarthritis, as well as being associated with increased frequency of risk factors for cardiovascular disease [2]. Approximately 9% of national healthcare costs have been attributed to excess weight [3]. The US Preventive Services Task Force has recommended that body mass index (BMI) is routinely assessed and weight management recommended for obese patients [4].

Behavioral intervention with lifestyle and dietary modification usually achieves modest weight loss [4]. While generally safe, most regain the weight lost within 5 years. Pharmacotherapy for obesity is considered for patients who have failed efforts at lifestyle modification and who have a BMI ≥ 30Kg/M^2 or a BMI ≥ 27Kg/M^2 in the presence of comorbidities such as diabetes [5]. However, there have been significant concerns about the long-term safety of such medications and the currently available medications have relatively limited efficacy [6]. Bariatric surgery is usually considered for patients who have a BMI ≥ 40Kg/M^2 or a BMI ≥ 35Kg/M^2 associated with comorbidities such as diabetes [5]. Restrictive surgeries such as adjustable gastric banding (AGB) limit the capacitance of the stomach. Roux-en-Y gastric bypass (RYGB) is the most commonly performed bypass procedure and produces gastric restriction together with selective malabsorption. RYGB involves creation of a gastric pouch by separating the stomach across the fundus. Drainage of this 10-30ml pouch is achieved by a gastrojejunostomy. The distal end of the jejunum is then anastomosed ~ 150cm below the gastrojejunostomy effectively bypassing the distal stomach, duodenum and proximal jejunum. Duodenal switch (DS) is a variation of biliopancreatic diversion and involves a sleeve gastrectomy with division of the duodenum below the pylorus. The distal ileum is anastomosed to the short stump of the duodenum producing a ~ 100cm channel for nutrient absorption. The other end of the duodenum is closed and the remaining small bowel connected onto the enteral limb 75-100cm from the ileocecal valve. (See [2] for illustrations & review).

Observational studies suggest that bariatric surgery is the most effective intervention for weight loss producing an average weight loss of 30-35% that is maintained in ~ 60% of patients at 5 years [7]. This has led to a dramatic increase in the number of procedures performed annually from 13,365 in 1998 to an estimated 102,794 in 2003 [8]. A newer procedure, sleeve gastrectomy (SG) is a restrictive operation that has been performed much more frequently of late, comprising 34% of the ~ 110,000 bariatric surgeries performed in 2013. SG is projected to and may become the most frequent bariatric procedure in North America [9]. SG may be cheaper than RYGB in terms of operative costs and because it is not a malabsorptive procedure, the costs of follow-up, and care of morbidities arising from micronutrient malabsorption, should be lower [10]. Bariatric surgery effectively produces sustained weight loss in obesity and is widely performed in the United States

2) Comparative effectiveness of RYGB and SG. It has been suggested that remission rate is associated with the length of bypass (~85% for standard RYGB, ~93% for long-limb RYGB and ~98% with duodenal switch [11,12]. Recent prospective, randomized

controlled trials have however reported lower remission rates for diabetes with RYGB although, it remains superior to medical therapy [13-15]. Kashyap et al. has suggested that differences in fat loss and β-cell function between RYGB and SG occur ≥ 1 year after surgery [16]. Of the 2 studies with 3 year follow-up, one in nondiabetic subjects [17] did not demonstrate clear differences in weight loss while in the other RYGB was significantly superior to SG in terms of weight and glycemic control [18]. The obvious anatomic differences between the procedures result in differences in enteroendocrine secretion: postprandial GLP-1 concentrations are lower after SG compared to RYGB in the comparative studies undertaken in humans [16,19-22]. On the other hand, a liquid meal, especially after gastric restriction, may not recreate conditions present after a solid meal [23]. Whether these differences can explain a divergence in metabolic outcomes remains unknown.

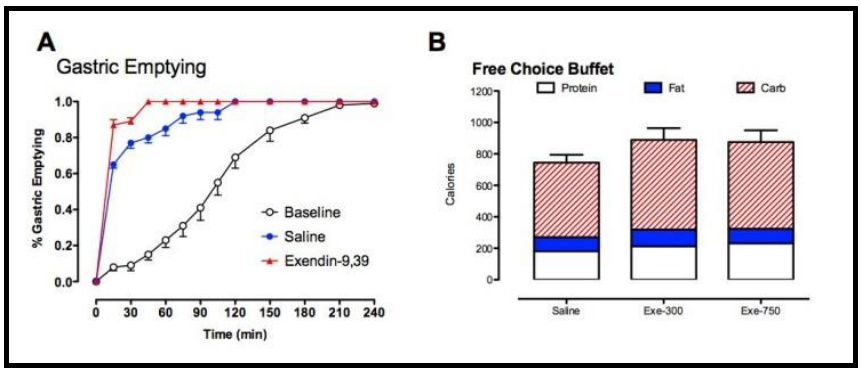

Figure 1: Gastric emptying (GE) at baseline and 4 wks after RYGB **(A)**. After surgery subjects were studied with (Exendin-9,39) or without (Saline). GLP-1R blockade accelerated GE. In a separate experiment, 240 minutes after a mixed meal, subjects ate from a free choice buffet. Calories consumed are recorded **(B)**. GLP-1R blockade increased food consumption.

3) **GLP-1 and appetite.** Both SG and RYGB increase GLP-1 concentrations which directly affect β-cell function; however, this is of lesser magnitude in SG compared to RYGB [24,25]. Our data shows that inhibition of endogenous GLP-1 action increases free-choice caloric intake, providing a mechanism underlying differences between procedures. Neuronal GLP1R mediates the anorectic effects of GLP-1[26]. Inhibition of GLP-1 action with Exendin-9,39 after RYGB (Fig. 1A) accelerates gastric emptying [25]. This observation suggests that factors other than anatomy regulate the upper gastrointestinal response to food ingestion. The attraction of certain foods decreases after RYGB[27] and appetite may be altered by enteroendocrine secretion[28,29]. A potential mechanism is via GLP-1 which alters gastrointestinal transit, gastric accommodation[25,30,31] and has direct effects on hypothalamic nuclei outside of the blood-brain barrier[32]. GLP-1 and GLP-1 receptor agonists decrease food intake and cause weight loss[33,34]. GLP-1 also modulates taste sensitivity in rodents[35-38]. The peripheral concentrations of GLP-1 observed in the early postprandial period in subjects post-RYGB are similar to those observed after infusion at 1.5pmol/kg/min – an infusion rate that alters GI function[39]. More recently, activation of the GLP-1 receptor decreased food intake and food-related brain responses in patients with type 2 diabetes and in obese subjects as measured by functional Magnetic Resonance Imaging (MRI). These actions were blocked by Exendin-9,39[40]. It is therefore reasonable to consider that the postprandial rise in GLP-1 might affect feeding behavior after RYGB, and to a lesser extent SG, where the increase in GLP-1 is less marked [16,19-22].

Given this background, the purpose of the present study is to address the following objective: -

SPECIFIC OBJECTIVES:

Determine the effects of liraglutide administration (3mg daily) on weight and cardiovascular risk factors in subjects who have undergone sleeve gastrectomy.

RESEARCH DESIGN AND METHODS

The study will only be initiated after it has completed review and approval by the Mayo Institutional Review Board (the IRB). Scientific review will initially be conducted by the Endocrine Research Unit and by the Clinical Research Trials Unit, prior to ethical approval by the IRB which will also approve all patient contact material, advertising and consent forms. The latter will be utilized to ensure informed, written consent is obtained at the time of screening where they will meet the principal investigator or a member of the team to ensure that participants meet entry criteria for the study, understand the risks of participation and the goals of the study.

All Mayo IRB approved studies adhere to the Declaration of Helsinki and are conducted in accordance with ICH good clinical practice (GCP) guidelines. Dr. Vella in his role as sponsor-investigator will comply with all these guidelines as well as the other applicable regulatory and legal guidelines during study conduct and when obtaining and documenting informed consent.

The nature of the information obtained for the purposes of the study will be explained in detail to each participant at the time of screening. Specifically, none of this information will become part of the medical record and cannot impact the availability and nature of care or access to healthcare. All information will be stored anonymously in the database and only the PI or one of his designates will have access to the data.

Study Hypothesis: Agonism of the GLP-1 receptor by Liraglutide 3mg will increase weight loss and lower blood pressure and LDL-cholesterol compared to placebo after sleeve gastrectomy.

1° Endpoint: Liraglutide administration (3mg daily) to participants after SG produces significantly greater weight loss from baseline compared to that observed in the group after sleeve gastrectomy who receive placebo.

2° Endpoints:

i. Liraglutide administration (3mg daily) to participants after SG produces will achieve weight loss that is inferior to that achieved by RYGB.
ii. Greater numbers of participants after SG will have an LDL ≤ 100mg/dL and a systolic blood pressure ≤ 130mmHg results when receiving Liraglutide (3mg daily) compared to placebo.
iii. Liraglutide administration (3mg daily) to participants after SG produces blood pressure and LDL-cholesterol lowering that is inferior to that achieved by RYGB.

We propose enrolling 60 non-diabetic adults scheduled for SG and 30 patients undergoing RYGB. Patients scheduled for SG will be randomized to receive Liraglutide (3mg daily) in a double-blind, randomized, placebo-controlled fashion (randomized in a 1:1 ratio). All participants will be followed longitudinally with serial measurement of outcome variables (weight, blood pressure, lipid profile, activity and satiety) over a three year period. Our power calculations suggest that 25 patients per group will be sufficient to accomplish our goals even with a loss of 5 subjects per group to follow up.

Bariatric Sx	2008		2009		2010		2011		2012		2013	
	ND	DM	ND	DM	ND	DM	ND	DM	ND	DM	ND	DM
RYGB	107	46	166	70	160	63	207	83	184	64	210	59
AGB	9	0	27	0	10	0	34	4	8	2	3	1
SG	0	0	25	0	32	10	62	29	78	25	102	36

Table 1: Total numbers of laparoscopic surgeries performed as 1st procedure at Mayo Clinic. AGB = Adjustable Gastric Banding; ND = Non-diabetic; DM = Diabetic patients.

a) Subjects: A total of 75 patients will be recruited from the Nutrition Clinic at Mayo Clinic Rochester prior to undergoing bariatric surgery. Of these25 will be scheduled for RYGB while the remainder (50) are scheduled for SG. Healthy status will indicate that the participant has no known active systemic illnesses or active macrovascular disease. To be eligible subjects must be willing to participate in all the studies outlined. **Baseline Visit:** Subjects will provide written informed consent. To ensure they are healthy, subjects will undergo a history and physical examination including supine and standing blood pressure; blood collection for complete blood count, HbA_{1c}, fasting lipid profile, electrolytes, hepatic panel and urine collection to exclude pregnancy in females of child bearing potential. Habitual activity levels[41], and bowel symptoms [42] will be assessed. Patients will also complete Stunkard's Eating Inventory[43], The Weight Efficacy Life-Style Questionnaire[44] & Eating and Weight Patterns-Revised[45] will be used. **Body Composition:** % body fat will be measured using dual-energy X-ray absorptiometry (iDXA scanner; GE, Wauwatosa, WI).

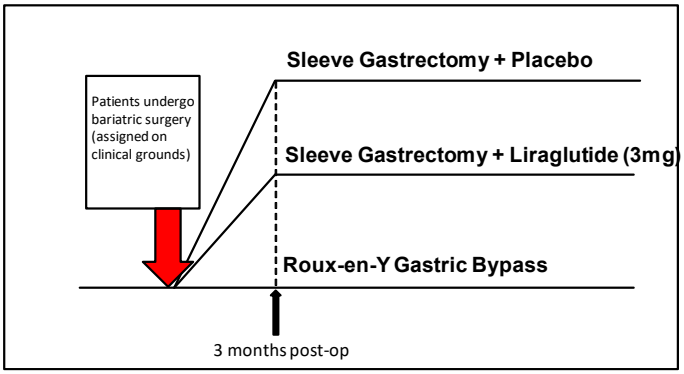

Figure 2: Study Design

b) Inclusion Criteria:

i. Participants will be eligible for bariatric surgery i.e., a BMI ≥ 35 kg/**M²** in the presence of at least one weight-related comorbid condition including hypertension, obstructive sleep apnea or dyslipidemia. Alternatively, a BMI ≥ 40 kg/**M²** without comorbid conditions is deemed to confer eligibility for bariatric surgery at the Mayo Clinic.

ii. Age will be between 20 and 65 years of age.

iii. Subjects will have no active physical illness which will interfere with mobility or weight loss after bariatric surgery.
iv. Prior to acceptance for surgery, patients seen in the bariatric clinic must undergo psychological assessment and complete a supervised comprehensive lifestyle program. Please refer to [46] for details.
v. Female subjects (randomized to study drug) who are sexually active and able to become pregnant, must agree to use birth control methods for the duration of the study

c) Exclusion Criteria:

i. Prior use of glucose lowering medication in the 3 months prior to screening.
ii. A fasting glucose ≥ 126mg/dl or an HbA1c ≥ 6.5% will be taken as evidence of type 2 diabetes and therefore patients will be deemed ineligible for participation.
iii. Prior abdominal surgery other than those that would not affect glucose metabolism, i.e., cholecystectomy, appendectomy, C-section or hysterectomy.
iv. Pregnancy or active consideration of pregnancy during the period of study. Subjects will be discontinued if they become pregnant during the study.
v. Hypersensitivity to liraglutide or any product components.
vi. Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2 in those who will undergo sleeve gastrectomy
vii. Prior history of pancreatitis, cholelithiasis or cholecystitis.
viii. Concurrent use of insulin or any other GLP-1 receptor agonist.
ix. Active, severe psychiatric disease
x. Pregnancy or breastfeeding

d) Surgery: Subjects will then undergo the surgery to which they had been assigned on clinical grounds. At present there are no clear guidelines in this regard and a patient is assigned to a bariatric surgical procedure based mainly on clinical factors. Clinical factors considered include the presence of specific obesity-related comorbid diseases and body mass index. Also considered are the patient's psychological complexity, social situation, and a patient's particular preference. A prior history of severe gastro-esophageal reflux is a relative contraindication to SG. **Note that the study team will play no role in that decision other than to ensure that participants in either group are matched for age, sex and BMI.** At Mayo Clinic, Rochester the standard protocol is to see patients back for care at 3, 6 and 12 months and then annually after bariatric surgery.

e) Randomization: Subjects undergoing SG will be randomized (1:1) at the time of the 3 month visit after bariatric surgery. A double-blind design will be utilized. Liraglutide will be started at 0.6 mg SUBQ daily for 1 week. Subsequently, Liraglutide will be increased by 0.6 mg SUBQ daily on a weekly basis till the maintenance dose of 3.0 mg/day is reached. The placebo dose will also be titrated in a similar fashion. The study medication will be dispensed by the research pharmacy which will handle randomization and ensure that blinding is maintained. SG subjects will return to the CRTU for dispensing of study drug at standard follow-up visits (months 6, 12, 24, 36) and also at months 18 and 30. Subjects undergoing RYGB will return to the CRTU at standard follow up visits, months 3, 6, 12, 24, 36. Recruitment will continue till 50 subjects after SG are randomized and 25 subjects after RYGB are enrolled.

f) Study Visits: These will be timed to coincide with the standard follow-up visits at 3, 6, 12, 24and 36 months after bariatric surgery. In addition to a history and physical examination, blood will be collected for creatinine, fasting glucose, HbA_{1c}, fasting lipid profile and hepatic panel, and urine collection to exclude pregnancy in females of child bearing potential. Supine and standing blood pressure will also be measured as well as body composition using DXA (at months 12, 24 and 36). Habitual activity levels [41], bowel symptoms [42], Stunkard's Eating Inventory [43], The Weight Efficacy Life-Style Questionnaire [44] & Eating and Weight Patterns-Revised [45] will be assessed. Collected data will include height, weight, blood pressure, pulse rate, medications used, and adverse events. During clinic visits, as per standard practice, subjects will meet with a dietitian and with a behavioral psychologist. Compliance will be assessed using an electronic record of food intake. The psychologist will use motivational enhancement and behavior change techniques to promote compliance with the dietary guidelines[47]. In addition, to ensure compliance with instructions to increase physical activity, which will be reiterated at each visit, we will gather information about daily step counts from step-counters or smartphones.

g) Telephone follow up: The study coordinator will schedule monthly calls with each subject (or more frequently if necessary) to rapidly identify problems and help ensure compliance.

h) Early Termination

For any patient enrolled in the study, the study participation will be concluded after the last visit at month 36, or at early termination. Should any patients withdraw or be withdrawn from the study, all of the Early Termination assessments should be completed before early termination, if possible, including; blood collection for creatinine, fasting glucose, HbA_{1c}, fasting lipid profile, hepatic panel, and urine collection to exclude pregnancy in females of childbearing potential. Supine and standing blood pressure will also be measured as well as body composition using DXA. Habitual activity levels, bowel symptoms, Stunkard's Eating Inventory, The Weight Efficacy Life-Style Questionnaire & Eating and Weight Patterns-Revised will be assessed. Collected data will include height, weight, blood pressure, pulse rate, medications used if applicable, and adverse events.

i) Power Calculation: See detailed power calculations below.

j) Adverse Event Monitoring: The most common adverse reactions associated with liraglutide use are nausea, dizziness, abdominal pain, increased lipase, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite and dyspepsia. Acute pancreatitis has been associated with liraglutide use. Relevant symptoms will be screened for at the time of routine follow-up as well as telephone follow-up.

1) Interpretation: We will accept our primary hypothesis that administration of 3.0mg liraglutide to participants after SG increases weight loss compared to placebo if after unblinding, the liraglutide group has significantly greater weight-loss from baseline

compared to the SG + placebo group. Similarly, we will reject our 2° (i) hypothesis if the weight loss observed in participants who undergo SG and receive Liraglutide does not differ from that after RYGB. Such a conclusion would support a role of GLP-1 in the weight loss achieved (and maintained) after RYGB. The questionnaires collected over the duration of the study will be utilized to help generate hypotheses related to food intake as it is affected by liraglutide use after SG compared to placebo. As before, we will determine whether the addition of liraglutide to SG improves effects of SG on cholesterol and blood pressure [15]. If this indeed the case, we will accept our 2° hypothesis (ii). If the high GLP-1 concentrations observed after RYGB modulate appetite and food intake as suggested by our preliminary data (Fig. 1), we would expect weight loss after RYGB to also lower cholesterol and blood pressure. We will reject our 2° (iii) hypothesis if the blood pressure and LDL-cholesterol lowering observed in participants who undergo SG and receive Liraglutide does not differ from that after RYGB.

STATISTICAL CONSIDERATIONS:

Using JMP® Pro 11.2.1 (SAS Institute) for the power calculation we established the following: -

In a prior experiment[15] we observed an overall [mean value ± (SD)] of % weight change after RYGB = -26.1 ± (8.7) at 1 year. Assuming similar variation, 25 subjects who complete the study in each group would provide approximately 80% power (at a 2-sided 0.05 α level), to detect a a 7.0% difference in weight change between SG + treatment vs. SG + placebo. An intention to treat analysis will be undertaken.

In another, as yet unpublished experiment, 12 subjects studied before and 4 weeks after RYGB lost 11.0 ± 3.4 Kg within 4 weeks. Assuming similar variation, 25 subjects per group would provide approximately 80% power (at a 2-sided 0.05 α level), to detect a difference of a 2.7 Kg in weight between groups.

Schauer et al.[14] observed an overall [mean value ± (SD)] of weight change after RYGB = --29.4 ± (8.9) Kg. Assuming similar variation, 25 subjects per group would provide approximately 80% power (at a 2-sided 0.05 α level), to detect a 7.2kg between-group difference.

In an experiment[47] where subjects were fed a diet similar to that consumed after bariatric surgery, we observed a weight change after 12 weeks of -14.8 ± (4.2) Kg. Assuming similar variation, 25 subjects per group would provide approximately 80% power (at a 2-sided 0.05 α level), to detect a 3.4kg between-group difference. Using % weight change, we observed a % change of -14.0 ± (3.0), giving us power to detect a 2.5% difference.

DATA HANDLING AND RECORD KEEPING:

The key personnel identified in this grant application have completed the required education on the protection of human research participants. The institution has established a formal program entitled the Mayo Investigator Training Program or MITP.

The MITP is a web based educational course designed to provide all personnel involved in human subject research with training about human subject protection. All Mayo personnel engaged in human subject research are required to complete the course. As detailed in the consent form, the **expected risks** include:

Blood sampling. Blood samples are collected by venipuncture for this study. Bruising can occur with venipuncture, as can fainting, etc. **Risk Monitoring / Risk Reduction:** The samples are collected using aseptic technique in designated venipuncture areas of the Clinic where facilities are available should untoward reactions (fainting, etc.) occur. Given the aseptic nature of the sample collection and the small risk of bruising, the monitoring plan is focused on advising volunteers to call the investigators should they have unusual pain or discomfort from the venipuncture site.

Radiation. Subjects will be exposed to radiation in this study. Lean body mass, percent body fat and visceral adiposity will be measured at the time of screening using DEXA (dual energy x-ray absorptiometry). Risk Monitoring / Risk Reduction: In all instances, the amount of radiation that a volunteer will receive will be well below levels that result in significant risk of harmful effects. Proposed radiation exposure will be reviewed by the Mayo Clinic Radiation Safety Board prior to initiation of any study. Women who could become pregnant will be required to have a negative pregnancy test prior to participation in each study utilizing radioactive tracers. The Mayo CRTU body composition core has a QDR4500 with fan scan technology which allows body composition to be performed in only a few minutes.

Confidentiality: All studies expose participants to the psychosocial risks arising from any breach in confidentiality. The risks include anxiety, confusion, and damage to family relationships or a compromised ability to obtain insurance or employment. These risks may not be confined to the individual but may extend to other family members. Risk Monitoring/Risk Reduction: The nature of the information obtained will be explained in detail to each participant – specifically none of this information will become part of the medical record and cannot impact the availability and nature of care or access to healthcare. All information will be stored anonymously in the database and only the PI or one of his designates will have access to the data.

Adequacy of Protection against Risk

Informed written consent. All protocols and all techniques to be used will be approved by the Mayo Clinic Institutional Review Board prior to initiation of any studies. Informed written consent will be obtained from subjects after the nature and possible consequences of the study have been explained. Eligibility will only be ascertained after informed, written consent has been obtained.

Confidentiality. Confidentiality of all medical records is strictly maintained by established procedures. The original study data are kept in the study facility and are entered into a computer under the direction of a biostatistician. Physical records are stored under lock and electronic records through security passwords. The PI will review all data. Physicians carry pagers. Volunteers have access to the Mayo Clinic paging operator 24 hr/day. Violations of confidentially will be immediately reported to the IRB

and Data Monitoring Board. Study records will not identify subjects by name, rather using a numeric code.

ETHICS:

The risks to the subjects are small being primarily those of blood withdrawal and exposure to radiation. An understanding of the mechanisms by which bariatric surgery causes weight loss and the role of the GLP-1 receptor could potentially benefit all patients with obesity. In our opinion, the proposed protocols will provide sufficient new information on the effect of sleeve gastrectomy and Liraglutide (3mg) on weight that the potential benefit to be derived from the studies outweighs the minimal risks inherent in the execution of the studies. The investigative team will comply with the Declaration of Helsinki and ICH-GCP. **Importance of the knowledge to be gained.** The incidence and prevalence of obesity continues to increase. Understanding how sleeve gastrectomy and GLP-1 receptor agonists interact to affect weight maintenance will help in the development of new therapies to prevent and treat obesity.

STUDY SCHEDULE:

Please see study design.

STUDY DRUGS AND MATERIALS:

Packaging and Labelling of Study Medication(s), Storage and Drug Accountability of Study Medication(s), Randomization and Blinding
Liraglutide 6 mg/ml, 3 mL prefilled pen-injector, solution for s.c. injection and Placebo, 3 mL prefilled pen-injector, solution for s.c. injection will be handled by the research pharmacy which will dispense medication as per our prior practice. Medication will be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC). It will be protected from light and will not be frozen. During use, after dispensing to study subjects it will be used within 30 days and stored at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). It will be protected from light and will not be frozen during this period.

ADVERSE EVENTS:

Definitions

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

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent

• Pre-existing conditions found as a result of screening procedures

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

Serious Adverse Event (SAE):
A serious AE is an experience that at any dose results in any of the following:
• Death
• A life-threatening* experience
• In-patient hospitalisation or prolongation of existing hospitalization
• A persistent or significant disability/incapacity
• A congenital anomaly/birth defect
• Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
• Suspicion of transmission of infectious agents

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

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an adverse event (AE) for which a causal relationship to the trial product is at least possible i.e., causal relationship is conceivable and cannot be dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR):
An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator.

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

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

Relationship to study medication Assessment Definitions:
• Probable: Good reasons and sufficient documentation to assume a causal relationship
• Possible: A causal relationship is conceivable and cannot be dismissed
• Unlikely: The event is most likely related to an etiology other than the trial product

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

All adverse events will be reported to the Mayo Clinic IRB and the Safety Monitoring Panel.

1. The Serious Adverse Events/Deviations Subcommittee of the Mayo Institutional Review Board meets at intervals of not less than every 2 weeks, except as otherwise determined by the Chair of the IRB.
2. The Subcommittee is comprised of two members, one member required from each of the following groups:
   Group 1: Chair of the IRB or one of the Co-Vice Chairs
   Group 2: Secretary of the IRB or Assistant Secretary of the IRB
4. The PI will report serious adverse events to the chair of the IRB using the Serious Adverse Event Reporting Form. If the investigator receives a report or other materials (i.e., Medwatch form) from an external source regarding the event(s), a copy of these supporting documents will be attached to the Serious Adverse Event Reporting (SAE) form. The PI will sign each Serious Adverse Event form. A copy of the current consent form will be submitted with the actual risk highlighted in the current consent form. Or, if the PI recommends any changes to the consent form document, a printed and electronic version of the revised consent form will be attached.
5. The IRB office will review the incoming reports and triage according to the nature of the event:
   - Reports of serious adverse events that result in taking immediate action will be given first priority.
   - Reports of serious adverse events for which the PI recommends changes to the consent form document will be given 2nd priority.
   - All other reports will then be prioritized.
6. The Subcommittee will review the reports in the order specified by the triage above. The members will review the SAE form and supporting materials. If additional information is necessary, the Subcommittee will contact the PI (or study coordinator if the PI is unavailable) by conference call. After review of the information, the Subcommittee will make an initial determination of the seriousness of the event and determine what actions, if any, will be required.
7. FDA regulations do not require non-serious adverse events (those that do not fall into the categories outlined in step 3 above) to be reported to the IRB. If non-serious

adverse events are reported to the IRB, these reports will be signed by a member of the Subcommittee and returned to the investigator. The IRB will not retain a copy of these materials in the IRB office or files.

8. For serious adverse events that the Subcommittee determines to be unrelated to the study drug/device/intervention, the original report and supporting materials will be kept in the IRB file. The Subcommittee will review such reports, and if the Subcommittee agrees with the determination that the event was unrelated to study drug/device/intervention, then a copy of the report will be returned to the PI. The IRB office will retain a list of the studies for which unrelated serious adverse events are reported. Serious but unrelated adverse event reports will not be included in the minutes of the meeting.
9. For all serious adverse event reports that are determined by the Subcommittee to be definitely, probably, or possibly related to the study drug/device/intervention, or if it is unknown what the relationship is at the present time, the Subcommittee will review the reports and related materials and include them in the minutes of the meeting. The Subcommittee meeting minutes will be referred to the Full Board for final action. For these adverse events which are unexpected and require a change in the consent form, the Chair or a Vice-Chair will be the primary reviewer upon referral to the Full Board.
10. The convened IRB shall take whatever action(s) it deems appropriate. These actions may include but are not limited to:
    - modification of the protocol,
    - modification of the consent form document,
    - modification to the timetable for continuing review requirements,
    - suspension of new enrollment into the study,
    - suspension of the study, or
    - termination of the study.

    Any studies that are suspended or terminated will be promptly reported to the sponsor that has provided funding for the study and/or to the FDA if the study involves an IND or an IDE.
11. All other events not requiring suspension or termination shall be reported to the FDA through the normal reporting channel (notification from the investigator to the sponsor to the FDA).
12. The minutes generated by the Subcommittee are approved by the convened IRB. The convened IRB will generate a subsequent minute excerpt only if additional action is taken (i.e., approval of revised consent form, revisions to the protocol, etc.).

Follow-up of Adverse Events

We will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study regardless of their insurance status. All adverse events classified as serious or severe or possibly/probably related to the trial product will be followed until the subject has recovered and all queries have been resolved.

Pregnancy

Study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant. We will report to Novo Nordisk any pregnancy occurring during the trial period. Further participation in the study will be discontinued but telephone follow-up will continue to monitor the pregnancy and its outcome. The investigator will report to Novo Nordisk information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant. Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this will be reported as a serious adverse event.

Dr. Vella will be responsible for reporting of all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) to the competent authority and IRB based upon federal regulations and local IRB policies.

Dr. Vella 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 PI becoming aware of such adverse events, whichever comes first.

State that the sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g., initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug (e.g., Norditropin Simplex®)
5. Reporter identification (e.g., Name, or initials)

Also 6) Causality, and 7) Outcome might be reported, but this is not mandatory.

Collection, Recording and Reporting 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 posttreatment follow-up period as stated in the protocol.

LIABILITY AND SUBJECT INSURANCE:

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

Dr. Vella will be responsible for the conduct of the study and Mayo Clinic 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.

PREMATURE TERMINATION OF STUDY:

We do not anticipate circumstances that would lead to premature termination of the study. However, adverse events which are unexpected and require a change in the consent form, will be reported to the IRB. The convened IRB shall take whatever action(s) it deems appropriate. These actions may include but are not limited to:

- modification of the protocol,
- modification of the consent form document,
- modification to the timetable for continuing review requirements,
- suspension of new enrollment into the study,
- suspension of the study, or
- termination of the study.

Any studies that are suspended or terminated will be promptly reported to the sponsor.

PUBLICATION PLAN:

We plan to submit relevant data in abstract form to either the Endocrine Society or Obesity Society annual meeting. Subsequently, we intend to publish results in a journal such as *Diabetes*, *Journal of Clinical Endocrinology & Metabolism* or *Obesity*. The study will be registered with clinicaltrials.gov.

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