Protocol Title

A Randomized Trial Examining the Effect of Subcutaneous Semaglutide (Ozempic) on Kidney Transplant Candidacy for Patients with Stage 4-5 CKD or dialysis-dependent ESKD

INVESTIGATOR-SPONSORED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN)
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BACKGROUND AND SIGNIFICANCE:

Prevalence of obesity continues to rise globally(1), accompanied by increases in type 2 diabetes and chronic kidney disease (CKD). In the U.S., approximately 24% of CKD is attributable to diabetes(2). Among persons with type 2 diabetes mellitus (T2DM), 10-year mortality is exceptionally higher for those with CKD than those without CKD (31.1% vs. 11.5%), accounting for the majority of excess mortality risk in T2DM(3). Patients with diabetes who progress to end-stage kidney disease (ESKD) requiring dialysis are at particularly high risk for death (~20 deaths per 100 person-years); transplant is associated with ~11 more years of life among patients with diabetes and ESKD(4). Unfortunately, patients with T2DM and CKD are frequently unable to be waitlisted for kidney transplant. While there are many reasons why patients are excluded for transplant (e.g. active malignancy, severe heart and lung disease), one of the most common reasons for exclusion is severe obesity, which increases risk for adverse transplant outcomes(5-8); a staggering 22% of U.S. patients with CKD have BMI ≥ 35 kg/m^2 (1).

Transplant policies regarding listing consider uncontrolled diabetes and severe obesity to be contraindications though there is great variability for exact BMI (35-45 kg/m^2) and A1c (9-10%) thresholds for listing by center(9). At Geisinger, exclusion criteria includes uncontrolled diabetes (A1c ≥9%) and severe obesity (BMI ≥ 40 kg/m^2; or BMI ≥ 35 kg/m^2 with waist circumference ≥120 cm). Pre-transplantation hemoglobin A1c increases risk of cardiovascular death with those with A1c ≥ 10% having a 4-fold higher risk of cardiovascular death(10). Currently, medical management to help potential transplant candidates achieve waitlisting is suboptimal. In a study of 170 patients with ESKD and severe obesity (majority with diabetes; A1c not reported) being evaluated for kidney transplantation at University of Cincinnati, no patient made the BMI cutpoint for transplant eligibility after 6 months of lifestyle management(11, 12)(11, 12)(11, 12). Sleeve gastrectomy was performed on 52 patients with many being waitlisted and transplanted with excellent outcomes in long-term follow-up(11,12). Unfortunately, the suboptimal medical management outcomes and increasing reliance on bariatric surgery in such patients reflects the experience at Geisinger and other institutions(13-15).

Glucagon-lowering peptide-1 receptor agonists (GLP-1 RAs) offer great promise, even in patients with GFR <30, and their preferred use along with sodium-glucose co-transporter-2 inhibitors, which are restricted to eGFR >45-60, have been endorsed in patients with T2DM and CKD by the European Renal Association-European Dialysis and Transplantation Association (16-19). In the SUSTAIN-6 trial that included 939 (28.5%) patients with eGFR < 60 ml/min/1.73m^2, and 107 (3.2%) with eGFR < 30 ml/min/1.73m^2, risk of the primary cardiovascular outcome was lower in the semaglutide group than the placebo group (6.6% vs. 8.9%), with similar effects in those with CKD(18). A1c was significantly lower at week 104 for semaglutide 0.5 mg qwk (-0.7%, 95% CI: -0.80, -0.52) and 1.0 mg qwk (-1.1%, 95% CI: -1.2%, -0.9%), compared to placebo. Dosing in renal insufficiency does not need to be adjusted as semaglutide exposure was similar across the spectrum of renal function after a single 0.5 mg subcutaneous semaglutide dose was given in a pharmacokinetic study(20). Other GLP-1 RA trials that have included individuals with T2DM and CKD have shown that GLP-1 RAs have reasonable safety and beneficial effects on cardiovascular disease and renal outcomes, driven mainly by new-onset macroalbuminuria outcomes(21-28).

A systematic review and meta-analysis found that subcutaneous semaglutide at the maximum diabetes dose (1.0 mg qweek) reduced weight by a mean of 3.5 kg and waist circumference by 2.6 cm(29). In a weight loss trial using subcutaneous semaglutide combined with lifestyle

intervention, the 0.1 mg per day dose resulted in greater reductions in weight (-8.6% vs. -2.3% for placebo) and waist circumference (-8.8 cm vs. -3.5 cm for placebo)(30).
The impact of GLP-1 RAs on reducing central obesity is particularly important as central obesity is a stronger predictor for mortality than BMI in dialysis and transplant populations(31, 32), partly because BMI does not distinguish between fat and muscle or between visceral and subcutaneous fat distribution. Thus, many transplant centers informally use central obesity to determine whether patients between BMI 35-40 kg/m^2 should be transplanted; median (25-75th percentile) waist circumference of CKD patients with BMI 35-40 kg/m^2 using NHANES data is 120 cm (114-126 cm)(33).

Geisinger preliminary data

Current transplant exclusion includes uncontrolled diabetes (A1c ≥ 9%) and severe obesity (BMI ≥ 40 kg/m^2; or BMI 35-40 kg/m^2 with elevated waist circumference ≥120 cm). Among 4,200 adults with T2DM and stage 4-5 CKD or ESKD who had an outpatient visit at Geisinger over the past 15 months, 30% had BMI ≥ 35 kg/m^2, 13% had BMI ≥ 40 kg/m^2, and 10.7% had A1c ≥ 9% **(Table 1)**. Use of GLP-1 RAs is quite low with only 6% taking GLP1-RAs, similar to the rest of the country (34) whereas 15% are on sulfonylureas, despite their increased risk of hypoglycemia, weight gain, and lack of evidence for cardiovascular benefit (35, 36). **Based on data from Geisinger, the proportion of patients with BMI ≥ 40 kg/m^2 are more than 4 times less likely to be transplanted. In short, there is a significant patient population that cannot be transplanted due to issues with obesity and/or uncontrolled diabetes. With better control of diabetes and weight loss, these patients can potentially be transplanted and lead a healthier and longer life.**

Table 1. Characteristics of Stage 4-5 CKD/ESKD patients with T2DM who had an outpatient Geisinger visit in last 15 months

Variable	eGFR <15 No Dialysis n = 676	eGFR 15-30 No Dialysis n = 2,543	Dialysis n = 981	Total n = 4,200
Age	71.1 ± 12.8	75.3 ± 11.7	67 ± 12.4	72.7 ± 12.5
Female	53%	57.1%	42.4%	53%
Black	6.4%	2.7%	8.5%	4.6%
Last BMI	32.4 ± 8.8	32.3 ± 8.1	31.3 ± 7.9	32.1 ± 8.2
Last A1c	6.9 ± 1.6	7.2 ± 1.5	6.9 ± 1.7	7.1 ± 1.6
BMI ≥ 35	29.8%	31.2%	28.0%	30.2%
BMI ≥ 40	15.4%	15.5%	11.4%	12.6%
BMI ≥ 40 and A1c ≥9%	2.2%	1.7%	2.0%	1.8%
A1c ≥ 9	9.7%	11.4%	12.1%	10.7%
Meglitinides	3.3%	3.6%	1.6%	3.1%
Biguanides	7.5%	9.1%	0.5%	6.9%
Thiazolidinediones	1.3%	2%	0.3%	1.5%
Sulfonylurea	12.1%	18.8%	7%	15%
DPP inhibitor	11%	14.1%	5.1%	11.5%
GLP1-4A inhibitor	**3%**	**8.3%**	**3.1%**	**6.2%**
SGLT inhibitor	0.3%	0.6%	0.2%	0.5%
Alpha-glucosidase inhibitor	0.3%	0.2%	0.1%	0.2%
Short-acting short-acting insulin	44.7%	38.9%	52.6%	43%
Intermediate or long-acting insulin	51.8%	44.9%	53.8%	48.1%
Any antidiabetic class medication	79.9%	78.1%	74.3%	77.5%
Prior history of visit with dietitian	25.9%	27.8%	33.4%	28.8%
Prior weight loss clinic	6.5%	6.9%	9.2%	7.4%

These numbers are just the tip of the iceberg as many more patients from other nephrology practices and dialysis centres are never even referred for transplant evaluation. The transplant centers send a list of contraindications (including BMI cut offs) to referring physicians and dialysis units. Due to this reason a significant number of patients are never referred for transplant. Access to transplant offers significant benefits in terms of mortality risk. **Patients who are transplanted have 5-fold lower mortality (even at BMI ≥ 35 kg/m^2), compared to those who remain on the waitlist (37, 38). Being on the transplant waitlist (without receiving transplant yet) is associated with nearly 7-fold lower mortality compared to patients on dialysis not on the waitlist (38).**

A combined lifestyle modification program with optimal medical management for T2DM patients with overweight/obesity and stage 4-5 CKD/ESKD could be very valuable in helping patients get listed for transplant and improving survival. To our knowledge, the only published medical management to increase transplant listing of obese CKD patients was a non-randomized study with orlistat, which showed some success compared to non-participants in the program (35% vs 6%)(39). Use of GLP-1 RAs for patients with T2DM, overweight/obesity, and advanced CKD, in combination with lifestyle counseling, could be particularly helpful in helping control A1c, reduce weight, and waist circumference.

In this study, we aim to evaluate the effect of subcutaneous semaglutide 1.34 mg/ml (up to 1.0 mg per week) in combination with lifestyle counseling in patients with T2DM, overweight/obesity, and advanced CKD or dialysis-dependent ESKD on patients' eligibility for kidney transplantation in terms of diabetes control (A1c <9%) and obesity (BMI <35 kg/m^2 or 35-40 kg/m^2 with waist circumference <120 cm) at the end of 9 months.

Study rationale: Despite demonstrated CVD benefits of GLP-1 agonists, these agents are greatly underutilized, particularly among patients with advanced kidney disease, for which there is limited data. Clearly, this is a huge unmet need and a great opportunity to improve outcomes in patients with T2DM, overweight/obesity, and advanced CKD who are unable to be listed for transplant. The purpose of this study is to determine the effect of subcutaneous semaglutide 1.34 mg/ml (up to 1.0 mg per week) on patients' eligibility for kidney transplantation.

SPECIFIC OBJECTIVES:

Primary objective.
The primary objective of this study is to determine the effect of using subcutaneous semaglutide 1.34 mg/ml (up to 1.0 mg per week), on top of standard of care (SoC), on patients' eligibility for kidney transplantation.
Secondary objectives.
1 – Evaluate the efficacy of subcutaneous semaglutide 1.34 mg/ml, on top of SoC) on lowering A1c, weight, and waist circumference, and % body fat.
2 - Provide additional data on the safety profile of subcutaneous semaglutide 1.34 mg/ml in patients with advanced CKD or dialysis-dependent ESKD.

RESEARCH DESIGN AND METHODS

Study Hypothesis (hypotheses):

We hypothesize that use of subcutaneous semaglutide 1.34 mg/ml (up to 1.0 mg per week) will increase the proportion of patients achieving Geisinger Medical Center transplant requirements for glycemic control (A1c <9%) and obesity (BMI <35 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference <120 cm), compared to placebo in patients with advanced CKD or dialysis-dependent ESKD.

Endpoints:

Primary endpoint is kidney transplant candidacy, defined as alive at 9 months and meeting glycemic control criteria (A1c <9%) and obesity criteria (BMI < 35 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference < 120 cm); or alive at 9 months and had referral/listing for kidney transplant during the 9-month follow-up period. If patients have A1C better controlled, they can be referred for transplant, and depending on the time to achieve A1C/weight goal, patients can be listed as well.

Secondary endpoints: change in A1c, change in BMI, change in waist circumference, change in body fat percentage (at 9 months compared to baseline), and kidney transplant

Note: In patients with ESKD, there are some limitations with A1c. While other glycemia markers such as glycated albumin and fructosamine have been proposed, A1c remains the gold standard used clinically(40). Continuous glucose monitoring is another option considered for this trial but will not be performed due to budget constraints. It is recognized that transplant listing and kidney transplantation may be dependent on many other factors and longer-term follow-up is needed to examine these outcomes.

Other endpoints: changes in automated office blood pressure (AOBP)-measured systolic blood pressure (SBP) and diastolic blood pressure (DBP), fasting triglycerides, and fasting low-density lipoprotein (LDL) cholesterol

Safety outcomes: gastrointestinal disorders, gallbladder disorders, hepatic events, injection-site reactions, allergic reactions, neoplasms, hypoglycemia events, and acute pancreatitis events, all-cause hospitalizations, CVD events, doubling of creatinine or ESKD, death, change in urine albumin/creatinine ratio (only among non-dialysis patients), change in estimated glomerular filtration rate (eGFR) using CKD-EPI_{cr} equation (only among non-dialysis patients).

Study type: This will be a multi-site, two-arm, parallel, double-blind, placebo-controlled randomized trial conducted at 3 sites at Geisinger (Geisinger Medical Center in Danville, PA; Geisinger Wyoming Valley Medical Center in Wilkes-Barre, PA; Geisinger Lewistown Hospital in Lewistown, PA).
The intervention will last 9 months with final study outcomes measured at 9 months follow-up.

Rationale for study Design
Limited data exists on use of GLP1-Ras in advanced CKD/ESKD, particularly in the context of an intensive lifestyle intervention to help patients' eligibility for kidney transplantation. There could be great benefits to this strategy in relation to lowering future risks of cardiovascular events and mortality in this patient population.

Study population:

Planned number of subjects to be electronically screened: 300-1000 patients (200 patients referred or being seen in Geisinger's transplant weight loss clinics; the remainder recruited using EHR data pulls, followed by mailings/phone calls)
Number of subjects to be studied: 200

Planned number of subjects to be treated in run-in period: 200
Planned number of subjects to be randomized/started on study medication(s): 150

Inclusion Criteria
1 - Age ≥ 18 years
2 - BMI 25-45 kg/m^2
3 - T2DM
4 - Advanced CKD* (last eGFR <30 ml/min/1.73m^2 in EHR or ESKD on dialysis prior to screening) or Stage G3B/A2-3 CKD (eGFR 30 to <45 ml/min/1.73m^2 with albumin/creatinine ratio >30 mg/g).
5 - Fulfill kidney transplant listing criteria except for one or more of the following reasons (1: uncontrolled diabetes [A1c ≥9%); 2: severe obesity (BMI ≥ 40 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference >120 cm). *See exclusion criteria for general contraindications used for transplant listing used by majority of U.S. transplant centers].*
6 – Ability to provide informed consent before any trial-related activities
7 – Access to a telephone
*The cause of the CKD does not need to be due specifically to diabetes

Exclusion Criteria
General contraindications used for transplant listing used by majority of U.S. transplant centers
1 - Active malignancy
2 - History of pancreatitis
3 - Active substance abuse
4 - Severe COPD
5 – Pulmonary fibrosis
6 - Symptomatic angina or recent myocardial infarction within 6 months
7 - Severe peripheral vascular disease
8 – Cirrhosis
9 – New York Health Association (NYHA) Class III-IV congestive heart failure
10 - Severe cognitive impairment
11 - Drug addiction
12 - History of non-adherence to therapy
13 - Active infection
14 - Expected life expectancy < 5 years

Additional exclusion criteria
15 - Type 1 diabetes mellitus
16 - History of diabetic ketoacidosis within the last 12 months
17 - Planning on undergoing bariatric surgery in next 9 months.
18 – Pregnant, breast-feeding, or planned pregnancy prior to the end of participation or not using adequate contraceptive measures
19 – Self-reported average consumption of > 21 alcoholic beverages per week or binge drinking
20 – Psychiatric hospitalization in past year
21 – Principal investigator discretion (i.e. concerns about safety, compliance)
22 – Known or suspected allergy to trial medication
23 – Previous participation (i.e. randomized) in this trial
24 – Use of GLP1-RA or pramlintide within 90 days prior to screening

25 – For patients with eGFR < 30 ml/min/1.73m^2: Use of metformin
26 – Use of DPP-4 inhibitors within 30 days prior to screening
27 – Personal or family history of medullary thyroid cancer, multiple endocrine neoplasia types 2A and 2B syndrome
28 – Last hemoglobin A1c ≥ 12%
29-For patients on anti-diabetic medications: last hemoglobin A1C ≤5.7% (likely to be more indicative of risk of hypoglycemia).

Withdrawal Criteria
1 - Subjects may withdraw at will at any time.
2 - Pregnancy or intention of becoming pregnant.

Rationale for Study Population
These are patients who are either in need of listing for kidney transplant or will likely need to be listed for a kidney transplant, but who currently do not meet requirements for eligibility at Geisinger Medical Center. The exclusion criteria at Geisinger for uncontrolled diabetes is A1c ≥9% and for severe obesity is BMI ≥ 40 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference ≥120 cm. Listing requirements vary from center-to-center though the inclusion/exclusion criteria listed match the practice of the majority of U.S. centers. Additional eligibility criteria are in place to ensure adequate patient safety and compliance. Every effort will be made to recruit patients who could qualify for this study. For instance, for patients on DPP-4 inhibitors interested in the study, we will discuss with their primary care provider whether they can be changed to a different medication prior to screening visits.

The study will evaluate the effect of initiation of GLP1-RA, and patients will be encouraged to continue participation in the trial, even if they decide to stop taking the intervention medication. In the event of kidney transplantation, participants will be encouraged to continue the study drug as GLP1-RAs are acceptable post-kidney transplant (41, 42).

Subject Replacement
We will not replace study participants who withdraw from the study. However, statistical analyses have accounted for estimated drop-out.

VISIT PROCEDURES
Recruitment
Participants will be recruited from transplant clinic, nephrology clinics, and transplant weight loss clinic. A number of patients, who are referred for transplant but do not meet for listing due to BMI and A1C issues will also be enrolled.

Colleagues within the nephrology, endocrinology, and family medicine/internal medicine will be contacted and asked to refer potentially qualifying patients to participate in this study. Targeted recruitment using existing data analytics, combined with use of telehealth to ease patient burden for frequent visits with clinicians, and dietitians will enable us to easily recruit patients for this trial. In a pilot study completed, we demonstrated that use of remote delivery (e.g. telephone) to provide intensive lifestyle coaching can be used to reduce weight and cardiometabolic risk in patients with CKD (43). In addition to these sources of recruitment, other potentially qualifying patients identified via electronic health record (EHR) data pulls will be

contacted by study team members by recruitment letters, MyGeisinger messages, or recruitment emails followed by recruitment telephone calls.

Patient providers will be made aware of their potential eligible patients through an electronic message or letter.

Screening/baseline visit and informed consent (V1)
Potential participants who meet inclusion criteria will be invited to a screening/baseline visit in which trained research staff will obtain informed consent, including consent to access their EHR data and receive communication via text messaging and/or MyGeisinger. We will obtain physical measurements (weight, height, waist circumference, waist-to-hip ratio, AOBP), fasting morning labs (HgbA1c, LDL, triglycerides, serum creatinine, serum potassium, serum albumin, urine ACR for non-ESKD patients). Females of childbearing potential will have a pregnancy test performed. At this visit, patients will meet with the study physician. They will also either meet with a research dietitian, or schedule a time to meet with them after the visit.

Run-in period (RI)/Randomization
Participants will be required to complete baseline specimen collection as above and have at least 1 contact with the RDN via telephone to confirm their willingness to participate in their trial and comply with study procedures. Participants will be expected to complete these tasks in 2 weeks although the run-in period will be up to 4 weeks if there are explanations for delay (e.g. travel, vacation, scheduling issues). Assessment of successful completion of the run-in period will be done remotely. Following successful completion of the run-in period, participants will be contacted and invited to come to an in-person randomization/training visit. They will then be randomized 1:1 to the semaglutide 1.34 mg/ml or placebo arm. Randomization assignments will be generated using a permuted block design by a computer program, stratified by ESKD status.

Training Visit (V2)
Participants will receive patient education and training on injecting the study drug, in accordance with the Directions for Use (DFU) that is provided global clinical supply (CS). Patients will have their body fat percentage and weight taken.

Treatment of subjects: Patients with T2DM, overweight/obesity, and CKD stage 4-5 or ESKD on dialysis will be randomized 1:1 to SQ semaglutide 1.34 mg/ml vs placebo for 9 months, on top of SoC, which includes intensive lifestyle counseling.

Table 2. Study Drug Titration Schedule

Trial periods	**Screening**	**Treatment period 1**	**Treatment period 2**	**Treatment period 3**
Visits	V1	V2	V3	V4-V10
Duration of each period	2-4 weeks prior to randomization	Weeks 1-4	Weeks 5-8	Weeks 9-36
Treatment arm				
Subcutaneous semaglutide 1.34 mg/ml (n=75)	Screening	0.25 mg qweek	0.5 mg qweek	1.0 mg qweek
Placebo				

Subcutaneous Placebo (n=75)	Screening	0.25 mg placebo qweek	0.5 mg placebo qweek	1.0 mg placebo qweek

Dose escalation will occur every 4 weeks to mitigate risk of gastrointestinal side effects. If patients are experiencing GI side effects (nausea and/or vomiting) or unable to tolerate dose at a study visit, dose will not be escalated. If the patient is later tolerating the dosage well, the dose will escalated the following monthly study visit. If the patient is unable to tolerate the 1.0 mg or 0.5 mg qweek dose, dose de-escalation is permitted and will administered doses and reasons for changes will be carefully tracked.

In the case of missed doses, participants will be advised to take it as soon as possible, provided the time to the next scheduled dose is at least 48 hours away. If the dose is missed and the next scheduled dose is <48 hours away, the subject should not administer a dose until the next scheduled dose. If multiple doses are missed due to unforeseen circumstances unrelated to safety of trial product as determined by the investigator (e.g. hospitalization without access to trial product), dosing should be continued as early as is possible. If more than one dose is missed, a protocol deviation will be reported.

Injection site: Injections can be administered in thigh, abdomen, or upper arm, at any time of day irrespective of meals. Participants should administer injections the same day of the week during the trial.

Background diabetes medication: We will take a pragmatic approach allowing for other treatments for glucose-lowering, blood pressure, or other cardiovascular or kidney risk-reduction agents at the discretion of the investigators based on individuals' needs. All adjustments, including any needed changes to basal or prandial insulin dosing, will be coordinated with the subject's primary care provider or endocrinologist.

For patients on insulin: Subjects on insulin will be advised to self-monitor plasma glucose regularly and inform study team in case of hypoglycemia. During the first 12 weeks after randomization, subjects will have insulin doses adjusted based on 3 fasting pre-breakfast self-measured plasma glucose values, preferably 3 consecutive days before a phone contact or clinic visit by a study nurse or physician. These touchpoints are considered standard of care to ensure safety with diabetes medication changes. They will occur as needed at the discretion of the study physician. Increasing insulin dose will be avoided during the first 12 weeks as semaglutide 1.34 mg/ml reaches steady dose, unless there is a need to control acute hyperglycemia or prevent diabetic complications acutely. Adjustment of insulin dosing, frequency, and timing will be at the investigators' discretion in coordination with the subject's primary care provider or endocrinologist.

Diabetes medication adjustments to optimize safety prior to starting the study drug:
1 – If patients are taking sulfonylureas, these will be stopped since they are not considered to be guideline-recommended if eGFR < 30 ml/min/1.73m^2 and because of potential increased risk of hypoglycemia with intensive lifestyle intervention and weight loss. If A1c is severely uncontrolled at baseline (>9%), additional adjustments to other diabetes medications will be made at the investigators' discretion in coordination with patient's primary care physician or endocrinologist.

2 – If A1c <8% and on basal insulin, dose of basal insulin will be adjusted according to physician's medical judgement to ensure risks of hypoglycemia are minimized with weight loss and the added use of semaglutide 1.34 mg/ml for some subjects.

Suggested actions for any non-study diabetes medication changes that are needed during the trial:
1 – Avoid use of other GLP-1 RAs as well as DPP-4 inhibitor and pramlinitide (also an exclusion criteria during screening) since they also affect the incretin pathway
2 – Avoid use of sulfonylureas, metformin in stage 4-5 CKD/ESKD due to higher risk of hypoglycemia and lactic acidosis
3 – Avoid new prescription of SGLT2 inhibitors for those with eGFR <30 ml/min/1.73m^2 as not currently approved to start at lower eGFR level for diabetes

Hypoglycemia episodes will be defined as per the ADA. If a patient experiences hypoglycemia with blood glucose <56 mg/dL or symptomatic hypoglycemia (<70 mg/dL with typical symptoms of hypoglycemia), patients are instructed to call their provider and the study team and use glucose tablets or food immediately to raise blood sugar, and insulin doses or other medications will be decreased as appropriate. For asymptomatic hypoglycemia, insulin dose will be decreased. These episodes will be documented in detail.

Table 3. Safety Levels and actions

Timeframe	Safety Level	Action
	Hyperglycemia	
First 12 weeks	Average 3 pre-breakfast glucose ≥ 250 mg/dL	Per investigator discretion in coordination with subjects' PCP or endocrinologist
Weeks 13-36	Average 3 pre-breakfast glucose ≥ 200 mg/dL	Per investigator discretion in coordination with subjects' PCP or endocrinologist
	Hypoglycemia	
Entire study	Lowest of 3 pre-breakfast glucose <56 mg/dl	-4 Units in basal insulin (for doses >45 U, suggest dose reduction of 10%); **contact provider and study team, and use glucose tablets or food immediately to raise blood sugar**
Entire study	Lowest of 3 pre-breakfast glucose 56-70 with symptoms	-2 Units in basal insulin (for doses >45 U, suggest dose reduction of 5%); **contact provider and study team, and use glucose tablets or food immediately to raise blood sugar**
Entire study	Lowest of 3 pre-breakfast glucose 56-70 without symptoms	-2 Units in basal insulin (for doses >45 U, suggest dose reduction of 5%)

Subject Diary: Patients will be provided with a diary and instructed to make entries of the following data:

1 – date, time, dose, and injection site of first dose of trial product
2 – date, time, dose of last injection of trial product prior to each visit/phone contact
3 – hypoglycemic episodes
4 – concomitant medication
5 – adverse events
6 – For insulin-treated subjects: total daily insulin dose and date, time, and value of the fasting glucose values for 3 consecutive days, preferably on 3 days before each visit/phone contact in the initial 12 weeks after randomization. Subsequent glucose measurements will be per patient as agreed upon with the investigator.

Background registered dietitian nutritionist (RDN) medical nutrition therapy: As part of routine clinical care, RDNs will complete individualized assessment of needs based on patient's comorbidities, needs, and preferences. This will be done initially and throughout the intervention. Visits will be done via telephone, depending on patient preference. Participants will receive intensive behavioral counseling to reduce weight with a weight loss goal of ≥5% at 6 months and to maintain weight loss at 12 months, with goal of biweekly sessions x 2 months, then monthly sessions to achieve 5% weight loss similar to ADA guidelines (9, 23). In addition, RDNs will be instructed to focus on key factors common to healthy dietary patterns, including nonstarchy vegetables, minimizing added sugars and refined grains, choosing whole foods over highly processed foods, reduced sodium intake (<2300 mg/d), replacing saturated fats with unsaturated fats, lean sources of protein. RDNs will also encourage patients to engage in ≥ 150 minutes per week of moderate-vigorous activity and to increase walking/light activity. Participants will be encouraged to use step trackers or devices as they are able to afford, and devices will be connected to Geisinger patient portal through an existing link that can be used by the RDNs and clinicians to monitor/encourage patients.

Follow-up study visits during 2-8 months (V3-V10).
Monthly in-person study follow-up visits will be scheduled with the research staff (study physician or research nurse). When possible, visits will be scheduled in correlation with routine clinical visits with providers for convenience of the participant and to enhance adherence. Participants will receive the study drug at these visits along with physical measurements (weight, , waist circumference, waist-to-hip ratio, ,). Participants will also bring in self-reported glucose logs, and research staff will additionally collect data on adverse events. All adverse events will be communicated with the study physician immediately and addressed.

At months 3 and 6 (V5, V8), non-fasting labs will be completed for all patients including HgbA1c and serum albumin. Non-fasting labs for non-ESKD patients will also include serum creatinine, potassium, and urine ACR. Data will be collected on adverse events and study drug compliance by count of remaining semaglutide 1.34 mg/ml doses.

Final outcome visit at 9 months (V11)
At the final outcome visit, participants meet with the research staff (study physician or research nurse) and will complete physical measurements (weight, waist circumference, waist-to-hip ratio, AOBP, heart rate, body fat percentage), fasting morning labs (HgbA1c, LDL, triglycerides, albumin, and for non-ESKD patients serum creatinine, potassium and urine ACR), collect data on adverse events, and assess study drug compliance by count of any remaining semaglutide 1.34 mg/ml doses.

As participants receiving GLP-1 RAs would be expected to likely require medication changes following withdrawal of the study product, participants will be warned about this possibility and instructed to monitor their glucose levels and weights after study closeout and notify their providers as soon as possible if they notice worsening glycemia. Participants will be asked to confirm that they want to be notified of their randomization assignment (when deemed appropriate by investigators; see blinding section), whether results can be shared with their care providers (primary care/nephrology/ endocrinology), and whether they wish to receive final study results. A letter or electronic health record message (electronic preferred) will be sent to providers to remind them of their patient's participation in this trial, along with their pre/post A1c, weight, and medication changes during the trial (blinding will be preserved). They will be reminded to consider use of GLP-1 RAs in helping patients achieve optimal glycemic control and weight for kidney transplant eligibility. Recommendations will be made to follow-up with their primary care provider or endocrinologist within 1 month with the research staff helping facilitate scheduling if needed.

Study Close-out visit (V12)
This visit will be scheduled in-person with the research staff (study physician or research nurse) to ensure participants receive adequate post-trial follow-up as their blood sugars and weight may worsen following participation in the trial. At the study close-out visit, participants will be provided details about changes in A1c, weight, and cardiometabolic measures during the trial. If needed, research staff will help facilitate follow-up with their primary care provider or endocrinologist if this has not already been set up. Participants will also be scheduled for follow up in Geisinger's transplant evaluation clinic and continue to receive RDN follow-up to help them achieve transplant listing.

Disclosure of allocation and results of the study will be provided to study participants within a month of primary results being released in a journal publication.

Assessments for Efficacy
Efficacy and outcomes will be evaluated using data collected at study visits, blinded transplant committee adjudication reviewing their clinical data (independent of investigators), and EHR data as shown below. Assessment of outcomes is done in a manner to provide high accuracy and efficiency (i.e. without the need for external adjudication). All study labs are performed at a Geisinger Laboratory. Listing for kidney transplant is dependent on many factors (e.g. psychosocial, insurance, changes in health status, cardiovascular disease). Thus, the primary outcome is the proportion listed for kidney transplant or meeting kidney transplant candidacy for A1c (<9%) and obesity (BMI <35 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference < 120 cm) at the end of the 9-month period. Participants who are referred/listed for kidney transplant or received a transplant during the 9-month period will also count as having achieved the primary outcome. While all efforts will be made to retain participants in the research study and make sure compliance to the study schedule is adhered to, there will inevitably be participants who drop-out or are non-adherent to the study. To address this, we also will collect clinical EHR weight and A1c data +/- 3 months to impute missing data in sensitivity analysis (see statistical methods section).

If patients withdraw from the study, no further prospective data collection will occur. These patients will continue to receive clinical care from our Nephrology department unless instructed otherwise.

Table 2. Study Outcomes	Data source	Timing of Outcome Assessment	Additional notes
Primary Outcome			
Proportion either listed for kidney transplant at 9 months or meeting kidney transplant candidacy criteria for A1c (<9%) and obesity (BMI <35 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference < 120 cm)	Study visit data	Assessed at end of 9 months	
Secondary Endpoints			
Change in hemoglobin A1c	Study visit data	Assessed every 3 months	HgbA1c will be collected using routine procedures and measured on the same day at the central Geisinger laboratory by Turbidmetric inhibition immunoassay.
Change in BMI	Study visit data	Assessed at end of 9 months	Weight will be measured at each study visit in light clothing without shoes by trained, certified staff using a calibrated, digital scale. Scales will be calibrated annually. Height will be measured at the initial study visit to the nearest 0.1 cm using a calibrated, wall-mounted stadiometer without shoes on a firm, level surface, with head in the horizontal plane.
Change in waist circumference	Study visit data	Assessed at end of 9 months	Waist circumference will be measured at each study visit to the nearest 0.1 cm using a Gulick II tape measure.
Change in waist-to-hip ratio	Study visit data	Assessed at end of 9 months	Hip circumference will also be measured to the nearest 0.1 cm using a Gulick II tape measure, and waist-to-hip ratio will be calculated.
Change in % body fat	Study visit data	Assessed at end of 9 months	% Body fat will be measured using a bioelectrical impedance analysis device
Activation on the transplant list	EHR data; transplant meeting data	Assessed at end of 9 months	Assessed by Geisinger kidney transplant committee (blinded to randomization assignment, independent of investigators)
Receipt of kidney transplant	EHR data	Assessed at end of 9 months	
Other Endpoints			
Change in LDL	Study visit data	Assessed at end of 9 months	Fasting LDL and fasting triglycerides will be collected at a Geisinger lab using routine procedures and measured on the same day at the central Geisinger laboratory by spectrophotometry.
Change in triglycerides	Study visit data	Assessed at end of 9 months	
Change in SBP	Study visit data	Assessed at end of 9 months	Automated office blood pressure (AOBP) will be measured (attended) using the OMRON 907-XL machine, with a 5-minute rest period in the seated position, followed by 3 measurements separated by 1-minute time intervals by trained research staff. Mid-arm circumference will be measured, and a cuff of appropriate size will be identified and the same size cuff will used for both visits.
Change in DBP	Study visit data	Assessed at end of 9 months	
Safety Outcomes			
Change in albuminuria (%) among participants without ESKD (44, 45)	Study visit data	Assessed at end of 9 months	Testing at the central Geisinger laboratory, using immunoturbidity (albumin) and Jaffe/Enzymatic (Urine Creatinine)
Change in eGFR among participants without ESKD	Study visit data	Assessed at end of 9 months	Testing at central Geisinger lab; Creatinine-based CKD-EPI equation
All-cause hospitalizations	EHR data	Entire study period	Collected using Geisinger EHR data
CVD events	EHR data	Entire study period	manual EHR review for CVD-related hospitalizations
Doubling of creatinine or ESKD	EHR data	Entire study period	manual EHR review
Death	EHR data	Entire study period	manual EHR review; discussing directly with patients.
Gastrointestinal disorders	Study visit data	Entire study period	Assessed at each study visit
Gallbladder disorders	Study visit data	Entire study period	Assessed at each study visit
Neoplasms	Study visit data	Entire study period	Assessed at each study visit
Hepatic events	Study visit data	Entire study period	Assessed at each study visit
Allergic reactions	Study visit data	Entire study period	Assessed at each study visit

Injection-site reactions	Study visit data	Entire study period	Assessed at each study visit
Hypoglycemia events	Study visit data	Entire study period	Assessed at each study visit
Acute pancreatitis events	Study visit data	Entire study period	Assessed at each study visit

Assessments for Safety

Safety outcomes will be assessed at each study visit and RDNs will also be instructed to report any patient adverse events to the study team. Lab assessments take place at 3 months, 6 months, and 9 months. All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Adverse events will be defined as any unfavourable and unintended sign, including abnormal lab findings, symptoms, or disease temporally associated use of the randomization drug, whether or not considered related to the drug.

Subject Compliance

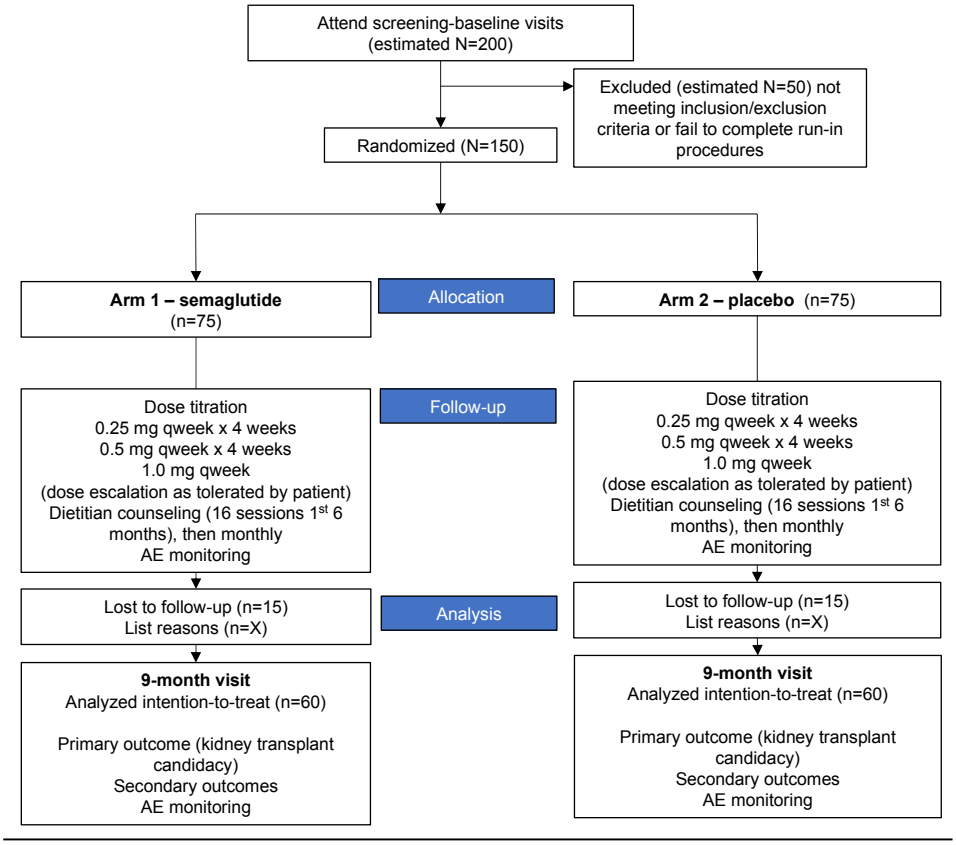
Compliance will be assessed by count of any remaining study drug at each study visit.

Schedule of Events

Trial Periods	**Screening**	**Run-in**	**Treatment**										
Visit	V1	RI	V2 (randomization/training)	V3	V4	V5	V6	V7	V8	V9	V10	V11 (final outcome)	V12 (Close-out)
Week	Up to -4 weeks	-2 weeks	0	4	8	12	16	20	24	28	32	36	40
Visit window (days)		+/- 2 weeks	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/-5 days	+/- 5 days
Visit type	In-person	Remote	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person
Informed consent	X												
Inclusion/exclusion criteria	X	X	X										
Demographics	X												
Medical history review	X												
Medication review	X		X	X	X	X	X	X	X	X	X	X	X
Physical measurements	X		X	X	X	X	X	X	X	X	X	X	
Self-reported glucose measurements			X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X												
Blood Pregnancy Test *If patient is not able to provide urine test.	X												
A1c, creatinine, potassium, albumin)	X					X			X			X	
Lipid profile	X											X	
Urine collections	X					X			X			X	
Randomization			X										
Dispense study drug			X	X	X	X	X	X	X	X	X		
Training*			X										
Research Dietitian Calls		X	X	X	X	X	X	X	X	X	X	X	
Consideration of dose escalation (if not at max dose)				X	X	X	X	X	X	X	X		
AE monitoring				X	X	X	X	X	X	X	X	X	
Transplant committee outcome assessment												X	
EHR-based outcome assessment												X	
Facilitate post-trial follow-up with providers												X	X

***** Training according to DFU can be conducted at every in-person visit upon the discretion of the investigator.

Note – all patient labs are considered to be standard of care. The study team will accept lab results that were collected within 30 days pre/post their applicable study visit date. Lipid panel and A1C will be accepted if they were within 60 days pre/post the applicable study visit date.



STATISTICAL CONSIDERATIONS:

Analysis Plan: All analyses will be done using intention-to-treat principles. Analyses will be conducted at conclusion of the 9-month follow-up for all study patients. Blinding will not be broken until within a month of primary results being released in a journal publication.

Sample Size Calculation (updated 9/29/22)
Originally,we calculated the effect size that can be detected with 150 subjects.

Assumptions: Using data from SUSTAIN-6 for the semaglutide 1.0 mg/week diabetes dose, we assumed an estimated mean A1c decrease of -1.4% (SD 1.3%) for semaglutide 1.0 mg/d vs. -0.4% (1.3%) for placebo(18). This does not exactly reflect our study design as there was no lifestyle modification program in addition to semaglutide, so weight loss could be expected to be greater with our study design. Using data from a dose-ranging, phase 2 trial comparing subcutaneous semaglutide, liraglutide, and placebo, in combination with intensive lifestyle counseling, (30) BMI decrease for the 0.1 mg/d dose (corresponding roughly to 0.5 to 1.0 mg/week diabetes dose) was -3.36 (SD 3.3) kg/m^2) for the semaglutide arm vs. -0.88 (SD 3.4) kg/m^2 for the placebo arm, and decreases in waist circumference was -8.8 (SD 9.1) cm for the semaglutide arm vs. -3.5 (9.4) cm.

Since drop-out rate was 17% in a trial of dulaglutide in stage 3-4 CKD. We expect patients with advanced CKD/ESKD to be a more challenging population although potentially more motivated as they are undergoing transplant evaluation; thus, we used a 15% drop-out rate for sample size

calculations (27). For the primary outcome of eligibility of kidney transplantation (meeting criteria for diabetes A1c < 9% and obesity [BMI <35 kg/m^2 or BMI 35-40 kg/m^2 with waist circumference < 120 cm), we estimate that we would have >80% power to detect an absolute difference of 21% (15% in the placebo arm vs. 39% in the semaglutide group), at an alpha of 0.05(this corresponds to an odds ratio of 3.6). For the secondary outcomes, the effect size was calculated using the size of the detectable standard deviation unit (SDU). The SDU corresponds to a beta coefficient in a regression model when we assume the standard normal deviate (i.e. N(0,1)). For an alpha error of 5%, there is 80% power to detect an SDU of 0.50. This corresponds to between-arm-differences in A1c change of 0.65%, BMI change of 1.68 kg/m^2, and waist circumference change 4.65 cm.

As recruitment has been slower than expected (15 participants in the first 15 months of the study with only 1 drop-out), power calculations were re-evaluated 9/29/22 and discussed with the Novo Nordisk and also with the Data Safety Monitoring Board 11/14/22, who agreed with continuing the study until the end date. Assuming 28/30 participants complete the trial and 7.14% of the control group meet the primary endpoint, we would have >80% power to detect a significant difference at an alpha level of 0.05 if >60% of the control group meets the primary outcome.

Statistical Analysis:
Descriptive statistics will include evaluation of all data for underlying distribution and summary statistics, using means with standard deviations and medians with interquartile range for continuous variables, and frequency with percentages for categorical variables. The data will be summarized for all patients enrolled and will be stratified by randomization arm. We will assess the quality of data, evaluating outliers and patterns of missing data using graphs such as histograms and stem-and-leaf plots. The primary outcome will be examined by comparing groups using logistic regression in an intention-to-treat analysis. Analyses will adjust for the stratification factors (ESKD status, site) in the randomization scheme. Additional analyses will be employed using linear mixed models for continuous variables. Stopping rules will be outlined in the data safety and monitoring plan.

Missing Data Considerations: We will make every possible effort to minimize missing data and to capture final assessments for participants opting to discontinue study participation by querying the EHR for follow-up visits and sending reminders to each participant to schedule and attend appointments. Missing data, however, are inevitable in a longitudinal study due to dropout. We anticipate that no more than 15% of randomized subjects will fail to complete the study and reasons for dropout will be documented. Before proceeding with primary analyses, we will characterize patterns of missingness using exploratory analyses to provide insights into how to handle the missing data. Participants with missing data will be compared to participants with complete data to ensure there are no differences. Depending on the amount of missing data, we will use a non-parametric missing data imputation method based on random forests(46). This method has been shown to perform as well as or better than more traditional methods of imputation, and it has the advantage of imputing of both continuous and categorical data. By using random forests, we can capture non-linear relationships and interactions present in the dataset that may otherwise be missed when using a different method. At least 5 complete datasets will be created and combined using the multiple imputation methods of Rubin(47).

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. 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:

IRB approval will be obtained prior to any study activities begin. Informed consent will be obtained for every study participant, who will be informed about the scientific rationale of the study, the procedures and potential risks involved, as well as the rights of the participant in the study. 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.

We have determined that our research trial can be conducted without an IND. Per FDA guidance on IND applications, "*a clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:*

1) *The drug product is lawfully marketed in the United States.*
2) *The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.*
3) *In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.*
4) *The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).*
5) *The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).*
6) *The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product)."*

Our trial meets the exemption criteria as follows:

1) In this trial, the drug product Ozempic® will be used as an adjunct to diet and exercise to improve glycemic control for adults with type 2 diabetes as currently approved by the

FDA. Per the FDA label, "No dose adjustment of OZEMPIC is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed."

2) This investigation does not intend to support a change in the labeling of the drug.
3) This investigation does not intend to support a change in the advertising for the drug.
4) This investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk associated with the use of the drug product.
5) This investigation will be conducted in compliance with the requirements for review by an IRB and the requirements for informed consent.
6) This investigation is not intended to promote or commercialize the drug product.

All personnel will complete and maintain 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.

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:

Study Activation (tentative, depending on trial initiation) : January 2021
Recruitment Period: February 2021-June 2023
Start of Study or FPFV: February 2021
Last Patient First Visit: June 2023
End of Study or LPLV: March 2024
Final Report: June 2024

PUBLICATION PLAN:

Study Design/Rationale paper - September 2021

Abstract Submission/Presentation – November 2024 ASN Kidney Week

Main paper - March 2025

STUDY DRUGS AND MATERIALS:

Study medication(s) / devices(s)

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

The clinic variant of the cartridge is produced with an army green closure cap compared to a dust green closure cap in the marketed Ozempic® product. Ozempic® are marketed in different pen variants for different intended dosing regimens. The push button and cartridge holder are light grey, and the pen can be found in both a 1.5 ml and 3.0 ml variant, dependent on the country. The clinical pen can be found in one variant to support 0.25mg, 0.5mg and 1mg doses in a 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 the differences in colours have no impact on the stability of the product.

Packaging and Labelling of Study Medication(s)

Blinded packaging design as per Novo Nordisk. Labelling will be in accordance with local law and study requirements.

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 or clinical medication 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-investigator or destruction as indicated by sponsor-investigator.

Auxiliary Supply

N/A

Randomization and Blinding

Study investigators and participants will be blinded to treatment allocation. We will use block randomization and stratification by ESKD status, generated by a computer program. We will request Novo Nordisk global clinical supply to conduct the blinded randomization. Novo Nordisk will provide 2 versions of the same randomisation list: one blinded version from which the blinded investigator allocates a randomization number to the subject, and one unblinded randomization list from which unblinded trial staff reacds which treatment (semaglutide/placebo) the randomization number of the subject matches. The unblinded staff then allocates the correct trial product according to the randomized treatment.

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) chronic kidney disease, or (d) medications taken to treat an SEA 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 events are expected or unexpected.

Adverse Event (AE):
An AE is any untoward medical occurrence in a patient or clinical investigation subject administered/using a product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. 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 the end of the treatment follow-up period as defined in the protocol.

Only the following AEs will 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
  - stage 2-3 acute kidney injury
  - gallbladder disease
  - malignant neoplasms
  - diabetic retinopathy
  - medication errors or misuse/abuse of trial product

The following should not be recorded as AEs:
- 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
- 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 regarded as clinically significant by an investigator 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 Study Drug by the Sponsor-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.

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 SADRs and SAEs related or possibly related to study drug use 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).

The study physician will report reportable events to MedWatch in accordance with standard of care practices.

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.

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 Kidney Health Research Institute**.**

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 patient and/or their insurance company will be responsible for the applicable medical care. The study is not responsible for those costs.

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:

If legitimate (e.g. safety) reasons arise prompting consideration of premature termination, a decision will be made by the principal investigator. A Data Safety Monitoring Board (DSMB) will evaluate adverse event reports and may review individual cases if deemed necessary. The DSMB will be compiled of three Geisinger clinicians who are independent of the study – Dr. Gurmukt Singh (the lead), Dr. Christopher Still, and Dr. Madiha Alvi. They will meet quarterly as well as on an as needed basis. No member of the DSMB will receive reimbursement.

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 DSMB and corresponding IRB within 5 days. Serious adverse events are defined as: death, life threatening injuries, inpatient hospitalization, or persistent or significant disability/incapacity. For all serious adverse events determined by the IRB to be definitely, probably, or possibly related to the study or interventions, the 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 IRB 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 final analytic plan. Important clinical findings related to the study aims will be discussed among study personnel and shared with Novo Nordisk. 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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