A Phase 2, Prospective, Randomized, Multicenter, Open-Label, Controlled Trial to Assess to the Efficacy and Safety of Exenatide SR for the prevention of diabetes after kidney transplantation

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Name of Investigational Product: Exenatide SR

Title of Study: A Phase 2, Prospective, Randomized, Multicenter, Open-Label, Controlled Trial to Assess to the Efficacy and Safety of Exenatide SR for the prevention of diabetes after kidney transplantation**.**
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Study hypothesis
In renal transplant recipients who have prediabetes as determined by 4 or 12 months after kidney transplantation, treatment with the GLP-1 receptor agonist - Exenatide SR + standard-of-care (SOC) vs. SOC alone will reduce the incidence of diabetes at 24 months after kidney transplantation.

Intervention group
Patients randomized to the intervention group will, in addition to standard care, receive Exenatide SR 2 mg SQ weekly at the time of randomization and continue until 24 months post transplant. The decision to continue beyond 24 months of follow-up will be left to the discretion of the caring physician.

Standard care
Participants randomized to the standard care group will receive standard post-transplant care as per Mayo Clinic usual practice. Standard immunosuppression includes a tacrolimus, mycophenolate with/without prednisone as per Mayo Clinic immunosuppression protocols.

The current lifestyle standard care after kidney transplantation at Mayo Clinic hospital includes advice for regular exercise and a nutritional assessment. The nutrition care involves giving patients resources guiding them on healthy eating and food safety after transplant.

Study objectives.

Primary:
To compare the rate of progression from prediabetes from prediabetes at 4 months or 12 months to frank diabetes at 24 months (as defined by increase in HbA1C or fasting BS to diabetic range based on the ADA criteria) after transplantation in kidney transplant recipients on Exenatide SR + SOC vs. standard-of-care alone in a multicenter randomized study.

Secondary:

- To evaluate the rate of progression to diabetes by 24 months after transplantation
- To evaluate the safety and tolerability of Exenatide SR
- To compare hemoglobin A1c levels in patients treated with Exenatide SR + SOC vs. SOC alone at 24 months after kidney transplantation.
- To compare the incidence of mesangial expansion >20% in patients treated with Exenatide SR + SOC vs. SOC alone at 24 months after kidney transplantation.
- To compare transplant kidney function in the two arms
- To compare the incidence of death by any cause in the two arms
- To compare the incidence of graft loss by any cause in the two arms.

Inclusion criteria:
- Recipients of solitary kidney transplants (i.e. not combined liver-kidney, pancreas-kidney etc.)
- Labs consistent with prediabetes, as determined at 4 and 12 months after transplantation: Prediabetes (fasting blood glucose 100-125 mg/dl; or 2 hr glucose 140-199 or HgbA1c 5.7-6.4%)

Exclusion criteria:

- Diabetes pre-transplantation
- Diabetes at 4 and 12 months
- <18 years of age
- eGFR <30 ml/min (estimated by MDRD equation from serum creatinine)
- Active acute cellular rejection including borderline (If treated and resolved, these patients can be included)
- BK nephropathy active
- History of pancreatitis, pre-existing moderate-to-severe gastroparesis, liver cirrhosis or family /personal history of multiple endocrine neoplasia 2 or medullary thyroid cancer
- Pregnant or breastfeeding women
  Female Subject must be either:
  a. of non-child bearing potential
     1) Post-menopausal (defined as at least 1 year without any menses) prior to screening , or
     2) Documented surgically sterile or status post-hysterectomy
  b. Or if childbearing potential,
     1) Agree not to try and become pregnant during the study for at least 90 days after the final study drug administration.
     2) And have a negative serum or urine pregnancy test.
     3) And if heterosexually active, agree to consistently use two forms of highly effective birth control.
- Hypersensitivity to Exenatide

Criteria for Discontinuation of Medication:

- Decrease in renal function to eGFR to < 30 ml/min after study initiation
- Decrease in eGFR by 50% on the 2 consecutive measurements without otherwise identified cause which maybe correctable (like high immunosuppressive medication level, rejection, urinary tract infection, etc)
- Intolerable GI side effects despite the optimal therapy
- Thyroid tumor
- Pancreatitis
- Hypoglycemia

Study design/schedule

This is a Phase 2, Prospective, Randomized, Multicenter, Open-Label, Controlled Trial. Patients are randomized to treatment with Exenatide SR + SOC vs. SOC alone at 4 months or 12 months post transplant after kidney transplantation and followed until 24 months after kidney transplantation. Patients who discontinued medication for AEs will be contacted within 30 days to follow up on the resolution of symptoms.

Study participants with prediabetes at 4 months or 12 months after kidney transplantation will be randomized 2:1 to receive either Exenatide SR or diet and exercise only with no medication. We plan to enroll approximately 50% of subjects at 4 months post transplant and 50% of subjects at 12 months post transplant

Primary Endpoint is the incidence of diabetes at 24 months after kidney transplantation.

Patients will be followed for 2 years after transplantation (20 or 12 months after enrollment) for progression to all endpoints. Therefore, there will be three SOC biopsies—4, 12 and 24 months after transplantation. Hemoglobin A1C will be performed at the same time points. In addition 2hOGTT will be performed if clinically indicated per our SOC.

Study Sites: This is a multicenter study involving the three Mayo Clinic kidney transplant programs. This group has a common IRB and can contract centrally. Collectively, they perform approximately 600 kidney transplants per year. They have a has a history of multicenter research trials—they enrolled 480 patients along with a fourth center in a recent NIH-sponsored trial that required a 1 year kidney biopsy (NCT01782586 Validation of Gene Expression Markers of Renal Allograft Functional Decline (https://clinicaltrials.gov/ct2/show/NCT01782586?term=stegall&rank=10). Thus, this consortium is large enough to ensure enrollment in the time frame suggested, yet small enough to ensure collaboration and uniformity needed for these studies.

The patient visits and follow-up including safety laboratories all fall within the SOC follow-up at all sites. These include the biopsies. All clinical standard of care labs and biopsies are followed by clinical operating protocols and are followed by clinical nursing and physician staff.

Study drug:
Exenatide SR

Background.

Diabetes is the leading cause of kidney failure and the leading indication for kidney transplantation in the U.S.[1,2] New onset diabetes, known as post-transplant diabetes mellitus (PTDM), occurs with a 5-fold higher risk in the first 2 years after kidney transplant (30%) compared with wait-listed patients (6%).[3] Hispanic kidney transplant recipients have a greatly increased risk of PTDM, and diabetic patients have the worst post-transplant mortality and morbidity.[4-6] PTDM is associated with a 46% increased risk of death-censored kidney graft failure and an 87% increased mortality hazard.[7] Diabetic changes are prevalent in protocol biopsies of transplanted kidneys. Moderate-to-severe diabetic nephropathy was present in 35% of transplant biopsies at 10 years, more prevalent than findings related to alloimmune injury.[8] 77% of patients with diabetic nephropathy on protocol biopsy did not have diabetes pre-transplantation, and 46% were in patients without overt diabetes, but with characteristics of prediabetes.[8] Prediabetes also occurs frequently after kidney transplant (33% at 1 year).[9] Prediabetes has been associated with microalbuminuria and chronic kidney disease (CKD) in non-transplant patients,[10-12] but little evidence is available regarding early renal histological changes.

Contemporary anti-diabetic medications have not been rigorously studied in transplant populations. GLP-1 receptor agonists have established efficacy in weight loss and diabetes prevention as well as improvements in metabolic syndrome and cardiovascular protection, all crucially important considerations in transplant patients.[13] This trial will assess GLP-1 receptor agonists as a potential therapeutic opportunity for prevention of diabetes in kidney transplant recipients. Our aims will address critically understudied areas related to (1) prevention of post-transplantation diabetes mellitus (PTDM) in kidney transplant recipients, and (2) elucidating the impact of prediabetes on kidney transplant outcomes, specifically the development of diabetic nephropathy in the allograft.

Since 2005, more than 30 new anti-diabetic medications have been approved including several new classes of medications such as glucagon-like peptide-1 (GLP-1) receptor agonists. Little research has examined the efficacy and safety of these medications in the transplant population. Current standard of care in transplant recipients is predominantly predicated on insulin use, and diabetes prevention remains critically understudied in this unquestionably high-risk population. Lifestyle modification including diet and physical activity counseling have been shown to be effective therapy for diabetes prevention when weight loss and activity goals are met, and is the recommended first-line therapy according to the American Diabetes Association and the American

Association of Clinical Endocrinologists.[13,14] However, most patients fail to achieve or maintain the necessary weight loss, and weight regain is a characteristic feature.[15] Weight gain after transplantation is the norm with an average increase of 8-14 kg over the first year after transplant.[16]

Rationale for the use of GLP-1 receptor agonists

GLP-1 receptor agonists represent a promising therapeutic option in transplant patients given their FDA approval for type 2 diabetes and obesity and their demonstrated efficacy in reversal of prediabetes and diabetes prevention.[17,18]

GLP-1 receptor agonists act directly on beta cells to improve beta cell function.[19] They act by augmenting insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner, limiting the risk of hypoglycemia.[19] These medications have demonstrated efficacy in preventing diabetes in patients with IFG, IGT, and elevated HbA1c and in achieving significant weight loss.[17,18,20,21] Additionally, multicenter trials have established cardiovascular protective effects with at least 2 GLP-1 receptor agonists.[20,22] Cardiovascular death remains the leading cause of mortality in kidney transplant recipients.[23,24] GLP-1 receptor agonists also have established efficacy in prevention of steroid-induced glucose intolerance, an effect which is particularly advantageous in transplant recipients.[25] GLP-1 receptor agonists also have been associated with reduced endothelial dysfunction and improved renal outcomes including reduced excretion of urinary albumin, preservation of glomerular filtration rate, and decreased renal failure and related deaths.[20,22,26]Gastrointestinal side effects including nausea, vomiting, and diarrhea represent the most common side effects with GLP-1 receptor agonists, but these symptoms are commonly transient, mild to moderate in most cases, and did not attenuate quality of life in non-transplant trial participants.[17,27] Potential interactions with immunosuppressive medications, most notably mycophenolate mofetil which causes similar gastrointestinal side effects, is an important gap in knowledge.

Overall, studies targeting preventing the progression of PTDM and treatment of prediabetes in kidney transplants are critically lacking. Current evidence of efficacy and safety of GLP-1 receptor agonists in kidney transplant recipients is limited to a case series of 5 patients treated with liraglutide. In this study, there were no hypoglycemic episodes, serious adverse events, changes in renal function, or changes in immunosuppression trough levels.[28] GLP-1 receptor agonists are associated with a greater degree of weight loss and greater risk reduction of diabetes development compared with metformin.[21,29] GLP-1 receptor agonists act directly on beta cells to improve beta cell function, a mechanism that does not occur with metformin.[19] TZDs represent another established agent in diabetes prevention. However, concerns regarding weight gain, edema, and exacerbation of heart failure temper enthusiasm regarding the use of this class in kidney transplant recipients who are at greatly increased risk for these problems. Finally, GLP-1 receptor agonists have greater potency than DPP-4 inhibitors with greater improvements in HbA1c, 2-hour plasma glucose, and weight loss.[30,31] Further analysis of the efficacy, tolerability, and safety of different available anti-diabetic medications including potential interactions with immunosuppressive medications is needed to address critical gaps in knowledge related to best care for prediabetic and diabetic transplant recipients.

Our aims are three-fold (1) to determine if treatment with a GLP-1 receptor agonist, comparing to placebo reduces the development of PTDM and reduces weight, improves glucose tolerance, and enhances beta-cell function in prediabetic recipients, (2) to determine if GLP-1 receptor agonists are safe and well-tolerated in kidney transplant recipients, and (3) to investigate changes over time in kidney allografts related to diabetic nephropathy.

PRELIMINARY DATA: Diabetic nephropathy plays an important role in long-term kidney graft survival. Recent data from the Mayo Clinic series of kidney transplant protocol biopsies at 10 years post-transplantation showed a high incidence (35%) of diabetic mesangial glomerulosclerosis

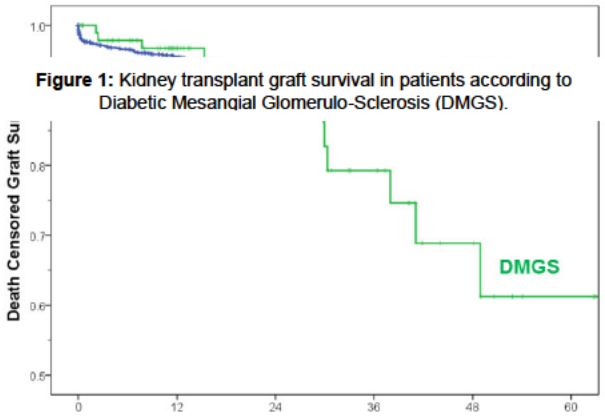

Figure 1: Kidney transplant graft survival in patients according to Diabetic Mesangial Glomerulo-Sclerosis (DMGS).

(DMGS). 77% of patients with diabetic nephropathy on 10 year biopsy did not have diabetes pre-transplantation, and 46% were in patients without overt diabetes pre- or post-transplantation, but with characteristics of prediabetes including fasting hyperglycemia and obesity. Furthermore, kidney transplants with DMGS had greatly inferior graft survival (Figure 1). These data suggest that a paradigm shift is needed to improve the long-term graft survival for kidney transplants.

PTDM is a pervasive problem. In a review of UTHSA kidney transplant recipients, the incidence of PTDM was 43% among Hispanics and 33% in non-Hispanic whites. Patients with PTDM had a higher BMI (BMI=30.4 kg/m^2) compared with patients without PTDM (BMI=27.7 kg/m^2). Based on preliminary data from our collaborative analysis of the University of Michigan Transplant Center cohort, 15% of 345 kidney transplant recipients who did not have diabetes pre-transplant had developed PTDM based on an OGTT done at 6 months post-transplant, and another 24% were prediabetic based on 2-hour glucose values which met the criteria for IGT. Similarly, the Mayo experience (a predominantly Caucasian population) noted a 33% incidence of IFG at 1 year among kidney transplant recipients without diabetes pre-transplant.

Study endpoints

Primary Efficacy Endpoint:
Incidence of diabetes at 24 months after kidney transplantation.
Diabetes is defined based on ADA criteria for diagnosis of diabetes;
HbA1C>6.5%
or FPG>126 mg/dl fasting is defined as no caloric intake for at least 8 hours)
or 2h plasma glucose >200 mg/dl during an OGTT
or random plasma glucose >200 mg/dl in patient with classic symptoms of hyperglycemia

Based on published data, we expect that 30% of untreated patients with prediabetes at 4 months will develop diabetes by 12 months after transplantation. See statistical assessment section.

Patients also will be followed up to 20 months after enrollment for progression to other endpoints

Secondary endpoints

- To evaluate the prevention of progression to diabetes by 24 months after transplantation
- To evaluate the safety and tolerability of Exenatide SR
- To compare hemoglobin A1c levels in patients treated with Exenatide SR + SOC vs. SOC alone at 24 months after kidney transplantation.
- To compare the incidence of mesangial expansion >20% in patients treated with Exenatide SR + SOC vs. SOC alone at 24 months after kidney transplantation.
- To compare transplant kidney function in the two arms
- To compare the incidence of death by any cause in the two arms
- To compare the incidence of graft loss by any cause in the two arms.

Subject Safety

The consent process will inform a volunteer about the study, indicate that participation is voluntary and he/she has the right to stop at any time. Risks will be enumerated in the informed consent form and described orally during the consent process.

The potential risks to study participants include side effects of Exenatide SR (table 1) and medication interactions.

Table * Adverse Reactions Reported in ≥5% of Exenatide Extended ReleaseTreated Patients with Type 2 DM in Monotherapy Trial

Symptom	Percent
Nausea	11.3
Diarrhea	10.0
Infection-site nodule	10.5
Constipation	8.5
Headache	8.1
Dyspepsia	7.3

*From the package insert

It will also inform volunteers about the rare more severe complications including: pancreatitis, renal impairment, hypersensitivity, C cell thyroid tumors (the risk in humans is not determined), development of antibodies to the medication, hypoglycemia when use with other medications for diabetes (oral or insulin)

DRUG INTERACTIONS

• May impact absorption of orally administered medications.

• Warfarin: Postmarketing reports with exenatide of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation of BYDUREON therapy

Patients will be monitored for any drug interactions with immunosuppression and other medications. Immunosuppression levels will be monitored as outlined below. Recipients on Warfarin will be ask to monitor their INR through the local Anticoagulation Clinics or PCP as per patient's preference frequently and per local protocols until INR levels are stable.

Stopping Rules.

In general, the study drug is well-tolerated and we expect the same in kidney transplant recipients.

Enrollment will be suspended for any of the following:

- 2 hospital admissions that are deemed related to study drug
- A patient death in the study arm. This will be investigated for possible causal relation to study drug.

In addition, the investigator also has the right to withdraw patients from the study for any of the following reasons:

- Concurrent illness
- Occurrence of an unacceptable adverse event (see Individual stopping criteria, above).
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up

- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

Patients who discontinue treatment will be followed for 30 days to capture possible delayed onset AEs.

Safety reporting plan

Safety will be assessed using incidence of all adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) and AEs leading to study withdrawal; review of laboratory data, including hematology, renal function, biochemistry; new concomitant medication usage; hospitalization rates; and vital signs. Adverse events will be classified for serious adverse events using standard regulatory criteria. Other safety endpoints include the incidence of BK nephropathy, opportunistic infections, and malignancies.

Data Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

Study Documentation

All clinical data is maintained in Microsoft Excel. All study data is downloaded from this database and stored in tables within a separate Microsoft Access file. Study data is output into study files (xls, jmp, doc, ppt, etc.), which are used for summarizing study information. All active study files are stored within a folder on the Transplant Center research server. The investigator is required to ensure that all clinical data is complete for all participants

Study Coordination

Study coordinators will assist in monitoring participant safety, evaluating the progress of the study, and reviewing procedures for maintaining the confidentiality of data and the quality of data collection, management, and analyses.

Preliminary data:

We identified 17 kidney transplant recipients who were started on GLP-1 agonists for diabetes in our institution. Discontinuation rate was 17% (similar to non transplant population). Medication was effective in reducing weight, controlling diabetes and decreasing the insulin requirements. Abstract submitted to American Transplant Congress (attached).

Collecting, monitoring and reporting of serious adverse events.

Adverse events will be recorded by PI/co-PI or the care team member in patient medical record using a recognized medical term or diagnosis that accurately reflects the event. Patients will be encouraged to contact care team members by the phone or electronically and reported events will be reviewed by PI/co-PI. Patients will have labs monitored and visits scheduled per standard of care as outlined in the protocol. Additionally, PI/co-PI or designated person on research team will follow up with patient by the phone call or electronically at 7-14 days and 90± 7 days after initiation of drug with open ended questions. Adverse events will be considered based on patient reported symptoms, examinations and laboratory data. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca Patient Safety.

Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period.

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of investigational product. The investigators are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator will inform the FDA, via a MedWatch form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32 , and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report will be emailed to AstraZeneca (TCS vendor) at the time the event is reported to the FDA.

Sponsor must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

PI or co-PI will send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: [redacted]

If a non-serious AE becomes serious, this and other relevant follow-up information will be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

Safety/Tolerability Outcomes Measures:

1. Percentage of Participants with at Least 1 Grade ≥2 Treatment Emergent Adverse Event (TEAE) According to Common Terminology Criteria for Adverse Events (CTCAE)
   A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug (AE start date greater than or equal to [≥] first dose date) and within 30 days after receiving the last dose of study drug (AE start date - last dose date less than or equal to [≤] 30). A TEAE may also be a pre-treatment adverse event or a concurrent medical condition diagnosed prior to the date of first dose of study drug, which increases in intensity after the start of dosing.

2. Percentage of Participants with at Least 1 Serious Adverse Event (SAE)
   A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, is a congenital anomaly / birth defect or is medically important due to other reasons than the above mentioned criteria.

3. Percentage of Participants with at Least 1 Adverse Event Leading to Discontinuation of Investigational Study Medication
   Withdrawal due to an AE will occur if the participant experiences an AE that requires early termination because continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.

Safety reporting plan
Safety will be assessed using incidence of all adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) and AEs leading to study withdrawal; review of laboratory data, including hematology, renal function, biochemistry and microbiology and malignancies; new concomitant medication usage; hospitalization rates; and vital signs. Adverse events will be classified for serious adverse events using standard regulatory criteria.

Statistical analysis plan.
Study design and analysis will be performed according to intention to treat principles. Time to development of PTDM will be compared utilizing Kaplan-Meier curves generated according to the product limit method utilizing log-rank tests to evaluate intergroup differences. Risk adjustment for baseline differences between groups will be assessed according to multivariate proportional hazards models. Data on patients who withdraw or are lost to follow-up will be censored at the time of last visit. Comparisons of repeated measures between groups including the secondary endpoints outlined above will be performed utilizing general linear mixed models with transformation of data to logarithm forms when appropriate. These comparisons will be made with inclusion of subjects who withdraw within the follow-up period. Sensitivity analysis excluding these patients will also be performed.

Needed sample size was calculated according to development of PTDM based on utilization of a 2-sided chi-squared test at a 5% significance level and 80% power. The incidence of PTDM reported after kidney transplant varies from 2-50% with best estimates indicating that approximately 30% of patients will develop PTDM.[3,4,41,42] The SCALE trial comparing GLP-1 receptor agonists to placebo showed an 80% reduction in development of type 2 diabetes.[21] Other clinical trials evaluating prevention of diabetes showed a 30% risk reduction with metformin and 55-72% reduction with TZDs.[29,43] Thus, sample size was calculated based on a proportion of 30% incidence of PTDM in the control group and 80% risk reduction in the experimental group (consistent with SCALE trial). A total of 81 (54:27 according to 2:1 randomization) patients will be required to achieve the power and significance levels above. In our preliminary data, 24-33% of kidney transplant recipients meet prediabetes criteria. We would expect that full enrollment would take 24 months.

Data management plan
The coordinating center will be the primary contact for this study and the data coordinating center: Dr. Mark D. Stegall and his program coordinator, M[redacted] L[redacted] ([redacted] and stegall.mark@mayo.edu)

1. The FDA investigator-initiated IND will be held by Dr. Stegall
2. Contracts will preferentially be through the Coordinating Center with subcontracts to the other sites. Indirect costs will be charged only once (i.e. at the site where the funds are actually spent).
3. Protocols will be approved by local IRB (the three Mayo sites have a central IRB).
4. Data is entered into a common database with case-report forms similar to any FDA studies(MEDIDATA Rave case forms specific for transplant are already in place)
5. The Coordinating Center will be responsible for data cleanup, data reporting and reporting to the sponsors and the FDA.
6. Histology:
   Mesangial expansion by light microscopy

Schedule of visits

Enrollment Day 122 (4 months)

	Enrollment Day 122 after KTx range 90-180 days	Day 7±3 Days Post enrollment	Monthly labs to 1 year per SOC	Day 90±7	Day 365 ±90 after KTx	Labs q3 months from 12-24 months	Day 730 ± 90 after KTx
Consent	x						
Labs	x	x	x		x	x	x
Clinic visit	x				x		x
Communication through phone call or EMR		x		x		x	
HgbA1c					x	x	x
Biopsy	x				x		x
Pregnancy test	x						

Enrollment Day 365 (1 year)

	Enrollment Day 365 after KTx range 300-420 days	Day 7±3 Days Post enrollment	Labs q 3 months per SOC	Day 90±7	Day 730 ± 90 after KTx
Consent	x				
Labs	x	x	x		x
Clinic visit	x				x
Communication through phone call or EMR		x		x	
HgbA1c					x
Biopsy	x				x
Pregnancy test	x				

All labs are standard of care, except for the pregnancy test. Day 7 labs represent current practice of repeating labwork with any significant changes in medical therapy. Day 7 labs will include CBC, basic metabolic panel (BMP), which includes creatinine, BUN and electrolytes and immunosuppression levels, including Tacrolimus level and MPA (CellCept). CBC, BMP and Tacrolimus levels will be performed monthly thereafter up to 12 months post transplant and q3 months indefinitely. All labs obtained are standard clinical labs per local practice and monitored by the licensed clinical nurses or physicians following the patient's clinical care. Additional labs will be done as dictated per current standard of care. If there is a lab value out of reference, study staff would also bring it to the clinical staff's attention, but research staff would not dictate or change the clinical care of the patient unless it was directly related to study drug and were directed by the PI/Co-PI

Publication plan. Results will be written up for publication and submitted to a transplant journal such as the American Journal of Transplantation or Transplantation. Similar to prior studies, we also will submit this data as an abstract/oral presentation to the American Transplant Congress annual meeting.

POTENTIAL CHALLENGES: Performing this initial trial within the Mayo sites represents crucial evidence needed to determining the efficacy as well as safety and tolerability of GLP-1 receptor agonists in the

transplant population. Other trials are required to investigate the efficacy of these anti-diabetic medications in other solid organ transplant recipients such as liver transplant patients who also experience a high incidence of PTDM.

Determining significance in longitudinal changes in allograft protocol biopsies related to diabetic nephropathy in prediabetic patients is beyond the scope of this trial. However, this data based on samples collected per standing clinical protocols will provide innovative and generalizable knowledge related to the renal changes in prediabetics that has otherwise not been available. The preliminary data obtainable through the exploration of this specific aim will be of great value in broadening the scientific knowledge related to the relationship between prediabetes and diabetic nephropathy and determining key endpoints for designing future diabetes prevention trials in solid organ transplant recipients.

FUTURE DIRECTIONS: Given the pervasiveness of diabetes and prediabetes in kidney and other solid organ transplant recipients, well-designed clinical trials aimed at determining best therapy for preventing and improving treatment of diabetes after transplantation are desperately needed. The concomitant use of diabetogenic agents, including corticosteroids and calcineurin inhibitors, and the common weight gain experienced after transplant create a challenging environment to deal with these problems, but also emphasizes the importance of addressing these concerns. The completion of a prospective, feasibility trial will help obtain needed data about the safety, tolerability, and efficacy of GLP-1 receptor agonists in kidney transplant recipients and specifically Hispanic patients. Improved treatment of prediabetes and diabetes after kidney transplantation may portend the realization of goals to enhance long-term kidney graft outcomes, as well as improve the health and survival of these patients.

Specific Methods.

Prediabetes and diabetes are determined using standard serum blood glucose level determinations including: fasting serum glucose, 2 hour post serum glucose in an OGTT and HbA1c.

eGFR is based on serum creatinine levels using MDRD[48]

Light Microscopy

Light microscopy will be used to determine the percentage of (1) global glomerulosclerosis (GGS) involving >20% of the glomeruli (GGS; 0 = 0%, 1 = ≤20%, 2 = >20%); and (2) mesangial matrix expansion (or mesangial sclerosis, MS) as defined as mild (1), moderate (2) and severe (3) averaged over all of the glomeruli in each biopsy sample

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