GLP-1 Agonists as Neoadjuvant Therapy for Surgical Treatment of Type 2 Diabetes: A Randomized Controlled Trial

INVESIGATOR-SPONSORED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN):
U1111-1242-4068

NCT04624672

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BACKGROUND AND SIGNIFICANCE

Metabolic surgery is the most effective treatment for severe obesity and has been part of the standard of care since 1991. Even before metabolic surgery became an accepted therapy for obesity, anecdotal reports of rapid post-operative remission of Type 2 Diabetes (T2D) appeared. In the first large published surgical series Pories et al in 1995 reported 608 patients with severe obesity with 93% follow-up at 14 years documenting substantial long-term weight loss and a high percentage of normoglycemia among 146 diabetics in the series.[1] These observations of apparent resolution of T2D have subsequently been confirmed in numerous large series involving hundreds of patients,[2,3] prospective long-term observational studies,[4] and numerous prospective randomized controlled trials (RCT) comparing rates of diabetes remission in subjects undergoing metabolic surgery vs conventional treatment for T2D.[5-11] In RCTs, long-term remission rates have averaged approximately 40-50% of participants, as compared to the higher values reported in early observational studies. The high level of evidence accumulated in the multiple prospective controlled randomized trials has led to consensus guidelines supporting metabolic surgery as a primary treatment option for patients with T2D and BMI > 35 kg/m^2, and a secondary option for patients with T2D and BMI 30-35 kg/m^2 who do not respond to conventional treatment.[12,13]

As part of our patient-centered approach to improve surgical outcomes, we developed the first predictive algorithm, the DiaRem Score for diabetes remission after metabolic surgery.[14] This scoring system has been validated by many investigators, and is the most widely used scoring system currently for predicting remission of T2D. The scoring system is a surrogate for the severity of diabetes and allows identification of patients with a high (>80-90%), intermediate, or low (<20%) probability of achieving remission of diabetes after surgery. The overall one-year rates of diabetes remission after metabolic surgery is 60-63%.[15] The longer-term rate of remission needs additional study, but preliminary data suggest that at 5 years, the remission rate falls to 45% or less as significant numbers of patients do relapse.[16,17] Mechanisms of relapse after surgery are unclear, but may be related to weight regain.

The rapid improvement in glycemia parameters and insulin resistance, independent of weight loss after metabolic surgery has provided a window for investigators to study mechanisms underlying this metabolic improvement. One of the most exciting areas of study relates to the gastrointestinal hormone Glucagon-ilike-peptide-1 (GLP-1), produced by L cells in the small intestine. GLP-1, for which post prandial blood levels are increased after metabolic surgery[18] has numerous effects that appear to be beneficial to the restoration of normal metabolism including stimulation of insulin release in response to nutrients, reduced glucagon secretion, preservation and expansion of beta cell mass, and stimulation of fatty acid oxidation in liver.[19,20] Experimental evidence suggests that the elevated levels of GLP-1 may contribute to these beneficial effects after surgery. Of additional interest is the remarkable overlap between the expanding list of suggested effects of GLP-1 and the health benefits of metabolic surgery.[21.] (Figure 1)

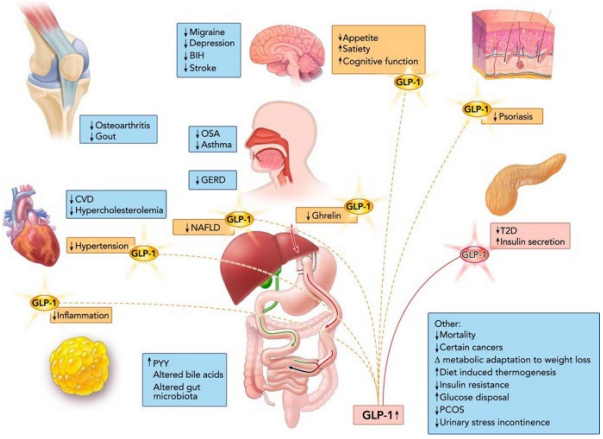


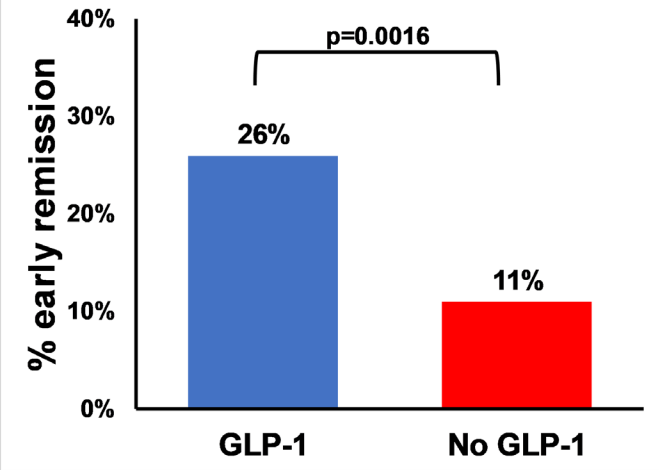
Figure 1. Taken from Manning et al. GLP-1: A mediator of the Beneficial Effects of Bariatric Surgery. *Physiology* 2015; 30:50-62.[21] (orange: likely mediated by GLP-1; blue: unlikely mediated byGLP-1).

Recognition of the beneficial metabolic effects have led to the development and study of GLP-1 agonists which have emerged as effective treatments for T2D. Semaglutide, a recently approved long-acting GLP-1 agonist has been extensively validated in well-designed prospective clinical trials and has been shown to be superior to

many comparative oral agents for glycemic control and weight loss.[22,23] In addition, longer-term trials have confirmed that Semaglutide is associated with a reduction in cardiovascular events.[24] It is now widely utilized as a second-line agent for treatment of T2D.[25]

In our original Geisinger Obesity Institute study cohort of metabolic surgery patients, those with T2D and a minimum of 1-year follow-up after metabolic surgery for weight management were studied. We found that pre-operative insulin treatment was associated with a low rate of diabetes remission after metabolic surgery (<20%). Due to the poor prognosis for these patients on pre-operative insulin, we looked for patient factors that were different in those on insulin that had remission versus those on insulin and didn't have remission and found that the use of a GLP-1 agonist in association with insulin was associated with a statistically significant increase in diabetes remission.[26] Preliminary unpublished data from our updated analysis of this cohort (N=1296 patients with T2D who underwent metabolic surgery) demonstrates that for patients taking insulin for Type 2 Diabetes prior to surgery, the simultaneous use of a GLP-1 agonist is an independent predictor of diabetes remission after surgery. (Figure 2)

Figure 2: Among insulin users, those receiving GLP-1 analogs prior to surgery (n=50) had a significantly higher remission rate compared to those not on GLP-1 (n=426). For non insulin users, GLP-1 analogues did not result in a statistically significant difference in remission rates.



Additional data supporting the important role of GLP-1 in diabetes remission after metabolic surgery comes from a recent clinical study in which GLP-1 levels were measured before and after Roux-en-Y Gastric Bypass (RYGB, N=77) and in obese and non-obese volunteers with and without diabetes (N-93). Findings included decreased baseline levels of GLP-1 in patients with obesity and diabetes, and an increase in GLP-1 levels after RYGB. In addition, the pre surgical levels of GLP-1 in the study patients whose diabetes remitted after surgery were significantly higher than the pre op levels in those who did not remit.[27] Further evidence supporting adjuvant use of GLP-1 agonists comes from the recently published GRAVITAS Trial, a randomized double-blind, placebo controlled multicentered trial wherein patients with persistent or recurrent diabetes (HbA1C levels > 6.5%) following RYGB or Sleeve Gastrectomy were treated with Liraglutide vs placebo. A significant improvement in glycemic control as measured by a change in HbA1C was found in the cohort receiving liraglutide.[28]

Despite the growing body of evidence, the association of GLP-1 with remission of diabetes after bariatric surgery remains unclear. The evidence of existing research, including our own, is dampened by potential for confounding resulting from the lack of randomization. In addition, our preliminary data suggesting an association between the preoperative use of GLP-1 analogues and rates of diabetes remission after surgery is unadjusted for the specific medication used, the duration of treatment and the medication dosage. Therefore, we propose a randomized, blinded, prospective placebo-controlled trial with a standardized treatment approach in order to establish the role of GLP-1 in remission of diabetes after bariatric surgery.

SPECIFIC OBJECTIVE

We propose to conduct a randomized prospective blinded placebo-controlled study of once-weekly semaglutide 1.34 mg/ml in candidates for metabolic surgery with T2D and pre-operative use of insulin.

STUDY HYPOTHESIS:

The neoadjuvant use of once-weekly semaglutide 1.34 mg/ml in patients with severe obesity and Type 2D will increase the rate of diabetes remission in those patients with more severe diabetes whose likelihood of surgically-induced diabetes remission is low.

STUDY ENDPOINTS:

PRIMARY OUTCOME:

PARTIAL REMISSION OF DIABETES (to be defined according to 2 recent guidelines)

BUSE CONSENSUS GUIDELINES:[29]

HbA1C < 6.5%
Fasting Glucose <125 mg/dl
No medications or active treatment for one year
At least one-year duration

ADA GUIDELINES:[30]

HbA1c < 6.5%
No medications or active treatment for one year
At least one-year duration

We will record the rates of diabetes remission using both definitions, but will report the data using the ADA Guidelines[30]

SECONDARY OUTCOME

COMPLETE REMISSION OF DIABETES

BUSE CONSENSUS GUIDELINES:[29]

HbA1C < 6.0%
Fasting Glucose <100 mg/dl
No medications or active treatment for one year
At least one-year duration

ADA GUIDELINES:[30]

HbA1c < 5.7%
No medications or active treatment for one year
At least one-year duration

STUDY TYPE:

This will be a prospective randomized single-center double-blinded placebo-controlled study.

RATIONALE FOR STUDY DESIGN:

The evidence to date supporting the association between treatment with GLP-1 agonists and diabetes remission after metabolic surgery is based on retrospective studies and systematic approaches to this important research questions are needed. Therefore, we propose a 2:1 randomized, blinded, parallel, prospective placebo-controlled trial with a standardized treatment approach in order to establish the role of GLP-1 in remission of diabetes after metabolic surgery. Please also refer to the paragraph below entitled Rationale for Study Population (page 5).

STUDY POPULATION:

Number of subjects to complete the study: 100 total (33 in the Placebo/Control Group and 67 in the Test Group)
Planned number of subjects to be screened: 168
Planned number of subjects to be randomized/started on study medication(s): 126. This will reflect those patients who are screened, but eliminated from consideration because of exclusion criteria. In addition, some screened patients will not have surgery because of insurance and other issues and will be withdrawn from the study. The Geisinger Medical Center is a larger regional referral center for metabolic surgery which will provide a continuous pool of potential replacement study subjects.

Inclusion Criteria

1. Candidates for Roux-en-Y Gastric Bypass Surgery with an established diagnosis of Type 2 diabetes requiring insulin treatment for glycemic control
2. Ability to provide informed consent before any trial-related activities

Exclusion Criteria

1. Prior metabolic surgery procedure
2. Use of GLP-1 analogues for diabetes treatment at the time of recruitment
3. Known or suspected allergy to semaglutide or the excipients in semaglutide, or related products
4. Contraindications to semaglutide which include a personal or first degree relative(s) history of medullary carcinoma of the thyroid or multiple endocrine neoplasia syndrome-2 (MEN-2)
5. Previously randomized for participation in this trial
6. Pregnant, breast-feeding or the intention of becoming pregnant or not using highly effective contraceptive measures
7. Type 1 diabetes
8. Malignant neoplasms other than basal and squamous cell skin cancer in the last 5 years

Withdrawal Criteria

The subject may withdraw at will at any time. Patients may be asked to withdrawal from the study for the following reasons:

- Pregnancy or intention of becoming pregnant
- Surgical conversion to a vertical sleeve gastrectomy or other metabolic surgical procedure
- The development of refractory gastrointestinal side effects while taking study drugs
- Endoscopic modification of the gastric bypass procedure (i.e. plication of an enlarged gastric reservoir or gastrojejunal anastomosis)
- study patients who do not complete the preoperative program and do not have surgery

Subject Replacement:

Additional study patients will be recruited from eligible candidates for metabolic surgery as needed to replace study subjects who either withdraw or become ineligible for the study.

Rationale for Study Population:

Despite the growing body of evidence, the association of GLP-1 with remission of diabetes after bariatric surgery remains unclear. The evidence of existing research, including our own, is dampened by potential for confounding resulting from the lack of randomization. In addition, our preliminary data suggesting an association between the preoperative use of GLP-1 analogues and rates of diabetes remission after surgery is unadjusted for the specific medication used, the duration of treatment and the medication dosage. Therefore, we propose a randomized, blinded, parallel, prospective placebo-controlled trial with a standardized treatment approach in order to establish the role of GLP-1 in remission of diabetes after bariatric surgery. The primary and secondary outcomes of diabetes remission will be determined by the two current definitions for diabetes remission,[29,30] but the priority definition for the primary aim will be the ADA Guidelines.[30] Assessment of outcomes according to both definitions will allow greater options for publication of the findings, and will add to the small number of studies which have compared remission rates using both of these definitions.[31.] In addition, we will measure C-peptide levels in order to further study the impact of an extended course of semaglutide 1.34 mg/ml on beta cell function.[32,33]

Study Design:

This study will be conducted at Geisinger Medical Center Weight Management Center where approximately 35% of candidates for metabolic surgery have T2D. The preoperative program for Metabolic Surgery involves multidisciplinary health evaluation and care as well as patient education lasting approximately 6 months. Surgery Candidates with T2D who require insulin for treatment of T2D will be identified early in the program and offered participation in the clinical trial. The current volume of metabolic surgery procedures at the Geisinger Medical Center is 400 procedures per year and 14% of surgical candidates are taking insulin for treatment of T2D. We estimate that the pool of patients who are eligible will approximate 56 per year.

VISIT PROCEDURES

Patients will be consented at a standard of care clinic visit by appropriately trained study personnel. Study participants may withdraw from the study at any time by contacting the Principal Investigator in writing. Consenting study participants will undergo **baseline study laboratory assessment (LAB 1)** to include, complete metabolic profile (blood urea nitrogen sodium, potassium, chloride, glucose, creatinine, albumin, ALT, AST, alkaline phosphatase, bilirubin calcium, total protein, CO2, and estimated GFR), Hemoglobin A1C, and C-peptide. Study subjects will then be allocated to two groups by blinded randomization: a **test** and a **control** group. During the neoadjuvant treatment phase of this trial, the **Test Group** will receive once-weekly semaglutide 1.34 mg/ml for a minimum of 4 months, at the titrated dose, prior to surgery in addition to their current treatment regimen for T2D. For the small number of study patients whose surgery may be delayed, the neoadjuvant phase will be extended, and these patients can remain in the trial unless the delay exceeds 2 months. If this occurs, they will be withdrawn from the study. Semaglutide 1.34 mg/ml will be administered subcutaneously in accordance with the dose escalation according to prescribing information, with the final dose reaching 1 mg by injection per week. The **Control Group** will receive matched placebo to supplement their treatment regimen for T2D (Figure 3). During the neoadjuvant phase of the study, glycemic control will be carefully monitored and extra study visits during this phase will be implemented for the purpose of adjusting dosage of insulin and other medications as glycemic control changes. Compliance with study drug and dosage will be assessed at each study visit.

After completing the preoperative treatment, study subjects will undergo **laboratory assessment at surgery (LAB 2)** to include Hemoglobin A1C and C-peptide followed by metabolic surgery which will be limited to Roux-en-Y Gastric Bypass. Following metabolic surgery, during the post-operative phase of the trial, glycemic control will be managed according to the current standard of care for perioperative glucose control (The care plan for the management of diabetes in the Geisinger Health system is enclosed as a separate document). Both Test and, Control patients will be managed according to the standard of care. For all study patients, glycemic control will be closely monitored during surgical weight loss and medications will be reduced and/or adjusted as glycemic control improves. Because of the importance of maintaining safe glycemic control in this trial and the awareness that the addition of semaglutide 1.34 mg/ml will necessitate prompt adjustment of diabetes treatment, additional study visits for patient education and glycemic monitoring are included in both the neoadjuvant and postoperative phases of this trial. Study patients in both groups will undergo follow-up lab assessments to include Hemoglobin A1C and C-peptide at 3, 6, 9 and 12 months during the first year of the postoperative phase after surgery (**Labs 3-6)**, and again at 18 and 24 months after surgery during the second year of the postoperative phase of the study (**Labs 7,8,** Figure 3). Complete metabolic profile will be added to lab tests for study patients at **LAB 4** (6 months after surgery), **LAB 6** (12 months after surgery), and **LAB 8** (24 months after surgery). All study subjects will have an additional tube of blood drawn for biobank storage at LABS 1,2,4,6 and 8. When normoglycemia is achieved, medications will be withdrawn according to the standard of care.

Assessment of efficacy

All study patients will be followed for two years after metabolic surgery. Efficacy and outcomes will be evaluated by comparative analysis of laboratory results (Labs 1-6) which monitor longitudinal glycemic control. Outcomes will then be compared between Test and Control groups (Table 1). The major study outcomes will be diabetes remission as defined by the American Diabetes Association.[29] Secondary outcomes will include measures of improvement in glycemic control and beta cell function (change in fasting glucose levels, HbA1C, and C- peptide). All study labs and chemistry analysis will be performed at the Geisinger Medical Laboratory which is accredited by the College of American Pathologists and the Centers for Medicare and Medicaid – Clinical Laboratory Improvement Amendments (CLIA) and licensed by the Pennsylvania Department of Health Division of Laboratories. Other research we have performed in the support of this proposal[14,26] has utilized the Geisinger Medical Laboratory. Evaluation of the continued need for medications for diabetes treatment will be the responsibility of the study team. Longitudinal information relating to medication use will be derived from direct patient contact at study visits, and review of standard of care medicine reconciliations from the Electronic Health Record.

Figure 3: Study Flow Diagram

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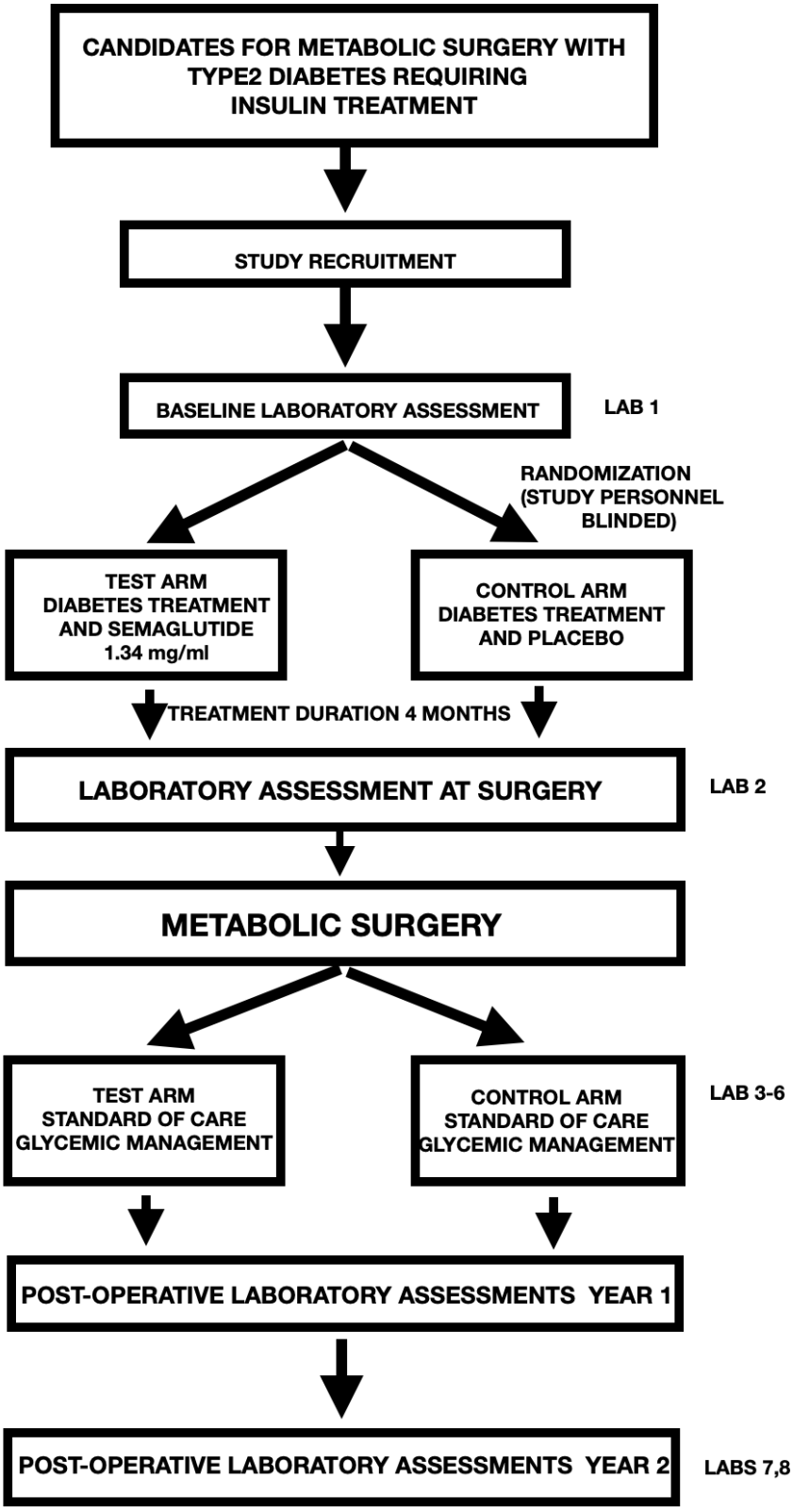

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Schedule of Events

Study Period	Dose Titration		Dose Maintanence					Study Follow-up						
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Surgery	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Early Terminiation Visit
Months in Relation to Surgery	-6 months +/- 14 days	-5 months +/- 14 days	-4 months +/- 14 days	-3 months +/- 14 days	-2 months +/- 14 days	-1 month +/- 14 days	0	+3 months +/- 28 days	+6 months +/- 28 days	+9 months +/- 28 days	+12 months +/- 28 days	+18 months +/- 28 days	+24 months +/- 28 days	
	Lab 1					Lab 2		Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	
Informed Consent	X													
Inclusion/Exclusion Review	X													
Demographics	X													
Medical History Review	X													
Medication Review	X	X	X	X	X	X		X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X		X	X	X	X	X	X	X
Anthropometric Measurements (weight, height, waist circumference)	X	X	X	X	X	X		X	X	X	X	X	X	X
Self-reported glucose measures	X	X	X	X	X	X		X	X	X	X	X	X	X
Blood draw - Laboraotry Assessment - A1C and C-peptide	X					X		X	X	X	X	X	X	
Blood draw - Laboraotry Assessment - CMP	X								X		X		X	
Blood draw - extra tube of blood (serum) for future measurement of GLP-1 levels	X					X			X		X		X	
Randomization to treatment arm	X													
Training in pen handling/drug administration*	X													
Study drug administration**	Weekly dosing													
Dispense study drug	X	X	X	X	X	X								
Return study drug		X	X	X	X	X		X						X
RYGB Metabolic Surgery							X							
AE Monitoring***	X----------						-----X							X

Color Legend: Research

Standard of Care

*This training can be performed at all visits if needed.

**Pre-operative treatment will include 2 months of dose escalation, and a minimum of 4 months at the titrated dose but could be up to 6 months dependant on the patient's pre-operative clinical course.

***Events meeting the criteria outlined in the Adverse Events Section will be collected and reported from visit 1 (post-consent) through 30 days after subject's last study drug dose.

STATISTICAL CONSIDERATIONS

Analysis Plan: Statistical analysis will be based on intention-to-treat using all randomized patients. Although the major study outcomes will focus on diabetes remission, additional secondary outcomes will include the change in HbA1C, change in fasting glucose level, percent weight loss, removal of insulin medication, and change in beta cell function. The final analyses will be conducted at conclusion of the follow-up for all study patients.

Sample Size and Statistical Power:

The anticipated surgical volume is 420 RYGB procedures per year of which approximately 14% are receiving insulin for treatment of their type 2 diabetes. With a goal consent rate of 70%, we expect that about 20% will not undergo surgery (for insurance or other reasons) or be lost to follow-up within the first year. We expect to have about 33 patients per year that complete the study (420 * 0.14 * 0.70 * 0.80 = 33).

A sample size of 100 patients (67 in the test group and 33 in the control group) was selected in order to balance feasibility and cost, as well as to provide reasonable statistical power for detection of clinically relevant differences in in the primary endpoint of partial diabetes remission as well as sub endpoint markers of glycemic improvement and beta cell function. This will result in a **5-year study with a 3-year enrollment period**.

The power calculations were developed using preliminary data from the Geisinger bariatric cohort. The odds ratio for T2D remission in those with pre-operative insulin and GLP-1 versus those with pre-operative insulin and without GLP-1 was 2.56 (Figure 2 above). However, when adjusting for factors related to remission of diabetes such as pre-operative HbA1c and age, the odds ratio increased to 3.11. Assuming an overall Type 1 error of 5% and a loss to follow-up rate of 10%, a sample size of 96 per group (192 total) would be needed in order to achieve 80% power the primary outcome of T2D remission. We feel that the observed effect size may be conservative because it was based on preliminary data which included a variety of GLP-1 agonists with varying durations of use and inconsistent dosing. The currently proposed study addresses these limitations and may result in effect sizes that are larger than those observed in the preliminary data and the capability to detect clinically relevant differences in outcomes in a more cost and time-efficient study

We acknowledge that the current study may be underpowered to detect significant changes in rates of diabetes remission as defined here but feel confident that the study will provide meaningful results in regard to post-operative markers of glycemic control and beta cell function. In addition, we expect that the data from this study will enhance the accuracy of our DiaRem predictor tool.

Statistical Analysis: All statistical tests will be two-sided and p-values <0.05 will be considered significant. Assumptions of underlying statistical procedures will be evaluated, and transformations or nonparametric tests will be incorporated as needed. SAS version 9.4 will be used for data management and statistical analysis. The demographic and baseline clinical characteristics of the two randomized groups will be described using percentages and means with standard deviations. These descriptive measures will be compared between groups using chi-square tests, two-sample t-tests, or comparable nonparametric tests. All differences will be noted for consideration within statistical analyses of the primary outcomes. The primary outcome of early partial T2D remission which will be measured according to the two current definitions will be compared between groups using logistic regression. Assuming the randomization results in balanced treatment groups, the primary analysis will include indicator variables for each intervention group. Subsequent multiple logistic regression models will be used as supplementary analyses to evaluate the effect of potential confounding variables including any unbalanced patient characteristics revealed in primary analyses. The pattern and amount of missing data due to loss of follow-up will be evaluated for appropriate imputation strategy. For example, if the missing data appear to be missing at random, then we will use multiple imputation. Due to the prospective design and prior experience with research of the Geisinger bariatric cohort, we expect the rate of missing data will be low and have little impact on the study outcomes. The secondary outcomes of complete remission measured by the two current definitions and the percent without insulin treatment will be evaluated using similar methods as described above for the primary endpoint. Since the secondary outcomes of change in HbA_{1c} and weight loss are continuous data types, this endpoint will be compared between groups using longitudinal mixed effect linear regression models. Other endpoints for exploratory analysis may include: mean and change from baseline in levels of C peptide and blood glucose, fasting homeostasis model of assessment of insulin resistance (HOMA-IR), and percentage of patients meeting different HbA_{1c} targets.

DATA HANDLING AND RECORD KEEPING

Study data will be collected and managed using REDCap (Research Electronic Data Capture) and stored on the Geisinger secure network. This network has a high level of security, controlled access, daily back-up, and long-term retention of back-up files. All members of the research group will have individual computers that are part of the institution network with institutional oversight of security. Field and range checks will be used to minimize data entry errors. Data distribution will be checked periodically, and outliers verified; missing data will be tracked and checked. Only the minimal amount of data necessary will be shared with Novo Nordisk, such as a limited data set including dates of visits. All patient information will be identified using a study ID number. Before delivery to Novo Nordisk, a Geisinger Clinic Data Broker will review the data and ensure that it does not include unapproved PHI.

ETHICS

This study will be reviewed and approved by the Geisinger IRB before study activities commence. Each patient will meet one of the investigators or study staff members who will explain the scientific rationale of the study, the procedures and potential risks involved, as well as the rights of the participant in the study. The Geisinger IRB will approve the consent form prior to use. Before any procedures specified in this protocol are performed, a participant must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions, take time to consider the decision to participate, and demonstrate understanding of the study.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

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.

The key personnel identified in this proposal report having completed the required education on the protection of human research participants. The Geisinger Clinic has a formal program entitled the "Collaborative Institutional Training Initiative (CITI)". CITI is a web based educational course designed to provide formal training in human subjects' research for all personnel involved in human subject research.

The study will be conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice guidelines.

Confidentiality of all medical records is strictly maintained by established procedures. The privacy of study participants is very important to our study team, and it will be protected as much as possible. In compliance with HIPAA requirements, the names, addresses, phone numbers, social security numbers, or any other identifying information on our study participants will not be released. If study data are sent outside of the study team for further analysis, these data will be sent with a study ID number and/or a limited data set which may include dates of visits. Similarly, any publications generated from the data collected from the proposed studies will exclude identifiers.

STUDY SCHEDULE: (*ACTUAL DATES TO BE MODIFIED PER REVIEW AND APPROVAL TIMELINE***)**

Study Activation: March 2020
Recruitment Period: April 2020 – Jan 2023
Start of Study or FPFV: June 2020
Last Patient First Visit: Feb 2023
End of Study or LPLV: Feb 2025
Final Report: Feb 2025

STUDY DRUGS AND MATERIALS:

Study medication(s) / devices(s)

Semaglutide solution for subcutaneous injection: 2mg/1.5 ml (1.34 mg/ml), prefilled pen -injector for subcutaneous injection

Placebo solution for subcutaneous injection: 1.5 ml, prefilled pen-injector for subcutaneous injection

Packaging and Labelling of Study Medication(s)

Ozempic® is marketed in different pen variants for different intended dosing regimens; push button and cartridge holder are light grey, and the pen can be found in a 1.5 ml variant. For this trial, semaglutide and matched placebo solution for injection will be provided by Novo Nordisk in a 1.5 ml pre-filled pen-injector for subcutaneous injection. The clinical pen for this trial can be found in one variant to support 0.25 mg, 0.5 mg and 1.0 mg doses in a single 1.5 ml variant. The push button and cartridge holder are light brown. Neither closure cap nor the pen is in contact with the product, and differences in colors have no impact on the stability of the product. The investigator will provide each subject with directions for use for the pen-injector at first dispensing visit and when considered needed.

All trial products will be packed and labelled by Novo Nordisk and provided in non-subject specific boxes. Trial products will be dispensed to each subject as required according to the treatment group assigned. Un-blinded trial staff will be available to use the un-blinded lists to dispense trial product to the subjects.

The investigator will ensure availability of proper storage conditions and record and evaluate the temperature at least every working day. A log to document the temperature must be kept. Storage of the study medication will be done according to the label.

The semaglutide/placebo pen-injector must be protected from all sources of light, and the pen cap should be kept on when the pen is not in use. The semaglutide/placebo should not be used if it does not appear clear and colorless. Subjects will be instructed to use a new needle for each injection.

In case of incorrect storage, the Investigator or site staff will not dispense trial drug to subjects.

AUXILLARY SUPPLIES

Subjects will continue to use blood glucose meters, test strips and control solutions prescribed prior to trial participation. These will not be supplied by the site.

Administration: After randomization, semaglutide or placebo will be introduced at a dose of 0.25 mg/weekly. A fixed dose-escalation procedure will be used, with a starting dose of 0.25 mg for 1 month that is escalated to 0.5 mg as per protocol in SUSTAIN-6. After an additional 4 weeks, the dosage will be increased to 1 mg once weekly. Dose increase period can be extended based on the subject's tolerance to the trial product. If the maximum dose of 1 mg once weekly is not tolerated or otherwise associated with unacceptable adverse events, reduction in the dose is allowed at the investigator's discretion. Subjects unable to tolerate 0.5 mg/week will be taken off drug but will remain in study. Injection can be done at any time of the day and irrespective of meals. It will be recommended that the time of injection is consistent from one injection to another.

If a subject misses a dose of investigational product during the trial, they will be instructed to take it as soon as possible within 5 days after the missed dose. If more than 5 days have passed, they will be instructed to skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. Subjects should be instructed not to "make-up" for the missed dose by taking a double dose at the same time. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 2 days (> 48 hours).

Storage and Drug Accountability of Study Medication(s)

Geisinger's Investigational Drug Service is a division of Geisinger Enterprise Pharmacy responsible for protecting the safety of patients participating in investigational or clinical medication studies by providing a process for the safe and appropriate use of investigational drugs within the Geisinger Clinic. The sponsor-investigator, in collaboration with the Geisinger Investigational Drug Service, will ensure the availability of proper storage

conditions and record and evaluate the temperature. The Investigational Drug Service will store drug within temperature range and storage conditions indicated on package directions. Temperature is tracked every 15 minutes via TempTrack with daily summary reports available. No trial medication(s) will be dispensed to any person not enrolled in the study. Unused medication(s) will be stored separately from used trial medication(s). Drug accountability is tracked electronically using the Investigational Drug Accountability System (IDAS) (Vestigo). Unused trial product(s) are returned to the Investigational Drug Service for return to sponsor or destruction as indicated by sponsor.

Randomization and Blinding

Pen-injectors will be blinded regarding the pen-injector itself, the label and the box. On the box, a unique Dispensing Unit Number (DUN) is stated, which together with the Total DUN List (TDL) provided by CS HQ can identify the treatment administered. Only dedicated unblinded site staff can access the TDL and can allocate the trial product according to the treatment that a subject has been randomized to. Both study investigators and participants will be blinded to treatment versus placebo. The study biostatistician will use a random number generator to create randomization schedules for the study participants. Block randomization will be used to ensure equal representation into the two groups at a 2:1 ratio. Participants will be randomized according to order that consent was received. Randomization sequences will be computer-generated by the study statistician.

Breaking of Blinded Codes

The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject or if demanded by the subject. Whenever a code is broken, the person breaking the code will record the time, date and reason as well as his/her initials in the source documents. All codes (whether broken or not) will be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

Concomitant illness: any illness that is present at the start of the trial *(i.e. at the first visit).*

Concomitant medication: any medication other than the trial product(s) that is taken during the trial, including the screening and run-in periods.

A subset of concomitant medications will be collected in the eCRF for this study. Only those medications used for the treatment of (a) diabetes or diabetic complications, (b) obesity, (c) or medications taken to treat an SAE or AE of interest will be captured. These will be recorded at trial entry (i.e. at the first visit). Any changes in these specific concomitant medications must be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the PI must be informed.

The information collected for each concomitant medication includes, at a minimum, trade name or generic name, indication, dates of administration, and dose.

For each concomitant illness, date of onset, date of resolution or continuing, at a minimum, should be recorded.

ADVERSE EVENTS:

Definitions

The current version of the FDA approved Prescribing Information or any updates thereof will be used for assessment of expectedness.

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 30 days after the last study drug treatment .

Only the following AEs should be recorded in the eCRF:

• serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), or serious adverse drug reactions (SADRs)

- AEs leading to discontinuation of trial product
- The following AEs of clinical interest
  - pancreatitis
  - nephropathy or acute renal failure
  - gallbladder disease
  - malignant neoplasms
  - diabetic retinopathy
  - medication errors or misuse/abuse of trial product

The following should not be recorded as AEs:

- Pre-planned procedures, 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. This includes the RYGB metabolic surgery planned in this study.
- Pre-existing conditions found as a result of screening procedures
- Any AE occurring after 30-days post final dose of study drug

Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality. For this study, only those lab results deemed by an investigator to be clinically significant will be reported in the eCRF (i.e. requiring change of medication dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation). Every attempt should be made to consolidate symptoms into a comprehensive diagnosis term for reporting.

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 hospitalisation 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.

Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

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

FDA approved Prescribing Information will be used to evaluate all unexpected events and adverse reactions. US Prescribing Information or any updates hereof will be used for assessment of expectedness.

Outcome Categories and Definitions:

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

Collection, Recording and Reporting of Adverse Events

Adverse events reporting will comply with all local legal, regulatory, and IRB requirements.

The study team will be responsible for reporting serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) and adverse events of interest to the competent authority and independent ethics committee/institutional review boards based upon federal regulations and local/IRB policies.

The study team 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 sponsor-investigator becoming aware of such adverse events, whichever comes first.

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

Study name
Subject identifier

Patient identification (sex, age)
Event term (Preferably diagnosis)
Event description including pertinent medical history, concomitant medications and assessments
Trial drug
Reporter identification (Name and date reported)
Causality
Outcome

The investigator will copy Novo Nordisk when expediting SARs to Health Authorities and will report all SARs related to Novo Nordisk Product to the local Novo Nordisk affiliate safety department. The submission to Novo Nordisk must be within day 15 from the investigator's first knowledge about a valid case. The investigator will also expedite SARs to Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the sponsor-investigator and institution will provide adequate medical care to the study subject for any study-related adverse events specified above. This medical care for study subjects will be provided regardless of their insurance status.

All adverse events of interest classified as serious or severe or possibly/probably related to the trial product must be followed for 30 days post last dose of study drug or until final outcome of the event is known or subject lost to further follow-up. US Prescribing Information or any updates hereof will be used for assessment of expectedness.

Pregnancy

Study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant.

The study team will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by sponsor-investigator should occur within the same timelines described above for reporting of Adverse Events.

Pregnancy complications should be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

Precautions/Over-dosage

In the event of study drug overdosage, supportive care and treatment will be provided to address clinical signs and symptoms. Because of the prolonged half-life of the study drug, an extended period of observation and treatment will be necessary. Overdose will be managed by the clinicians affiliated with the Geisinger Weight Management Center**.**

LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in trial, the sponsor-investigator and his/her 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. This medical care for study subjects will be provided regardless of their insurance status.

The sponsor-investigator will be responsible for the conduct of the study. Liability language will be addressed in the contract.

EVALUABILITY OF SUBJECTS

The principal investigator will be responsible for excluding subjects or observations from the analysis. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation.

PREMATURE TERMINATION OF STUDY

Premature termination of the study will be decided by a Data and Safety Monitoring Board (DSMB). As described above in the statistical considerations section, interim analyses will be used to decide if stopping the trial early is warranted based on higher than anticipated effect size or for futility. In addition, the DSMB will evaluate adverse event reports. Any serious adverse events that are definitely or probably related to the protocol and any deaths (regardless of relationship to the study) will be reported to the full DSMB and corresponding IRBs within 5 days. - For all serious adverse events determined by either IRB to be definitely, probably, or possibly related to the study or interventions, the corresponding IRB will take whatever action(s) it deems appropriate, including but not limited to:

i. Modification of the protocol
ii. Modification of the consent form document
iii. Modification to the timetable for continuing review requirements
iv. Suspension of new enrollment into the study
v. Suspension or termination of the study.

Any unanticipated adverse events that are definitely or probably related to the protocol will be reported to the DSMB and corresponding IRBs within 5 days. Other adverse events will be reviewed at each DSMB meeting, documented by standard procedures and will be reported at the annual IRB protocol review.

PUBLICATION PLAN

The study findings will be reviewed in accordance with the scheduled interim and final analyses. Important clinical findings related to the study aims will be discussed among study personnel and shared with the study sponsor. A mutually agreeable plan for presentation of the findings at national meetings and/or submission to peer-review journals will be carried out. Preparation of abstracts and manuscripts will take place during the final year of the trial. The study team will register the trial with clinicaltrials.gov.

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