

PERL
PREVENTING EARLY RENAL LOSS IN DIABETES

STUDY PROTOCOL

'A pilot study of fenofibrate to prevent kidney function loss in type 1 diabetes'

NCT04929379

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PROTOCOL SUMMARY

Study Title	A pilot study of fenofibrate to prevent kidney function loss in type 1 diabetes
Study Phase	Phase 2
Objectives	1. To define the nature of the acute decline in estimated GFR following initiation of fenofibrate treatment. 2. To generate further data on the long-term beneficial effects of fenofibrate on GFR decline in persons with T1D and DKD who are at high risk of GFR decline and ESKD. 3. To determine the effects of fenofibrate on biomarkers of increased risk of ESKD.
Study Design	Multicenter, double-blind, placebo-controlled, parallel-group randomized clinical trial
Participating Centers	Joslin Diabetes Center (Boston), University of Michigan (Ann Arbor)
Subject Population	40 T1D subjects.

Inclusion criteria:

1. Male or female T1D patients between 18 and 70 years of age, inclusive.
2. T1D continuously treated with insulin within one year from diagnosis. If the onset was after age 35, the presence of one or more of the following will also be required: **a.** documentation of the presence of circulating T1D-associated autoantibodies at diagnosis or at any other time; **b.** history of hospitalization for DKA; **c.** plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl)
3. Duration of T1D ≥ 8 years.
4. Diabetic kidney disease at high risk of progression to ESKD, defined as follows: PERL allopurinol study participants: iGFR or eGFR decline ≥3 ml/min/1.73 m^2/year during the trial and micro- or macro-albuminuria (AER=30-5000 mg/24 hr or ACR=30-5000 mg/g if not on RASB agents, or AER=18-5000 mg/24 hr or ACR 18-5000 mg/g range, if on RASB agents) on at least two occasions during or after the PERL allopurinol trial. All others: microalbuminuria (AER=100-5000 mg/24 hrs or ACR=100-5000 mg/g) on two occasions during the three years before and/or at screening;
5. Estimated GFR (eGFR) based on serum creatinine between 40 and 99.9 ml/min/1.73 m^2 at screening. The upper and the lower limits should be decreased by 1 ml/min/1.73 m^2 for each year over age 60 (with a lower limit of 35 ml/min/1.73m^2) and by 10 ml/min/1.73 m^2 for strict vegans.
6. Valid baseline (Visit 2) iGFR measurement.
7. Current treatment with RASB, unless contraindicated.
8. Willing and able to comply with schedule of events and protocol requirements, including written informed consent.

Exclusion criteria:

1. Renal transplant or dialysis.
2. Non-diabetic kidney disease.
3. Allergy to fibrates or iodine containing substances.
4. Current therapy with fibrates or other PPAR-α agonists.
5. Specific contraindications or indications for fibrates.
6. History of photosensitive skin rash or myositis.
7. Elevated blood pressure (SBP>150 and/or DBP >95 mmHg) at screening.
8. Persistent elevated unexplained blood creatinine phosphokinase level >3 times the upper limit of normal.
9. History of pancreatitis, deep vein thrombosis (DVT) or pulmonary embolism.
10. History of cholelithiasis unless gallbladder has been removed.
11. Cancer treatment (excluding non-melanoma skin cancer treated by excision)

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within two years of screening.
12. Current or past history of decompensated cirrhosis (defined as variceal bleeding, ascites, or hepatic encephalopathy and/or diagnosis of cirrhosis based on liver biopsy, imaging, or elastography and/or aspartate or alanine aminotransferase (AST or ALT) >2 times the upper limit of normal at screening and/or total bilirubin >1.3 times the upper limit of normal at screening (in the case of Gilbert syndrome, direct bilirubin >1.5 times the upper limit of normal at screening).
13. History of acquired immune deficiency syndrome or human immunodeficiency virus (HIV) infection.
14. Hemoglobin concentration <11 g/dL (males), <10 g/dL (females) or platelet count <100,000/mm^3 at screening.
15. Alcohol or drug abuse in the past 6 months.
16. Blood donation within 3 months of screening.
17. Breastfeeding, pregnancy, or unwillingness to be on contraception during the trial.
18. Poor mental function or any reasons to expect difficulty in complying with study requirements.
19. Serious medical problems other than diabetes, *e.g.* congestive heart failure, pulmonary insufficiency.
20. Participation in another interventional study.
21. Being incarcerated.

Study Duration	76 weeks of treatment followed by an 8-week drug wash-out. A screening visit will be followed by seven study visits (at -3 [baseline assessment], 0 [randomization], 8, 30, 52, 76, and 84 weeks) for the assessment of primary and secondary outcomes
Study Treatment, Dosage, and Route of Administration	145 mg oral fenofibrate daily for 76 weeks. Dosage is decreased to 48 mg daily if iGFR is or is estimated to be below 30 ml/min/1.73 m^2.
Efficacy Assessments	<u>Primary outcomes:</u> • Baseline-adjusted iGFR at 8 weeks after randomization (<u>Aim 1</u>) • Baseline-adjusted iGFR at the end of the drug-wash-out period (week 84) (<u>Aim 2</u>) • Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug-wash-out period (week 84) (<u>Aim 3</u>) <u>Secondary outcomes:</u> • Baseline-adjusted eGFR-SCr, eGFR-CysC, uAER, creatinine clearance, ERPF, renal hemodynamic indices (afferent and efferent arteriolar resistances, estimated glomerular hydrostatic pressure and filtration pressure) at 8 weeks after randomization (<u>Aim 1</u>) • Baseline-adjusted iGFR, eGFR-SCr, eGFR-CysC, and uAER at the end of treatment (week 76) (<u>Aim 2</u>) • Baseline-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the drug-wash-out period (week 84) (<u>Aim 2</u>) • Week 8-adjusted iGFR, eGFR-SCr, eGFR-CysC, and uAER at the end of treatment (week 76) (<u>Aim 2</u>) • eGFR-SCr and eGFR-CysC trajectories from week 8 to week 76 (<u>Aim 2</u>) • Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of treatment (week 76) (<u>Aim 3</u>) • Week 8-adjusted serum levels of biomarkers of increased ESKD risk at the end of treatment (week 76) (<u>Aim 3</u>)
Safety Assessment	Interim medical history, serum liver function tests, and serum creatine kinase at each study visit.
Statistical Methods	The majority of data analyses, including the primary analysis, will be performed according to an intention-to-treat approach. Differences between treatment

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	arms in the primary endpoints will be tested for significance by means of ANCOVA (Aims 1 and 3), linear models with correlated errors (Aim 2), and mixed-effect models (GFR and AER time trajectories in Aim 2).
Date of protocol	October 28, 2025
Version of protocol	10.0

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ABBREVIATIONS

AE: Adverse Event

ACE: Angiotensin Converting Enzyme

ACR: Albumin Creatinine Ratio

AER: Albumin Excretion Rate

ALT: Alanine Transaminase

ARB: Angiotensin Receptor Blocker

CBC: Complete Blood Count

CC: Coordinating Center

CKD: Chronic Kidney Disease

CRF: Case Report From

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

DMC: Drug Monitoring Committee

DN: Diabetic Nephropathy

DSMB: Data and Safety Monitoring Board

ESKD: End Stage Kidney Disease

GFR: Glomerular Filtration Rate

ITT: Intention to Treat

HbA1c: Glycated Hemoglobin

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

IRB: Institutional Review Board

MAP: Mean Arterial Pressure

PAH: Para-amino hippurate

PERL: Preventing Early Renal Function Loss in Diabetes Consortium

RAS: Renin Angiotensin System

RASB: Renin Angiotensin System Blocker

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SAE: Severe Adverse Event

SBP: Systolic Blood Pressure

SC: Steering Committee

SOP: Standard Operating Procedure

T1D: Type 1 Diabetes

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1. INTRODUCTION

1.1. The persisting problem of diabetic kidney disease.

Diabetic kidney disease (DKD) remains the leading cause of end-stage kidney disease (ESKD), with prevalence rates rising in parallel with the epidemic of diabetes worldwide.[1,2] The lifetime risk of DKD in persons with type 1 diabetes (T1D) has been estimated to be as high as 50-70%,[3] although risk may be lower in excellent care environments.[4] In addition to being at risk of ESKD, persons with T1D and DKD are also at a markedly increased risk of cardiovascular complications and premature mortality.[5] Intensive glucose control has been widely implemented to reduce the incidence of microalbuminuria after the Diabetes Control and Complications Trial (DCCT),[6] but longer follow-up has suggested that intensified glucose control delays but does not eliminate the risk of progression of DKD to ESKD.[7] In fact, ESKD annual incidence in persons with T1D in the US has been increasing, albeit delayed compared to earlier cohorts.[8] Although blood pressure control,[9,10] and more specifically, renin-angiotensin system inhibition[11-13] may slow the progression of relatively advanced DKD in some patients with T1D, evidence of glomerular filtration rate (GFR) preservation by these interventions at earlier stages is lacking.[14-17] SGLT2 inhibitors have recently emerged as new reno-protective drugs for ESKD prevention in T2D.[18,19] However, whether these new drugs can be safely used and are effective in T1D patients, especially those at high risk of DKD and ESKD because of chronically poor glycemic control, remains uncertain.

1.2. The quest for new treatments to prevent DKD in T1D: the PERL Consortium.

To seek new treatments to prevent diabetic kidney disease (DKD) and/or slow its progression to ESKD in T1D, we established a unique consortium of investigators from 16 academic centers in the US, Canada, and Denmark where large rosters of research committed T1D patients are available, and where there is long-standing expertise in the study of DKD and in the conduct of DKD clinical trials. Led by Drs. A. Doria and M. Mauer, the Consortium has been named **PERL** (**Preventing Early Renal Function Loss in Diabetes**) to emphasize its focus on intervening relatively early in the course of DKD in T1D, when renal damage can more easily slowed or arrested, and many additional years of useful renal function may be achieved. The first PERL study was a large 3-year clinical trial of serum uric acid reduction with allopurinol to limit glomerular rate decline (GFR) in 530 persons with T1D and early-to-moderate DKD. Despite sustained 35% serum uric acid reduction throughout the trial, there was no benefit of allopurinol on the rate of GFR decline or other kidney outcomes.[20,21] While obviously disappointed by these results, PERL is poised to leverage the expertise and infrastructure of the Allopurinol Study to continue the quest for novel interventions to prevent GFR decline in patients with T1D and early-to-moderate DKD.

1.3. Fenofibrate as a candidate intervention to slow GFR decline in early DKD in T1D.

The generic drug **fenofibrate** - an agonist of peroxisome proliferator–activated receptor-alpha (PPAR-α) used to treat dyslipidemia and prevent CVD – has surprisingly shown a beneficial effect on GFR decline among T2D individuals in the ACCORD and FIELD clinical trials.[22,23] Similar to other fibrates, the generic drug fenofibrate is an agonist of peroxisome proliferator–activated receptor-alpha (PPAR-α) - a transcription factor functioning as a master regulator of lipid homeostasis, energy metabolism, vascular inflammation, and cell differentiation.[24] PPAR-α activation reduces serum triglycerides, raises plasma high-density lipoprotein (HDL) cholesterol, and reduces systemic inflammation, with very limited side effects.[25] Despite these beneficial effects on lipid metabolism, fibrates are only modestly effective in reducing cardiovascular disease (CVD) events (a 10% risk reduction in a meta-analysis of 18 clinical trials).[26] Surprisingly, however, *post-hoc* analyses of some of these trials have shown a strong protective effect of fenofibrate on progression of diabetic retinopathy (a 30-40% risk reduction in the ACCORD and FIELD T2D populations),[27,28] apparently related to PPAR-□anti-inflammatory and anti-apoptotic actions[29] rather than its lipid-lowering effects. Based on this evidence, fenofibrate has been approved for the treatment of diabetic retinopathy in T2D in Australia. Importantly, ACCORD and FIELD have also shown **a beneficial effect of fenofibrate on GFR decline**.[22,23] This effect was initially masked by the acute increase in serum creatinine (SCr) caused by fenofibrate, resulting in an immediate 15-20% decrease in estimated GFR (eGFR) (**Fig. 1**).[30] However, after accounting for this acute effect, which was reversible and not associated with acute tubular damage,[31] subsequent eGFR decline was ~1.0 ml/min/1.73

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m^2/year slower with fenofibrate vs. placebo, potentially translating into a large long-term GFR benefit (**Fig. 1 and 2A**).[22,23] This was confirmed by a significantly higher eGFR in the fenofibrate group as compared to placebo after drug wash-out. [22,23] Also, a small study proposed that the initial eGFR decline with fenofibrate may not represent a true GFR decline,[32] suggesting that the GFR benefit may be substantially greater and become manifest earlier than the GFR trajectories estimated from SCr would indicate (see hypothetical trajectory depicted by the dashed line in **Fig. 1**). Consistent with the benefit on GFR decline, fenofibrate decreased albuminuria (**Fig. 2B**).[22,23] These clinical research data are further supported by reports of renal anti-fibrotic effects of fenofibrate in streptozotocin diabetic rats, apparently mediated by inhibition of the Wnt-signaling pathway resulting from PPAR-□activation.[33]

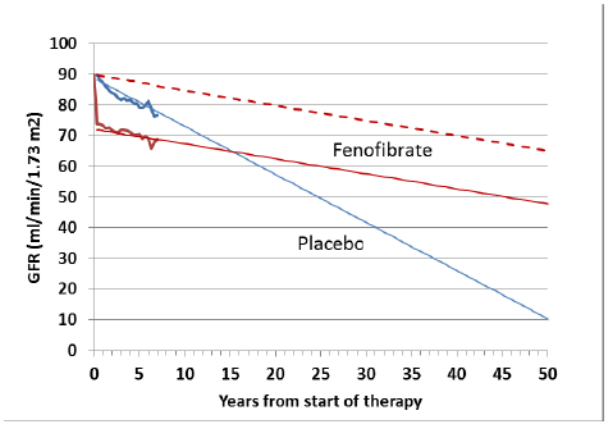


Fig. 1. Impact of fenofibrate on eGFR trajectories in ACCORD. Thick lines are eGFRs during the trial; thin lines are extrapolations based on the GFR slopes estimated during the trial. The dashed line is the GFR trajectory assuming that the acute GFR decline following fenofibrate treatment was an artifact.

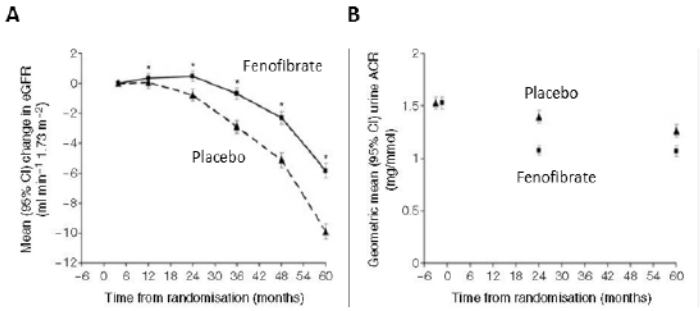


Fig 2. Impact of fenofibrate on kidney outcomes in FIELD. A. Change in eGFR from 4 months after randomization. **B.** ACR levels during the trial (Adapted from Davis et al., 2011).

2. STUDY OBJECTIVES

The FIELD and ACCORD findings suggesting a reno-protective effect of fenofibrate[22,23]raise the exciting possibility of using an inexpensive generic drug with an established excellent safety profile to prevent or slow GFR decline in persons with T1D, with the added benefits of slowing diabetic retinopathy and improving lipid profiles. However, these data were obtained through *post-hoc* analyses of T2D populations with clinical characteristics optimized for investigating fenofibrate effects on CVD complications. Thus, a clinical trial specifically designed to evaluate the effectiveness of this drug on GFR decline is needed in order to firmly establish a DKD indication for fenofibrate in persons with T1D. As a first step, we are conducting **a pilot study** to gather essential information for designing and planning a pivotal T1D DKD fenofibrate trial. Through this pilot study we intend to:

1. Define the nature of the acute effect of fenofibrate on kidney function. At this time, it remains unclear whether the acute reduction in eGFR observed with fenofibrate treatment is an artifact of fenofibrate-induced changes in creatinine production and/or renal tubular handling, or corresponds to an actual reduction in GFR (similar to what is observed with RASB or SGLT2 inhibitors). We intend to resolve this controversy, which has crucial implications for the design of DKD fenofibrate trials, by directly measuring GFR before and during fenofibrate treatment using plasma iohexol disappearance (iGFR) – a gold standard methodology with which the PERL sites are very experienced.

2. Generate further data on the longer-term effect of fenofibrate on GFR decline in persons with T1D and DKD who are at high risk of GFR decline and ESKD. The positive effects of fenofibrate suggested in FIELD and ACCORD were observed in individuals who were not selected for having DKD and who, if untreated, had a mean GFR decline barely above the physiological decline in kidney function due to aging. In order to seek support for a pivotal trial of fenofibrate for kidney

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outcomes, it is crucial to generate preliminary data on the effectiveness and safety of this drug in T1D persons selected for high DKD risk who are rapidly progressing towards ESKD.

3. Determine the effects of fenofibrate on biomarkers of increased risk of fast GFR decline. We will evaluate the impact of fenofibrate on an array of 21 biomarkers identified by the Joslin group as predictors of high ESKD risk in person with T1D. A salutary effect of fenofibrate on one or more of these biomarkers will corroborate any benefit of this drug on reducing GFR loss observed in **Aim 2**.

3. STUDY DESIGN

This pilot study will be a two-center, double-blind, placebo-controlled, parallel-group randomized clinical trial investigating the effect of fenofibrate on kidney function in individuals with T1D at high risk of GFR decline and ESKD. Participants (n=40) will be randomized 1:1 to oral fenofibrate (145 daily, decreased to 48 mg daily if the GFR falls below 30 ml/min/1.73 m^2) or placebo for 76 weeks followed by an 8-week drug wash-out (**Fig. 3**). After a screening visit, eligible individuals will undergo seven "In-person" and 1 "Phone" study visits (at -3 [baseline assessment], V2]), 0 [randomization, V3], 8 [V4], 30 [V5], 52 [V6], 76 [V7], and 84 weeks [V8]) for the assessment of GFR measured by iohexol plasma disappearance (iGFR) (V2, V4, V7, V8), GFR estimated by serum creatinine and cystatin C (eGFR-SCr and eGFR-CysC) (all visits except V3), creatinine clearance (V2 and V4), estimated renal plasma flow (ERPF) and hemodynamic parameters (V2 and V4), urinary albumin excretion rate (uAER) (all visits except V3), and safety parameters (all visits except V3), along with biospecimen banking for biomarker studies (V2, V4, V7 and V8).

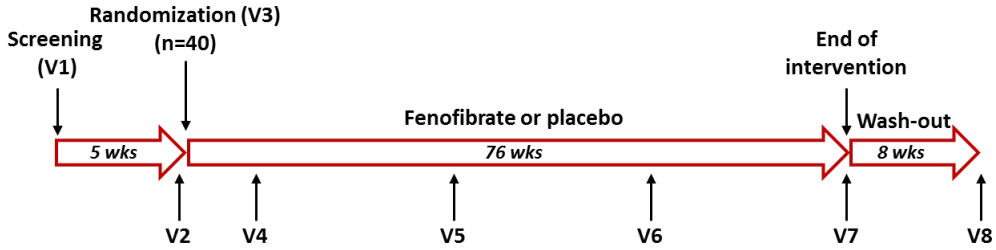


Fig. 3. Schematic representation of the study design.

4. STUDY ORGANIZATION

The study will be conducted at two PERL sites (Joslin Diabetes Center and U. of Michigan), selected for relatively high numbers of eligible participants based on former PERL participation as well as large numbers of other suitable patients. Bio-specimens will be analyzed and stored at the PERL Central Laboratory at the University of Minnesota. Clinical and Laboratory Data will be stored at the study Coordinating Center at the Joslin Diabetes Center and analyzed by the PERL Statistical Team at the University of Michigan (**Fig. 4**).

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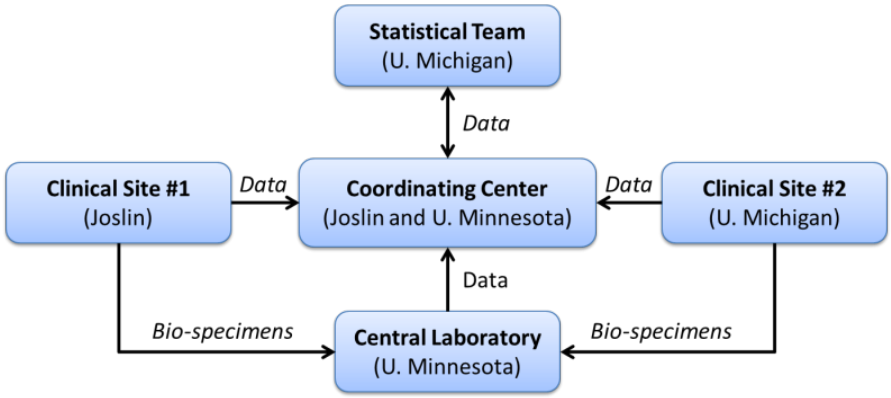


Fig. 4. Study organization.

5. SUBJECT SELECTION

5.1. Inclusion Criteria

1. Male or female T1D patients between 18 and 70 years of age, inclusive.
2. T1D continuously treated with insulin within one year from diagnosis. If the onset was after age 35, documentation of the presence of one or more of the following will also be required:
   - **a.** documentation of the presence of circulating T1D-associated autoantibodies at diagnosis or at any other time
   - **b.** history of hospitalization for DKA
   - **c.** plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl)
3. Duration of T1D ≥ 8 years.
4. Diabetic kidney disease at high risk of ESKD progression, defined as: PERL allopurinol study participants: iGFR or eGFR decline ≥3 ml/min/1.73 m^2/year during the PERL allopurinol trial and micro- or macro-albuminuria (AER=30-5000 mg/24 hr or ACR=30-5000 mg/g if not on RASB agents, or AER=18-5000 mg/24 hr or ACR 18-5000 mg/g range, if on RASB agents) on at least two occasions during or after the trial or after the trial. All other subjects: microalbuminuria (AER=100-5000 mg/24 hrs or ACR=100-5000 mg/g) on two occasions during the three years before screening and/or at screening.
5. Estimated GFR (eGFR) based on serum creatinine between 40 and 99.9 ml/min/1.73 m^2 at screening. The upper and the lower limits should be decreased by 1 ml/min/1.73 m^2 for each year over age 60 (with a lower limit of 35 ml/min/1.73m^2) and by 10 ml/min/1.73 m^2 for strict vegans.
6. Valid baseline (Visit 2) iGFR measurement.
7. Current treatment with RASB, unless contraindicated,
8. Willing and able to comply with schedule of events and protocol requirements, including written informed consent.

5.2. Exclusion Criteria

1. Renal transplant or dialysis.
2. Non-diabetic kidney disease.
3. Allergy to fibrates or iodine containing substances.

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4. Current therapy with fibrates or other PPAR-α agonists.
5. Specific contraindications or indications for fibrates.
6. History of photosensitive skin rash or myositis.
7. Elevated blood pressure (SBP>150 and/or DBP >95 mmHg) at screening.
8. Persistent elevated unexplained blood creatinine phosphokinase level >3 times the upper limit of normal.
9. History of pancreatitis, deep vein thrombosis (DVT) or pulmonary embolism;
10. History of cholelithiasis unless gallbladder has been removed.
11. Cancer treatment (excluding non-melanoma skin cancer treated by excision) within two years of screening.
12. Current or past history of decompensated cirrhosis (defined as variceal bleeding, ascites, or hepatic encephalopathy and/or diagnosis of cirrhosis based on liver biopsy, imaging, or elastography and/or aspartate or alanine aminotransferase (AST or ALT) >2 times the upper limit of normal at screening and/or total bilirubin >1.3 times the upper limit of normal at screening (in the case of Gilbert syndrome, direct bilirubin >1.5 times the upper limit of normal at screening).
13. History of acquired immune deficiency syndrome or human immunodeficiency virus (HIV) infection.
14. Hemoglobin concentration <11 g/dL (males), <10 g/dL (females) or platelet count <100,000/mm^3 at screening;
15. Alcohol or drug abuse in the past 6 months.
16. Blood donation within 3 months of screening.
17. Breastfeeding, pregnancy, or unwillingness to be on contraception during the trial.
18. Poor mental function or any reasons to expect patient difficulty in complying with study requirements.
19. Serious medical problems other than diabetes, *e.g.* congestive heart failure, pulmonary insufficiency;
20. Participation in another interventional study.
21. Being incarcerated.

5.3. Rationale of inclusion and exclusion criteria

This study focuses on patients with T1D due to the lack of novel reno-protective interventions for this type of diabetes. The requirement for a minimum T1D duration of 8 years reduces inclusion of individuals with non-diabetic kidney disease. The requirement for an eGFR in the 40-99.9 ml/min/1.73 m^2 range reflects the PERL consortium's goal of intervening relatively early DKD in T1D when renal damage can most likely be slowed or arrested and many additional years of useful renal function may be achieved with an effective intervention. A minimum eGFR of 40 ml/min/1.73 m^2 also decreases the possibility that the GFR approaches ESKD levels, prompting discontinuation of the study drug if an acute eGFR decrease in response to fenofibrate represents true, albeit reversible, GFR reduction. Inclusion criterion #5 enriches the study population with participants at high risk of kidney function loss, this key to the success of any chronic kidney disease (CKD) clinical trial, especially in a relatively short-term pilot study with limited enrollment. This is addressed through two complementary approaches: 1. enrolling participants included in initial PERL trial because of a history of micro- or macro-albuminuria who experienced a rate of iGFR loss ≥3 ml/min/1.73 m^2/year during follow-up; and 2. complementing this readily available pool of candidates with T1D patients outside the PERL allopurinol cohort with

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macroalbuminuria – a well-established risk factor for kidney function loss, which was associated in the PERL allopurinol trial with a median iGFR decline of 4.3 ml/min/1.73 m^2/year *vs.* 1.8 ml/min/1.73 m^2/year in the rest of the cohort. The RASB requirement reflects the need to provide standard of care. The exclusion criteria are mainly aimed at excluding non-diabetic kidney disease and maximizing safety.

5.4. Prohibited Medications and Restrictions

- Other PPAR-α agonists
- SGLT2 inhibitors
- Warfarin
- Colchicine
- Sulphonylureas
- Raltegravir or other HIV drugs
- Cyclosporine
- Any other drug for which there is evidence of interaction with fenofibrate

6. STUDY TREATMENTS

6.1. Study Drug Description, Dosage, Administration, and Accountability

6.1.1. Description

All eligible subjects who agree to participate will be **randomized to receive placebo or fenofibrate** – a fibric acid derivative marketed since 1975 to lower serum triglycerides and increase HDL cholesterol in patients with atherogenic dyslipidemia by activating PPAR-α - a transcriptional regulator of genes involved in lipid metabolism.[34] Since PPAR-α has pleiotropic effects, fenofibrate also has anti-inflammatory, anti-apoptotic, and anti-fibrotic actions independent of its lipid-lowering properties.[24,25] Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid, which mostly undergoes renal elimination with a half-life of 20 hours, allowing once daily dosing. Fenofibrate has an excellent safety profile (see **13. Protection of Human Subjects**).

6.1.2. Dosage

Participants randomized to fenofibrate will take 145 mg per day as a single tablet of a generic formulation. Dosage will be decreased to 48 mg daily if the iGFR falls below 30 ml/min/1.73 m^2 (the iGFR at 8 weeks will be directly measured; the iGFR at 30 and 52 weeks will be extrapolated from the 8-week iGFR applying the same percent changes from 8 weeks to those time-points as those observed for eGFR-SCr calculated from local creatinine measurements. While higher GFR thresholds are often used for reducing fenofibrate dosage, the FIELD clinical trial unequivocally demonstrated the safety of the full fenofibrate dose with GFR levels as low as 30 ml/min/1.73 m^2.[35] In that trial, 9,795 T2D subjects aged 50-75 years, were treated for 5 years with a fixed fenofibrate dose of 200 mg daily or placebo. No significant increase in ESKD or other serious adverse events was observed in the fenofibrate vs. the placebo arm among the subset of these subjects (n=519) who had eGFR in the 30-59 ml/min/1.73 m^2 range as compared to subjects with more preserved GFR. In fact, the subjects in this lower eGFR range benefited most from fenofibrate treatment in term of CVD outcomes.[35]

6.1.3. Randomization Procedures

Randomization (1:1) to fenofibrate or placebo will be stratified by center using permuted blocks, with block size known only to the Coordinating Center (CC). Clinical sites will then send a study medication request to the study pharmacy, including the participant's address, so that the medication can be directly mailed to the participant. Clinical sites will not have access to the drug assignment. This will be directly communicated or made electronically available to the pharmacy by the CC (see **6.1.4. Masking Procedures** below).

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6.1.4. Masking Procedures

Study participants, the investigators and research staff at the Clinical Sites, and one of the PERL PIs (Dr. Mauer) will be masked to treatment assignment whereas the CC staff (including the other PI - Dr. Doria), the pharmacy personnel, and the biostatistical team will have access to this information. The personnel at the Clinical Sites will be provided with telephone numbers to contact the CC and/or Pharmacy personnel having access to the treatment assignment on a 24-7 basis, should unmasking of a study participant's treatment allocation be necessary because of a medical emergency. If unmasking occurs, the circumstances that led to it will be reviewed and reported.

6.1.5. Dispensing Procedures

Dispensing of study medication will be handled by the study pharmacy, Belmar, Lakewood, CO. In the days following the randomization visit (V3) or a treatment period study visit (V4-V7) the clinical site will fax a study medication request to the study pharmacy. The medication request will include the participant's address so that the medication can be directly mailed to the participant. Upon receipt of the study medication request from the clinical site, the study pharmacy will access information on whether the participant has been randomized to active or placebo and participant's GFR so that the dose appropriate to the participant's kidney function can be dispensed according to the study protocol (145 mg if GFR≥30 ml/min/1.73 m2, 48 mg if GFR<30 ml/min/1.73 m2), by accessing a dedicated database made available by the Coordinating Center. The study med (active or placebo) will then be shipped to participants by mail. Once the new batch of medication is received, participants will be directed to immediately return via a pre-paid postage envelope any remaining study medication from the previous batch to the study center for drug accounting and adherence assessment. Alternatively, they may set aside the remaining pills from the previous batch and bring them next time they come to the clinic.

6.1.6. Replacements

Participants that withdraw consent before undergoing Visit 2 or who become ineligible at Visit 2 (e.g., because a valid iGFR cannot be obtained) before randomization will be replaced until the target number of randomized study participants is reached. Participants that withdraw consent from the study or discontinue the study drug after randomization will not be replaced.

6.1.7. Discontinuation of study drug

6.1.7.1. Reasons for discontinuation

The study drug will be *temporarily* discontinued if a participant:

- Has clinically significant persistent changes from baseline based on laboratory safety assessment results (the response to discontinuation will be monitored to assess whether the drug can be re-instituted, see next paragraph on permanent discontinuations).
- Requires treatment with fibrates or with other medications that make fenofibrate contraindicated (see 5.5.2).
- Becomes pregnant or breastfeeding (see 6.1.7.2).
- Develops an AE that is deemed to be related or possibly related to the study drug.

Whenever the reason for temporary discontinuation of the study drug ceases to exist, the study medication will be resumed with the consensus of the Drug Monitoring Committee.

The study drug will be *permanently* discontinued if a participant:

- Experiences an SAE related to the study drug or an intolerable AE such as a persistent allergy.
- Has clinically significant persistent changes from baseline based on laboratory safety assessment results which do not respond to temporary 2-week discontinuation of study drug and re-institution of drug at ½ of the initial dose.

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- Develops end-stage kidney disease (confirmed eGFR ≤15 ml/min/1.73 m^2 in the absence of acute kidney injury [AKI], institution of chronic dialysis treatment or kidney transplantation). If any of these renal function changes prove to be temporary, the study medication could be resumed as described above with the consensus of the drug monitoring committee.

6.1.7.2. Handling of study drug discontinuations

- Date and reason for drug discontinuation will be recorded on the relevant Case Report Form.
- All study discontinuations decided by a clinical site will have to be reviewed and approved by the Drug Monitoring Committee within 10 days from their start.
- If the study drug is discontinued due to treatment with medications that make fenofibrate contraindicated or due to pregnancy/breastfeeding, the possibility of resuming the study drug will be evaluated by the Drug Monitoring Committee once those medications have been discontinued or pregnancy/breastfeeding has ended.
- If the study drug is discontinued due to an AE reported as related or possibly related to the study drug, the possibility of resuming the study drug will be evaluated by the Drug Monitoring Committee once the AE has resolved (e.g. if cholelithiasis is reported as an AE and the gall bladder has been removed, the DMC may approve resumption of study drug).
- If the study drug is temporarily discontinued and then re-instated, the end-date of the intervention will remain the same as if the study drug had not been discontinued. All visits will be carried out as scheduled while the study drug is temporarily discontinued.
- Unless a participant withdraws consent all participants that are permanently discontinued from study drug or who discontinue study medication on their own will be followed for the full study period (i.e., 84 weeks, including the washout period) and all data will be collected as scheduled.
- If a participant reaches ESKD as defined above, he/she will be permanently discontinued from the study and invited to participate in a study close-out call or visit to be held within three months from the occurrence of ESKD. Data collection at this call or visit will be limited to standard adverse event reporting. In addition, sites should continue to contact participants who have reached end-stage renal disease to determine their final status at 84 weeks after randomization. Major attempts will be made to schedule an end-of-study assessment for all participants who are lost to follow-up during the course of the study.

6.1.8. Adherence and accountability

Skills will be taught and reinforced at each visit regarding scheduling and administration of pills at home and while traveling. Methods (*e.g.* record-keeping) will be taught to help participants monitor tablet usage and enhance compliance. To complement the regular compliance interventions at the scheduled visits, study information and motivational materials (postcards, newsletters, etc.) will be mailed. In addition, at midpoint between clinic visits, participants will be phoned by the clinic staff to review pill-taking. Patients will be provided with random but known numbers of excess medications, providing extras in case of pill loss. Adherence will be monitored by instructing participants to expect extra pills and to mail the pill bottles or the blister packs with the tablets remaining from the previous prescription to the study center upon receipt of a new batch of tablets. The number of extra pills included in each supply of medications will be decided by the pharmacist, who will keep a record of it and will transmit this information to the Study Site. Personnel at the Study Site will enter this information in the appropriate electronic Case Report Form along with the expected number of pills used during the period covered by the supply and the number of unused pills returned by the participant. These data will be used to analyze compliance. If poor adherence is noticed, measures will be taken to increase compliance, such as explaining the purpose of the study again, providing pill reminders, and more frequently contacting the study subject by phone. Participants at each visit will be asked about their perceived compliance and about any difficulties with taking the study medications, but the individualized strategies to improve compliance will not be openly linked to the pill counts, i.e. participants will not be

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informed of the results of pill counting. Participants showing poor compliance will not be withdrawn from the study.

7. STUDY OUTCOMES

7.1. Primary outcomes

Aim 1

- Baseline-adjusted iGFR at 8 weeks after randomization.

Aim 2

- Baseline-adjusted iGFR at the end of the drug-wash-out period (week 84).

Aim 3

- Baseline-adjusted serum levels of biomarkers of increased ESKD risk of the drug-wash-out period (week 84).

7.2. Secondary outcomes

Aim 1

- Baseline-adjusted eGFR-SCr, eGFR-CysC, uAER, creatinine clearance, ERPF, renal hemodynamic indices (afferent and efferent arteriolar resistances, estimated glomerular hydrostatic pressure and filtration pressure) at 8 weeks after randomization.

Aim 2

- Baseline-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the drug-wash-out period (week 84).
- Baseline-adjusted iGFR, eGFR-SCr, eGFR-CysC, and uAER at the end of treatment (week 76)
- Week 8-adjusted iGFR, GFR-SCr, eGFR-CysC, and uAER at the end of treatment (week 76).
- eGFR-SCr, and eGFR-CysC trajectories from week 8 to week 76.

Aim 3

- Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of treatment (week 76).
- Week 8-adjusted biomarkers of increased ESKD risk at the end of treatment (week 76).

8. STUDY PROCEDURES

8.1. Schedule of Events

Table 1 outlines the schedule of events for this study. After a screening (Visit 1), eligible participants will undergo a baseline visit (Visit 2) where they will have the complete battery of kidney function tests as described below. Subjects for whom a valid iGFR can be obtained will be randomized to fenofibrate or placebo (Visit 3). They will then be examined after 8 weeks (Visit 4) to assess the acute effect of fenofibrate on all kidney function parameters (**Aim 1**). Subsequently, participants will undergo 3 follow-up visits (Visits 5, 6, and 7) at ~5-month intervals. Treatment will be stopped at Visit 7 (week 76). The last study visit (Visit 8) will occur 8-weeks after that (at week 84) to examine the durability of the effects of fenofibrate on kidney function after drug wash-out (**Aim 2**). Visit 1 will be considered as Time 0 for scheduling Visit 2, Visit 2 as Time 0 for scheduling Visit 3, Visit 3 as Time 0 for scheduling Visits 4-7, and Visit 7 as Time 0 for scheduling Visit 8. Visit 2 will be carried out within 1 week before and 8 weeks after its scheduled visit date. All other visits will be carried out within 1 week before and two weeks after their scheduled dates. Additional blood or urine samples may be required in between visits if clinically significant changes are observed in blood or urine measurements that need to be confirmed or otherwise monitored. Laboratory safety tests (CBC, serum creatinine, K^+, ALT, CK, and pregnancy tests in women) as well as urinary ACR and serum creatinine measurements to determine eligibility will be performed by local laboratories. Outcome variables (plasma iohexol, serum and urine creatinine and cystatin C, urinary AER), and HbA1c will be measured by the PERL Central Laboratory at the University of Minnesota,

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directed by Dr. Amy Karger. Para-amino hippurate (PAH) will be measured in Dr. Davor Brinc's laboratory at University Health Network in Toronto, Canada.

8.1.1 Abbreviated protocol (Visits 1-4)

Due to the projected funding timeline and the need to complete all study visits by March 14, 2025, participants joining the study on or after September 1, 2023 will be enrolled in a shortened protocol. This protocol will consist of all study visits and procedures currently scheduled through study visit 4 and will be aimed at completing the primary outcome of Aim 1 - baseline-adjusted iGFR at 8 weeks after randomization, for which the study was powered. The schedule of events and visit timeline will remain the same as outlined for the standard protocol, with study completion occurring once study visit 4 has been completed with a successful iGFR measure. The physical exam normally occurring at visit 7 and the ECG normally occurring at visit 8 will both be completed at visit 4. Total duration of participation will be between 13 weeks and 25 weeks, depending on when in the window visits occur.

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Table 1. Schedule of events.

Week	-5	-3		0	8		30	52	76	84
Visit	V1	V2	V2a†	V3	V4	V4a†	V5	V6	V7	V8
Type of visit*	P/R	P	P	C	P	P	P/R	P/R	P	P
EVENT	SCREEN	BASELINE	BASELINE	RANDO	TREATMENT Fenofibrate or Placebo	TREATMENT Fenofibrate or Placebo				Wash-out EOS
Informed Consent	X									
Demographics	X									
Initial medical history		X								
Interval medical history		X	(X)		X	(X)	X	X	X	X
Concomitant medications	X	X	(X)		X	(X)	X	X	X	X
Blood pressure	X	X	(X)		X	(X)	X	X	X	X
ECG¶		X	(X)		(X)	(X)				X
Physical exam¶		X	(X)		(X)	(X)			X	
Eligiblity	X			X						
Randomization				X						
RAS and BP Med log	X	X	(X)		X	(X)	X	X	X	X
iGFR procedure		X	(X)		X	(X)			X	X
ERPF and kidney hemodynamics		X	(X)		X	(X)			X	X
Creatinine clearance		X	(X)		X	(X)			X	X
Study drug prescription				X			X	X		
Study drug compliance					X	(X)	X	X	X	
Protocol Deviations	X	X	(X)		X	(X)	X	X	X	X
Adverse Events	X	X	(X)		X	(X)	X	X	X	X
CENTRAL LAB										
Serum creatinine and cystatin C		X	(X)		X	(X)	X	X	X	X
Urine ACR/AER		X	(X)		X	(X)			X	X
Tot Chol, HDL Chol, TG		X	(X)		X	(X)	X	X	X	X
Iohexol for iGFR		X	(X)		X	(X)			X	X
PAH		X	(X)		X	(X)				
Total plasma proteins		X	(X)		X	(X)				
Biomarkers of increased ESKD risk		X	(X)		X	(X)			X	X
Biobank		X	(X)		X	(X)			X	X
LOCAL LAB										
Pregnancy test serum HCG	X	X	(X)		X	(X)	X	X	X	X
Pregnancy test urine dip stick		X	(X)		X	(X)			X	X
Multistix Analysis of urine		X	(X)			(X)			X	X
HbA1c	X				X	(X)	X	X	X	X
Serum creatinine	X	X	(X)		X	(X)	X	X	X	X
Urine ACR	X									
NA/K‡	X	X	(X)		X	(X)	(X)	(X)	(X)	(X)
LFT§	X	X	(X)		X	(X)	X	X	X	X
CBC	X	X	(X)		X	(X)	X	X	X	X
CPK	X	X	(X)		X	(X)	X	X	X	X

*Type of visit: P: In-Person Visit Required; C: Phone call; P/R: In-Person or Remote Visit

†If a valid iGFR cannot be obtained at V2 or V4, the visit procedures can be carried out at a repeat Visit (V2a/V4a)

‡If available in the EHR in the previous six months, can be skipped

§Liver Function Tests (LFT) include, but are not limited to ALT, AP, and Bilirubin

¶Participants enrolled on or after September 1, 2023 will complete a shortened protocol (V1-V4). ECG and physical exam normally occuring during V7 and V8 will occur at V4

Note: (X) indicates an optional assessment

8.2. Location of study visits

Study visits will generally be conducted at the Study Sites or their Satellites (hereby referred to as "In-Person Visits"), except for V3, which will always be conducted over the phone. If a participant lives far from a study site or satellite, or travel impediments are present, visits V1, V5, and V6 may be conducted remotely (Visit 2 and all the visits including an iohexol-GFR measurement, i.e., V4, V7, and V8, will always be "In-person"). In the case of remote visits, study procedures that do not require physical interactions (e.g., collection of medical history, compliance issues) will be carried out over the phone or other media such as Skype (otherwise referred to as "Phone Visits"). Blood draws and urine collections scheduled at the time of Phone Visits will be performed at local facilities close to where participants live (hereby referred to as "Remote Biospecimen Collections"). A Phone Visit and a Remote Biospecimen Collection will be both required for all Remote Study Visit. Phone Visits and Remote Biospecimen Collections will be conducted according to the following protocol:

Phone Visits

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- Phone Visits will be scheduled based on the same calendar and time-windows used for In-Person Visits (see paragraph 8.1 and Table 1).
- All Phone Visits will be carried out by the same trained study personnel and by the same standards as the In-Person Visits.
- If Visit 1 is a Phone Visit, a copy of the informed consent form (ICF) will be mailed, faxed, or sent electronically to the study subject before the visit. After reviewing the ICF content with the study personnel over the phone/Skype, subjects agreeing to participate in the study will be invited to mail, fax, or electronically send a signed copy of the ICF back to the study site. Phone Visit 1 and any other study activity will take place only after the signed ICF has been received by the study site.
- Study procedures that may be carried out during Phone Visits include:
    - Collection of demographic data.
    - Collection of medical history.
    - Collection of family history.
    - Review of concomitant medications.
    - Evaluation of eligibility.
    - Randomization.
    - Review of RASB medication and BP control.
    - Study drug prescription and instructions.
    - Review of study drug compliance.
    - Review of adverse events.
    - Any other study procedure that can be carried out by phone.
- Study procedures will be carried out according to the same protocol as the corresponding In-Person Visits and as described in the Manual of Operations.
- All study materials that would be provided to participants at In-Person Visits (e.g., urine collection instructions, urine containers, study drug instruction, BP monitoring logs) will be sent to participants right after the Phone Visit. In addition, specific instructions will be provided for presentation to the local lab for specimen collection, handling and tube labeling for specimens requiring shipment to the Study Site or Central lab. Pre-addressed shipping containers will also be provided.
- Following a Phone Visit, participants may be invited to an In-Person Visit at the Study Site, at their PCP's office, or at other local healthcare facilities if procedures that require physical interactions are deemed necessary (*e.g.,* BP measurement to confirm the self-report of elevated BP values, physical exam to confirm an AE). Sites for remote in-person visits will be chosen by the Study Site based on the participant's preference, logistic and financial considerations, and site's qualifications. Study personnel will discuss study requirements with the remote site health providers and operators who will also be provided with written instructions on how to carry out the procedures that will be conducted at their locations. All results will be reported to the Study Site by the remote staff.

<u>Remote Biospecimen Collections</u>

- Local sites for Remote Biospecimen Collections will be chosen by the Study Site based on the participant's preference, logistic and financial considerations, and site's qualifications.
- Specific written instructions will be provided for presentation to the local sites for collection, handling and tube labeling and labels for specimens requiring shipment to the Study Site or Central Laboratory. Pre-addressed shipping containers will also be provided along with an inventory sheet for faxing to the Study Site or Central Laboratory and inclusion with the shipment.

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- Blood samples for local lab tests (serum creatinine, NA, K, and ALT, AP, Bilirubin, CBC, HbA1c, and pregnancy tests) will be processed and analyzed at the facilities where samples are collected or shipped to commercial laboratories or to the Central Laboratory for testing. Results will be transmitted to the Study Site by fax or other secure methods.
- Blood and urine samples for central lab tests (serum creatinine, Cystatin C, HbA1c, Tot cholesterol, HDL cholesterol, triglycerides, and urinary ACR and AER) will be mailed to the Central Lab or to the Study Site where they will be processed, aliquoted, and forwarded to the Central Lab. Blood tubes and urine containers will be provided by the Study Site.

8.3. Screening (Visit 1)

Subjects who have a confirmed history of micro- or macroalbuminuria from the PERL allopurinol study or have a history of macroalbuminuria (as defined in Section 5.1) during the preceding two years as documented in their medical records will not need to bring urine sample to Visit 1. Subjects with incomplete or no previous evidence of micro- or macroalbuminuria or have unknown albuminuria status, will be mailed one or two containers before Visit 1 along with instructions for collecting urine samples from first morning voids in the days preceding the visit and for transporting these samples to the visit to assess their albuminuria status. During **Visit 1**, subjects will undergo the following procedures:

- Obtain written informed consent.
- Collect demographics
- Obtain past medical history
- Review prior and concomitant medications, with special emphasis on RASB and BP therapy
- Measure height, weight and vital signs.
- Collect samples for clinical laboratory assessment.
- Perform pregnancy test in women of childbearing potential.
- Provide a container and instructions for an overnight urine collection to be made immediately before Visit 2 if subject qualifies for the study.
- Upon receipt of laboratory measurements, confirm that inclusion/exclusion criteria are met.

The Screening Visit can be repeated after 4 weeks if the circumstances that led to the exclusion of a participant are deemed to have possibly changed.

8.4. Enrollment in the Study and Baseline Assessment (Visit 2)

After 2 weeks, participants undergo **Visit 2** with the following procedures:

- Obtain interval medical history
- Review concomitant medications and AEs
- Review RASB and BP therapy
- Measure height, weight and vital signs.
- Conduct a physical exam
- Perform ECG
- Collect samples for clinical laboratory assessments and for storage of serum, plasma, urine, DNA, and RNA for biomarker studies according to the schedule outlined in Figure 1.
- Perform pregnancy test in women of childbearing potential.
- Provide a container and instructions for an overnight urine collection before the Visit 4.

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- Measure iohexol GFR
- Measure ERPF and kidney hemodynamics (PAH)
- Review how the study medication should be taken and the potential side effects.

If, according to standard quality control measures (outlined is Section 8.8), a valid iGFR cannot be obtained at Visit 2, a repeat Visit 2 (V2a) can occur within 6 weeks of the original Visit 2. In this event, procedures carried out at Visit 2, including iGFR measure, will be carried out at Visit 2a.

8.5. Randomization (Visit 3)

After Visit 2, eligibility will be re-assessed based on whether a valid baseline iGFR measurement is available.

- Eligible participants will be telephoned by the study coordinator to discuss how the study medication should be taken and the potential side effects.
- Immediately after the phone call, the participants will be randomized.
- Immediately after randomization the first batch of study medication will be mailed to the participant by the research pharmacy along with written instructions on how to take it. Participants will be instructed to notify the study personnel by phone and start taking the study medication as soon as they receive it.
- If a valid iGFR measurement cannot be obtained, he/she will be discontinued from the study prior to randomization.

8.6. Treatment Period (Visits 4, 5 and 6)

During the treatment period, the following procedures will be completed at each visit for each participant:

- Obtain interval medical history
- Review concomitant medications and AEs
- Review RASB and BP therapy
- Measure height, weight and vital signs.
- Collect unused study medication, if not already sent by mail, and document adherence and drug exposure.
- Collect samples for clinical laboratory assessments and for storage of serum, plasma, urine, DNA, and RNA for biomarker studies according to the schedule outlined in Figure 1.
- Perform pregnancy test in women of childbearing potential.
- Provide a container and instructions for an overnight urine collection before the next visit.
- Measure iohexol GFR (Visit 4 only)
- Measure ERPF and kidney hemodynamics (PAH) (Visit 4 only)
- Review how the study medication should be taken and the potential side effects.

For participants enrolled in Abbreviated protocol, the following procedures will be completed at Visit 4;

- ECG
- Physical Exam

In the days immediately after each visit, upon completion of serum creatinine measurements, participants will receive a new batch of study medication by mail from the research pharmacy. Upon receipt of the new tablets, participants will be instructed to immediately mail the pill bottles or the blister

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packs with the tablets remaining from the previous prescription to the study center for drug accounting and adherence assessment (see 6.1.8). A pre-stamped and addressed envelope will be provided to participants for this purpose.

At some sites the study medication may be dispensed directly to the study participant at a relevant in person study visit or by mail from the site following a relevant in-person or phone study visit.

For participants enrolled in the abbreviated protocol, visit 4 will be the final study visit. Participants will not receive additional study medication after the visit. Participants will be directed to continue taking study medication until a valid iGFR has been received. If the iGFR measurement is invalid, the iGFR can be repeated on a separate occasion up to 6 weeks from the study visit. Once a valid iGFR measure has been received, study participants will be directed to return any unused study medication to the study center if they did not already bring the unused study medication at the visit

8.7. End of Intervention (Visit 7)

At the end of the treatment period (Visit 7), the following procedures will be completed for each participant:

- Obtain interval medical history
- Review concomitant medications and AEs
- Review RASB and BP therapy
- Measure height, weight and vital signs.
- Conduct a physical exam
- Collect unused study medication, if not already sent by mail, and document adherence
- Collect samples for clinical laboratory assessments and for storage of serum, plasma, urine, DNA, and RNA for biomarker studies according to the schedule outlined in Figure 1.
- Perform pregnancy test in women of childbearing potential.
- Provide a container and instructions for an overnight urine collection before the next visit.
- Measure iohexol GFR

Participants will be instructed to stop taking the study medication and to mail the pill bottles or the blister packs with the tablets remaining from the last prescription to the study center if they did not already bring the unused study medication at the visit. The importance of coming back in 8 weeks for the closing visit (Visit 8) will be emphasized.

8.8. End of Wash-out Period (Visit 8)

After the end of the treatment period, participants will enter an 8-week wash-out period at the end of which the following procedures will be completed:

- Obtain interval medical history
- Review concomitant medications and AEs
- Review RASB and BP therapy
- Measure height, weight and vital signs.
- Perform ECG
- Collect samples for clinical laboratory assessments and for storage of serum, plasma, urine, DNA, and RNA for biomarker studies according to the schedule outlined in Figure 1.
- Perform pregnancy test in women of childbearing potential.

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- Measure iohexol GFR

8.9. Iohexol GFR (iGFR) measurement

Plasma iohexol disappearance provides accurate and reproducible GFR measurements.[36,37] It is highly correlated with inulin clearance (the gold standard for measuring GFR)[38] and is a safe, cost-effective method to test hundreds of patients enrolled in multicenter clinical trials with GFR as the primary outcome,[15] based upon the requirement for substantially fewer participants to acquire the needed study statistical power using this more sensitive estimate of GFR change.[39] The method consists of injecting a 5 mL bolus of Iohexol (Omnipaque, 300 mg iodine/mL) and drawing blood samples at baseline and 120, 150, 180, 210, and 240 minutes after the injection. Plasma iohexol levels, measured by HPLC, are used to calculate the plasma clearance of iohexol (Cl=Dose/AUC, where AUC is the area under the plasma concentration time curve), which after appropriate body surface area corrections is taken as the measure of GFR. [30,31] The PERL group developed a stringent protocol for the allopurinol trial to quality control iGFR measurements. PERL sites performed >1,700 iGFR procedures during this trial; less than 3% had to be repeated because of technical problems. Among those accepted (98.8% of the total), the median R-square (R2) was 0.985 (IQR 0.98-0.99).[20] The same quality control procedures will be applied in this study.

8.9.1. iGFR quality control

The quality of iGFR results will be monitored by:

1. Systematically checking for deviations from the study protocol, such as deviations from the target blood draws time points during the test or the presence of medical conditions that should have prompted a postponement of the test.
2. Calculating the R2 of the regression between log-iohexol values and time. iGFR tests will be defined as technically acceptable if the R2 is >0.90. R2 calculations will be performed by the DCC using all 5 time points of the iGFR test.

8.9.2. Technically unacceptable iGFR measures

If an iGFR test is deemed technically unacceptable according to the above QC criterion ($R^2 \leq 0.90$), or a study protocol deviation is suspected, the following procedures will be followed:

1. Source documents related to the test in question will be reviewed to verify whether there was a protocol deviation or a technical error in the iGFR procedure (e.g., presence of contraindications to iGFR, swapping of tubes, wrong collection times, typos, etc.). In the case of an R2≤0.90, the iohexol measurements will be repeated by the Central Laboratory.
2. If a technical error is found and the error can be rectified, or the new laboratory measures yield an R2>0.90, the iGFR value will be recalculated after the appropriate corrections are made. The study site or the Central Laboratory, as applicable, will be alerted about the error and measures aimed at improving iGFR quality will be implemented.
3. If the error is confirmed and cannot be fixed, or no error can be found, the iGFR will be dropped and will be repeated within 4 weeks from initial iGFR results becoming available.
4. If the repeated test is technically unacceptable, or the test cannot be repeated within 4 weeks for logistical reasons, the iGFR value at that time point will be considered as missing for the analysis of the primary outcome.

8.10. Para-aminohippurate (PAH) estimated renal plasma flow (ERPF) measurement

ERPF will be measured using para-aminohippurate (PAH), as previously described. In brief, after collecting blood for PAH blank, a priming infusion containing 20% PAH (8-16 mg/kg depending on GFR) will be administered. Thereafter, PAH will be continuously infused at a rate calculated to maintain the plasma concentration constant at ~1.5 mg/dl. Blood samples will be collected for PAH determinations at 60', 90', 120', and 150' PAH levels will be measured by HPLC, and ERPF estimated from the steady state PAH concentrations according to the calculation method described by Schnurr *et al.*[40]

8.11. Estimates of renal hemodynamic profiles

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Renal hemodynamics will be estimated from ERPF and iGFR using the equations published by Gomez et al.[41-44] These equations assume: 1) that intrarenal vascular resistances are divided into afferent, post-glomerular, and efferent arteriolar resistances; 2) that hydrostatic pressures within the renal tubules, venules, Bowman's space, and interstitium are in equilibrium and assigned a value of 10 mmHg; 3) that there is filtration disequilibrium in the glomerulus; and 4) that the gross filtration coefficient is 0.0867 ml·s1 ·mmHg1, this based on normal kidney physiology. Variables including mean arteriolar pressure (MAP) (mmHg), glomerular filtration fraction (FF), ERPF (ml/ s), GFR (ml/s), renal blood flow (RBF, ml/s), hematocrit (Hct, %), and total protein (TP) (g/dl), are used to calculate efferent and afferent renal arteriolar resistance values (dyne/s/cm5), glomerular hydrostatic pressure (mmHg), glomerular filtration pressure (mmHg), and glomerular oncotic pressure (mmHg) using the published 'Gomez Equations'. These studies will allow for a complete evaluation of fenofibrate renal physiological influences (as has been done, for example, for SGLT2 inhibitors).[45] Creatinine clearance studies together with iGFR measurements will determine whether the creatinine based eGFR changes with fenofibrate reflect true GFR changes or creatinine production and/or tubular secretion influences.

8.12. eGFR and AER

eGFR-SCr and eGFR-CysC will be estimated from serum creatinine and serum cystatin C using equations developed by the CKD-EPI consortium.[46,47] Creatinine clearance and urinary AER will be measured in timed overnight collections according to standard procedures.

8.13. Biomarkers of increased ESKD risk

Dr. Andrzej Krolewski and his collaborators at the Joslin Clinic, using a new multiplexing OLINK platform including 1100 plasma proteins, identified a panel of 21 informative proteins associated with increased risk of rapid GFR decline and ESKD in T1D. In collaboration with Dr. Krolewski, OLINK has developed a specialized multiplex assay to measure these 21 proteins. These consist of 11 inflammatory proteins, including 5 capturing the Kidney Risk Inflammatory Signature (KRIS) described by Niewczas *et al*,[48] 6 pro-fibrotic proteins,[49] 3 proteins in the axon-guidance pathway,[50] and the kidney tubular marker KIM-1.[51] These proteins will be measured at baseline (V2), at 8 weeks (V4), at the end of treatment period (V7), and at the end of wash-out (V8) using the OLINK assay to assess whether their plasma levels are affected by fenofibrate and whether this effect correlates with fenofibrate's effect on GFR decline. If so, this would raise the possibility of using some of these biomarkers as surrogates of fenofibrate effectiveness in future trials.

8.14. Future biomarker studies

Plasma, serum, urine, DNA, and RNA specimens will be stored at the Advanced Research and Diagnostics Laboratory at the University of Minnesota and/or the Joslin Diabetes Center and at the NIDDK Central Repository for possible future studies of biomarkers of kidney disease in diabetes or other diabetic complications. Twelve ml of plasma, 12 mL of serum, and 24 ml of urine will be collected at Visit 2, 4, 7, and 8, with half of the aliquots of each stored at the University of Minnesota/Joslin Diabetes Center and half of the aliquots sent to the NIDDK Central Repository for storage. Altogether, the stored plasma and serum aliquots will correspond to about 210 ml of blood collected for this purpose over the entire study. Participants can elect to participate in the study while not having any or one or more of these biosamples stored.

8.15. Early Withdrawal

Unless the participant withdraws consent, all randomized participants will be followed for the full study period (through week 84) and all data will be collected as scheduled.

8.16. Study Termination

Premature termination of this pilot study may occur because of a regulatory authority decision, drug safety problems as determined by the Data Safety Monitoring Board (DSMB), or at the discretion of the

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funding agency (NIDDK).

9. SAFETY ASSESSMENTS

9.1. Demographic Data/Medical History

After collecting a detailed medical history at Visit 1, this information will be updated at each visit through a structured interview, with a special emphasis on symptoms and signs of allergic reactions, myopathy, deep vein thrombosis, and pulmonary embolism. Participants will be instructed to communicate to the study coordinator any change in their health status and between-visit hospitalizations. In particular, they will be instructed to discontinue study medication and immediately contact the study coordinator if they develop unexplained leg swelling, shortness of breath, chest pain, or muscle pain, tenderness, or weakness, especially if accompanied by malaise, fever, or brown urine.

9.2. Vital Signs

Blood pressure and heart rate will be recorded at each in-person visit.

9.3. Clinical Laboratory Tests

Serum ALT, creatinine, K^+, CPK, and HDL cholesterol, a CBC, and a pregnancy test if a female of child bearing potential, will be monitored at each visit. HbA1c will be measured at Visits 1, and 4-8. An ECG will be performed at Visits 2 and 8.

10. DATA MANAGEMENT

Comprehensive data coordinating functions for this pilot study, including database development, web-based data entry and data management, as well as the creation and export of study reports for the DSMB and NIDDK, will be provided by Dr. Alessandro Doria's group at the Joslin Diabetes Center.

10.1. Study database

A REDCap database will be built for this study using, as templates, the database structure, case report forms, and protocols for data transfer that were developed for the Allopurinol Study. Also incorporated will be the corresponding set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. REDCap[52,53] is a secure web application for building and managing online surveys and databases, which can be used to collect virtually any type of data in any environment, enabling compliance with 21 CFR Part 11, FISMA, HIPAA, GDPR, Good Clinical Practice (GCP), and other regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitoring access and data changes. We expect that the majority of data will be collected via Case Report Forms (CRFs); however, other data sources, such as data from the Central Laboratory, may be used. In these circumstances, the Coordinating Center will also utilize electronic data transfer.

10.2. Data quality control and assurance

The Coordinating Center will prepare the data management plan. This will describe the front-and back-end edit checks, as well as forms tracking procedures, that will be implemented to ensure timely and high-quality data collection. It will also define the periodic reports that will be shared with site coordinators and PIs that summarize sites' performance. The data management procedures will be consistent with the International Conference on Harmonisation (ICH E6) standards for Good Clinical Practice (GCPs).[54] Clinical monitoring and laboratory quality monitoring are described under the Data and Safety Monitoring Plan.

10.3. Study Record Retention

The source documents will be stored for at least 10 years after the study ends.

10.4. Data and Biosample Archiving in the NIDDK Central Repository

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In agreement with NIDDK's policy on the sharing of data from NIDDK-sponsored, multi-site studies, the data and biosamples collected during the trial will also be archived in anonymized form in the NIDDK Central Repository for future distribution to the scientific community. All samples and data transferred to the Repository will be under the custodianship of the NIDDK, although the study's Steering Committee will have proprietary control of and exclusive access to the sample and data for an agreed-upon period of time before these are made available to the wider scientific community.

11. STATISTICAL ANALYSIS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. The SAP will be finalized prior to database lock.

11.1. Analysis Population

For most of the analyses, including the primary efficacy analysis described in section 11.3, an intention to treat (ITT) analytical approach will be employed. Accordingly, the population for statistical analysis will consist of all randomized study participants considered in their original randomization group, regardless of treatment discontinuation or loss to follow-up. Selected secondary efficacy analyses will be performed using a per-protocol analytical approach. In this case, the analysis population will consist of the ITT population excluding data points which 1. had cumulative exposure to the study medication from randomization that was less than 80% of the theoretical full exposure; or 2. during major protocol deviations (e.g., treatment with prohibited medications), which could affect primary outcome.

11.2. Initial Data Analysis

The initial data analysis will be performed to detect any differences in distributions of characteristics measured at baseline and each follow-up visit. The number of patients screened, enrolled, and completing the study will be summarized within and across study centers. Measures of central tendency (means, medians) and variability (standard deviations, ranges) will be estimated from the data for continuous variables. Frequency distributions will be provided for categorical data. This preliminary analysis step will provide insight into data, distributions of the variables considered, and will allow for detection of additional invalid values not found during earlier during data validation.

11.3. Effectiveness analysis

Data analysis will be conducted for each aim as soon as the corresponding data have been collected for all randomized participants.

11.3.1. Aim 1

The goal will be to determine whether iGFR (primary endpoint) and eGFR-SCr, eGFR-CysC, uAER, creatinine clearance, ERPF, and other kidney hemodynamic parameters (secondary endpoints) are influenced by an 8-week treatment with fenofibrate as compared to placebo. This will be accomplished through multiple ANCOVA models (one for each dependent variable listed above) of this form:

M1: $\text{ENDPT_8}_i = \beta_0 + \beta_1 \text{ENDPT_0}_i + \beta_2 \text{FENO}_i + \beta_{31}\text{SITE1}_i + \beta_{32}\text{SITE2}_i + \beta_4 \text{ALLOP}_i$

where the subscript i is an index for a given subject, ENDPT_8 is a kidney endpoint after 8 weeks from randomization, ENDPT_0 is the baseline value of that kidney endpoint (before randomization), FENO is a dichotomous indicator of randomization to fenofibrate vs. placebo, SITE1, SITE2 are categorical indicators of the clinical centers where participants were enrolled and randomized, and ALLOP is a categorical indicator of whether the subject had previously participated in the PERL allopurinol trial. Based on our working hypothesis, the *primary* effect of interest in this model is that of fenofibrate treatment (FENO). Given the pilot nature of this study, the significant correlation among many of the endpoints that will be considered, and the fact that no formal interim analyses of the primary endpoints will be conducted, significance will be based on an unadjusted $p<0.05$.

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11.3.2. Aim 2

The goal will be to determine whether the **Aim 2** primary endpoint (iGFR at the end of the drug wash-out), and the secondary endpoints (eGFR-SCr, eGFR-CysC, and uAER at the end of the drug wash-out and iGFR, eGFR-SCr, eGFR-CysC, and uAER at the end of treatment) differ between participants assigned to treatment with fenofibrate as compared to those assigned to placebo. This will be accomplished through multiple ANCOVA models of the following forms:

M2: $ENDPT_84_i = \beta_0 + \beta_1 ENDPT_0_i + \beta_2 FENO_i + \beta_{31} SITE1_i + \beta_{32} SITE2_i + \beta_4 ALLOP_i$

M3: $ENDPT_76_i = \beta_0 + \beta_1 ENDPT_0_i + \beta_2 FENO_i + \beta_{31} SITE1_i + \beta_{32} SITE2_i + \beta_4 ALLOP_i$

M4: $ENDPT_76_i = \beta_8 + \beta_1 ENDPT_8_i + \beta_2 FENO_i + \beta_{31} SITE1_i + \beta_{32} SITE2_i + \beta_4 ALLOP_i$

where the subscript i is an index for a given subject, ENDPT_84 and ENDPT_76 are kidney endpoints at the end of wash-out (week 84) and at the end of treatment (week 76), respectively, ENDPT_0 and ENDPT_8 are baseline and week-8 values, repsectively, of that kidney endpoint, and FENO, SITE1, SITE2, and ALLOP are as indicated for model **M1**. Model **M2** will be used for baseline-adjusted endpoints at the end of wash-out, Model **M3** for baseline-adjusted endpoints at the end of treatment, and Model **M4** for 8-week adjusted kidney endpoints at the end of treatment. As with Model M1, the *primary* effect of interest in these models is that of fenofibrate treatment (FENO). eGFR-SCr, and eGFR-CysC trajectories between 8 and 76 weeks, *i.e.,* during treatment but excluding the acute effect of fenofibrate, will be estimated from all measurements available in that time interval using linear mixed-effects models.[55-57] As discussed above, significance will be based on an unadjusted $p<0.05$ for all endpoints, given the pilot nature of the study and the correlation among kidney outcomes.

11.3.3. Aim 3

Since the biomarkers of ESKD risk will be evaluated at individual time points (84 and 76 wks) in relation to baseline or week 8, we will use ANCOVA models of the same form as **M2-M4**. Since many inflammatory proteins will be correlated with each other, after the analysis of individual proteins, we will employ data reduction techniques such as *Hierarchical Cluster Analysis,* which provide a multi-resolution view of data that will be very useful for the identification of multi-marker inflammatory signatures influenced by fenofibrate. The number of clusters and their boundaries will be validated using *Resampling-based Consensus Clustering*, which generates a consensus across multiple runs of a clustering algorithm and assesses clusters' stability[58,59].

11.3.4. Incomplete Data

Missing values represent a potential source of bias. Efforts will be made to keep all participants in the study. If this is not feasible, at least some information regarding the status at the end of the trial will be obtained. For randomized patients, the number of completing and dropouts will be summarized. This procedure will help to compare characteristics of the participants' groups who drop out from the study with those who completed the study by treatment group, within and across study centers. The ANCOVA models used in Aims 1 and 3 require the stringent assumption of a missing completely at random (MCAR) mechanism, i.e., no relationship between whether a data point is missing and any values in the data set, missing or observed. The differences in distributions between characteristics of the groups may indicate potential sources of bias due to missing values, which may make the assumptions above unapplicable. We will therefore incorporate plausible missing values mechanism into the model as discussed in Little[43] and investigate how such mechanism may affect the estimates of treatment effect. To this end, sensitivity analyses will be conducted involving selection and/or pattern-mixture models[44] with an appropriate sub-model used to describe dropout.

11.3.5. Model assumptions and alternative analyses

Model assumptions will be thoroughly checked for individual and systematic departures, using informal, *e.g.* inspection of residuals, and formal methods, such as score test for extra parameter or methods based on likelihood displacement. If individual outliers are detected, their influence will be evaluated using influence diagnostics methods based on comparing estimates from models fitted to data with and

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without outlying values. Whenever we are not successful in fitting the parametric model (linear or non-linear), then non-parametric analyses and/or transformation of the variables involved in the analysis will be considered. To investigate the possible presence of heterogeneity in the response to fenofibrate, subgroup analyses (based on the primary efficacy analyses described in sections 11.3.1-11.3.3, with the inclusion of an interaction term of the treatment group by the subgroup variable) will be performed, if numerosity allows, by age groups (≤40 and >40 yrs), gender, racial/ethnic group (white vs. non-white), HbA1c (≤7.8 and >7.8%), baseline iGFR (≤70 ml/min and >70 ml/min/1.73m^2), AER at baseline (≤300 and >300 mg/24 hr), and previous participation in the PERL allopurinol trial.

11.3.6. Assessment of safety

Adverse events will be independently reviewed by an independent Data Safety Monitoring Board (DSMB, see **13. Data and safety monitoring plan**). All safety data will be available in data listing in the clinical protocol report. Data will be described in terms of descriptive statistics and presented by treatment group. Presentation will include graphs (scatterplots, boxplots, histograms), measures of central tendency (mean, median) and variability (confidence intervals) for continuous variables and frequency tables for categorical variables.

11.3.7. Interim Analyses

No formal interim analyses of efficacy to stop for benefit or futility are planned, given the pilot nature of the study.

11.3.8. Sample size

The study is powered based on Aim 1. To calculate the sample size required to address this aim, we assumed a baseline GFR of 68 ml/min/1.73 m^2 (based on data from the PERL Allopurinol Study, which had the same GFR inclusion criteria as this study) and a standard deviation (SD) of the residual error for GFR at 8 weeks equal to 10.2 ml/min/1.73 m^2 (as estimated from the root-mean-squared error from a regression model with eGFR at 4 mo. as the dependent variable and baseline eGFR as the independent variable fitted to data from the PERL Allopurinol Study). A sample size of 17 participants per group was estimated to provide 80% power (2-sided α=0.05) to detect an 8-week GFR reduction of the same magnitude as that reported in the literature (15% decrease from baseline, equivalent in this case to 10.2 ml/min/1.73 m^2 [68 ml/min/1.73m^2 x 0.15]). To account for study discontinuations of up to 15%, the number of participants was increased to 20 per group.

12. PROTECTION OF HUMAN SUBJECTS

12.1. Risks to the subjects

12.1.1. Human Subject Involvement and Characteristics

This pilot study will involve 40 individuals with type 1 diabetes enrolled at two locations (Joslin Diabetes Center, Boston, MA and University of Michigan, An Arbor, MI) based on the Inclusion/Exclusion criteria described above. Female patients of child-bearing potential will be included in the study but only if pregnancy is not planned during the time frame of the study. Women who become pregnant during the study will be discontinued from the study medication, if they had already been randomized, until pregnancy and breast feeding are complete; iGFR will not be obtained during or for 6 months after pregnancy is completed. Individuals younger than 18 will not be included since kidney complications are rare before this age. Individuals above 70 years are not included due to the potential confounding of aging on kidney function.

12.1.2. Sources of Materials

Bio-specimens will be sent by the clinical sites to the PERL Central Laboratory at the University of Minnesota where they will be analyzed. Samples will be stored for future studies at the University of Minnesota and/or the Joslin Diabetes Center and the NIDDK Central Repository. Stored bio-specimens will include:

- Plasma
- Serum

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- Urine
- DNA
- RNA

Data derived from this study and associated with the study bio-specimens will be entered by the participating sites in a secure way into a REDCap database established and maintained by the study Coordinating Center at the Joslin Diabetes Center. Data will include:

- Demographics and anthropometrics
- Results of biochemical tests
- Randomization assignment
- Adherence data
- Laboratory data (from the PERL Central Laboratory)
- Data on adverse events

12.1.3. Potential Risks

12.1.3.1. Risks associated with screening procedures and blood tests

After participating in the screening tests and procedures, subjects may find that they are not eligible to participate in the study. In that case, they will be told the reasons for their ineligibility and will be given the results of clinically approved tests such as creatinine, urinary albumin/creatinine ratio, and ALT. Thus, they may learn about yet unknown health problems such as anemia or liver disease, or more advanced kidney disease. This and/or the exclusion from the study may cause psychological distress. The drawing of blood samples may cause some pain and discomfort and hematoma formation at the site of venipuncture. The total amount of blood taken for the entire study will be about 450 mL (30 ml at Visits 1, 5, and 6; 90 ml at Visits 2, 4, 7, and 8); 0 ml at Visit 3).

12.1.3.2. Risks associated with kidney function tests

At the dose used in the study, there are no known risks to the infusion of the substances used for the measurement of renal function (iohexol and PAH) other than the very small risk of allergic reactions (<0.5%), diminished by the exclusion of patients with a history of contrast medium or iodine or allergy and by having appropriate treatment drugs for allergic reactions on hand. PAH may cause nausea, vomiting, facial flush, and a feeling of body warmth. These effects usually last only a short time. These are greatly reduced or eliminated by slowing the rate of the injection. For that reason, we will take at least five minutes to inject the PAH.

12.1.3.3. Risks associated with fenofibrate treatment

Fenofibrate has been used for several decades to decrease triglycerides and raised HDL-cholesterol in patients with dyslipidemia. The risks associated with its use are relatively low and include:

a. Hepatic: Increased serum transaminases (≥3 x ULN) have been reported in 5% to 12% of cases. Such increase is usually reversible but hepatocellular, chronic active, and cholestatic hepatitis have been reported after weeks to several years of therapy. Fenofibrate may also cause cholelithiasis (0.1-1% of cases).

b. Neuromuscular and skeletal: Myopathy with myalgia and increased serum creatinine phosphokinase (CPK) have been observed in about 3% of cases. Rhabdomyolysis has been observed on very rare occasions.

c. Renal: Fenofibrate treatment is associated with a reversible increase of serum creatinine (15-20% on average) above pre-treatment levels. It is unclear whether this is an artifact related to fenofibrate-induced changes in creatinine production and/or renal tubular handling, or corresponds to an actual GFR reduction as observed with RASB and SGLT2 inhibitors. A small study found no effect of fenofibrate on measured GFR (inulin clearance), supporting the former, whereas studies showing fenofibrate-induced increases in serum cystatin C suggest the latter. One of the goals of the present study (Aim 1) is to resolve this controversy.

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d. Respiratory: Nasopharyngitis, sinusitis, upper respiratory infections, and rhinitis have been reported in 3 to 10% of cases.

e. Central nervous system: Dizziness has been reported in 3 to 10% of cases.

f. Gastrointestinal: Abdominal pain, diarrhea, dyspepsia and constipation have been reported in 1 to 10% of cases. Pancreatitis has been reported on rare occasion in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

g. Hypersensitivity reactions: Skin rashes and urticaria have been reported in about 1% of cases. Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome and toxic epidermal necrolysis.

h. Hematologic: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S.

i. Cardiovascular: In the FIELD trial, pulmonary embolism (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate than the placebo-treated group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p = 0.022$).

j. A paradoxical, severe, and reversible decrease in HDL-cholesterol with a simultaneous decrease in apolipoprotein A1 has been occasionally reported within 2 weeks to years after initiation of fenofibrate therapy. The clinical significance of this finding is unknown.

k. Photosensitivity: photosensitivity reactions have been reported, sometimes days to months after therapy was initiated.

l. Experience with fenofibrate during human pregnancy is limited because women of reproductive age rarely require this treatment. Given this paucity of data, it is considered unsafe for the fetus or the mother to receive this drug. Fenofibrate has been found in the milk of mothers on this drug.

m. Interactions with other drugs: Treatment with other lipid-lowering medications (statins, ezetimibe, niacin) may increase the risk of myopathy associated with fenofibrate. However, fenofibrate has been safely used in combination with statins in of the FIELD and ACCORD clinical trials, including a total of ~20,000 participants. Fenofibrate may enhance the anticoagulant effects of warfarin. Drug interactions have been also described for sulphonylureas, raltegravir, and cyclosporine, although the conditions requiring these medications (T2D, HIV infection, and transplants) are exclusion criteria for this study.

12.2. Adequacy of protection against risks

12.2.1. Recruitment and Informed Consent

Potential participants will be sought (1) from among the patients who participated in the PERL allopurinol trial, (2) from among the patients attending the centers involved in the study, (3) by placing advertisements at other health care facilities and in newspapers or other media, and (4) by soliciting referrals from other health care providers. At each clinical site, potential candidates will be identified and contacted according to the procedures established by the local IRBs in compliance with local laws protecting patient confidentiality. Invitation letters to patients from the allopurinol study or attending the

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study centers will clearly offer the possibility to opt out of any further contacts with the study. Patients who agree to participate will be screened by means of a telephone or in-person interview to determine whether exclusion criteria apply. Subjects who respond to advertisements will undergo the same screening interview. Subjects who pass this initial screening will be given or mailed an informed consent form and will be invited to come to the clinic for a screening visit (Visit 1) during which a final eligibility determination will be made on the basis of a detailed medical history and laboratory tests. Written consent will be obtained on that occasion from all subjects undergoing the screening visit after explaining again the purpose and procedures of the study. In the initial contact and again at the time of the screening visit, study subjects will be encouraged to ask questions and they will be reassured that they may withdraw from the study at any time. Written consent will be obtained again at V2 if the consent at V1 was only for the screening procedures.

12.2.2. Protection against risks

12.2.2.1. General

Participants will be under constant medical supervision. They will be told that the data which are collected will be used for scientific report, but they will not be identified in such reports.

12.2.2.2. Specific

1. IV's for kidney function studies will be placed by trained skilled clinical research nurses or technicians or by experienced physicians.
2. Blood drawing for laboratory studies will be performed by trained skilled phlebotomy personnel at the respective institutions, thus limiting the risk of discomfort or local hematoma formation.
3. To minimize the impact of blood draws, subjects with low hemoglobin levels (<11 g/dL in males, <10 g/dl in females) will be excluded. Subjects who have just donated blood will have their entry into the study delayed for 2 months. Participants will be advised not to donate blood throughout the time they are in the study and for two months after participation in the study. Hemoglobin levels will be monitored at each visit.
4. Patients with a history of allergy to contrast medium, iodine-containing substances, or PAH will be excluded from the study. Appropriate treatment drugs for allergic reactions will be kept on hand at the time of iohexol and PAH injection during the kidney function tests.
5. Regarding possible drug toxicity:
    a. To avoid fetal risks from the study drug, women who are pregnant or are planning pregnancies will not be included. Sexually active female participants will be instructed to immediately discontinue study drugs if a menstrual period is missed by more than two weeks and, if found to be pregnant, the study medication will be discontinued and not resumed until pregnancy and nursing are completed. Pregnancy tests will be done at each visit on all women in the study.
    b. Primary care physicians will be notified (with the participants' permission) of the patients' participation in the trial, so that they avoid the prescription of drugs interacting with fenofibrate (e.g., warfarin) and notify the study personnel that treatment with such drugs is necessary.
    c. Subjects will be reminded at each visit to immediately notify the study personnel if they start a new drug, so that possible interactions with fenofibrate can be identified at once and appropriate precautions can be taken including discontinuation of the study drug.
    d. Subjects with clinical contraindications for fibrates will be excluded from the study.
    e. Subjects with known allergy to fenofibrate will be excluded from the study. Participants will be instructed to immediately report skin reactions and allergic symptoms and to immediately stop the study medication should these occur. Participant will be given antihistamines for symptom relief. Should an allergic reaction or skin rash occur, the study drug will be permanently discontinued.
    f. Measures or estimates of iGFR at study visits will allow titration of fenofibrate in relation to kidney function to avoid excessive medication dosage.

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g. To minimize the risk of liver injury, subjects with clinically significant hepatic disease (current or past decompensated cirrhosis or diagnosis of cirrhosis), and/or elevated liver enzymes above 2.0 x the upper limit of normal, and/or Total bilirubin >1.3 x the upper limit of normal (>1.5 x the upper limit of normal in the case of Gilbert Syndrome) at the screening visit will be excluded from the study. In those subjects that are enrolled in the study, liver enzyme levels will be monitored at each follow-up visit. If levels are >3x the upper limit of normal, the measurement will be repeated within 48 hrs while the drug is temporarily discontinued. The PERL Drug Monitoring Committee (DMC) will review the results of the repeated measurement and decide whether the study drug must be permanently discontinued and whether, on the recommendation of a hepatologist, study treatment can be reinstated after enzyme values have returned to normal.

h. To minimize the risk of myopathy, subjects with a history of myositis or with persistent elevated unexplained blood CPK levels will be excluded from the study. Participants will be instructed to immediately report unexplained muscle pain, tenderness, or weakness, especially if accompanied by malaise, fever, or brown urine, especially if they are treated with other lipid-lowering agents. Serum CPK will be measured at every clinic visit and on an *ad hoc* basis between visits in the case of reports of myopathy symptoms. The study drug will be permanently discontinued in the case of rhabdomyolysis. If CPK is elevated more than 3 times the upper limit of normal, it will be repeated within 24-48 hours. The study drug will be permanently discontinued if the repeated CPK value is in excess of 10 times the upper limit of normal in the absence of symptoms, or if it is in excess of 5 to 10 times the upper limit of normal in the presence of symptoms.

i. A CBC will be performed at each visit to allow the prompt detection of leucopenia or thrombocytopenia potentially representing drug toxicity.

j. To minimize the risk of pancreatitis, deep vein thrombosis, or pulmonary embolism, subjects with a history of these disorders will be excluded from the study. The study medication will be permanently discontinued if these disorders or cholelithiasis are diagnosed.

k. The study drug will be permanently discontinued if HDL-cholesterol becomes severely depressed (<25 mg/dl). HDL-cholesterol will be monitored until it returns to baseline.

l. Data monitoring will be performed on a regular basis. Data entry computers will be programmed to flag any parameters outside clinically acceptable ranges.

12.2.3. Protection of Confidentiality

12.2.3.1. Access to individually identifiable private information

Study personnel will have access to individually identifiable private information only for those participants who are enrolled at their site. Personnel at the other site, the Coordinating Center, and the Central Laboratory will only have access to coded data.

12.2.3.2. Data security

- Each study center will maintain a file on each study participant that includes personal identifiers, linking name and contact information to the unique study ID. These data will not be entered into the study data management system.
- All forms and specimens will be labeled with each study participant's unique study identifier.
- All data transferred to the Coordinating Center for accumulation in the central database will identify study participants only with their unique study identifier.
- Participants' names and addresses will be shared with the Pharmacy along with selected laboratory results (serum creatinine) for the purpose of adjusting the dosage and mailing the study medication.
- Identifiers may also be shared with the local laboratories if required by the laboratory ordering procedures.

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- Study participants' files will be kept in secure locations and the clinical centers will be responsible for taking every other reasonable measure (those set by the state, the site, and the study) to ensure and maintain record confidentiality and patient privacy.
- Participants will be given the opportunity to decide whether the clinical information gained from the study should be shared with their health care providers. Participants will be made aware that, despite these measures, confidentiality cannot be totally ensured.
- Each site will adhere as required by law to regulatory oversight by federal and state agencies that have authority over the conduct of clinical research such as the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, the Office of Human Research Protection, the Department of Social Services and the Data Safety Monitoring Board.
- Participants will be made aware that, despite these measures, confidentiality cannot be totally ensured.

As of October 31, 2025, all paper records will be scanned to digital files by RICOH as part of the Joslin sponsored scanning project associated with the building relocation. Participant study records and signed informed consent documents will be scanned as a complete set for each participant, and each scanned file will clearly identify participant using a participant ID. Digitization will follow Joslin CHS guidelines for Electronic Storage Best Practices. Scanned files will be certified and stored in secure servers appropriately to prevent unauthorized access. After documents are scanned, certified and securely stored, paper records will be destroyed as Joslin's Record Retention and Destruction Policy.

12.2.3.3. Handling of specimens

- Blood, urine, and other bio-specimens will be handled locally by trained personnel associated with the study, in tubes that do not carry identifying information.
- Bio-specimens will be stored in local laboratories until they are shipped to the PERL Central Laboratory or the Joslin Diabetes Center.
- Plasma, serum, urine, DNA, and RNA samples will be labeled only with a numeric code.

12.2.3.4. Access to other investigators

Coded data and bio-specimens will be stored at the Coordinating Center at the Joslin Diabetes Center and/or the PERL Central laboratory at the University of Minnesota. PERL investigators or external collaborators may request access to these data and/or specimens for research purposes that are not limited to the goals of the present study. To get access to these materials, investigators will have to submit a written request to the PERL Ancillary Study Committee and/or PERL Publication and Presentation Committee. The application will be reviewed, and approval granted based on the vote of the majority of committee members. Data and sample aliquots will also be stored at the NIDDK Central Repository. Bio-specimens stored at NIDDK will be handled as described above. The data and samples that will be shared with other investigators will be limited to those that are necessary to address the Specific Aims outlined in the application. The transfer of data and/or samples will occur only after the execution of a Material Transfer Agreement. Coded data will be transmitted in encrypted fashion. Samples will be labeled with masked ID.

12.3. Potential benefits of the proposed research to the subjects and others

The study is not being conducted to improve the participants' health and it is not expected that study participants will directly benefit from taking part in this study. However, sharing of the clinically approved tests conducted during the study with the health care provider(s) may help them determine the participant's risk of DKD progression more precisely. This in turn may help design appropriate preventive strategies for the participant. More generally, if we succeed in the aim of this pilot study of fenofibrate, patients with diabetes may benefit as this knowledge may be used to develop a new intervention to prevent diabetic kidney disease. Risks to subjects are deemed to be reasonable in relation to the anticipated benefits to research participants and others.

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12.4. Importance of the knowledge to be gained

DKD imposes the highest social and economic burden of all the long-term complications of T1D. After 40 years of diabetes, about one in three patients with T1D has developed kidney abnormalities, which frequently progress to ESKD. The improvements in glycemic and BP control, and the introduction of 'renoprotective' drugs such as RAS blockers (RASB) during the past 20 years, have not resulted in significant lowering the rate of increase in the US annual incidence of ESKD in T1D, leaving a large residual risk despite current evidence-based intervention strategies. Thus, DN remains one of the most important causes of morbidity and mortality in T1D and novel therapies to complement glycemic and BP control, including RAS inhibition, are urgently needed. The knowledge gained with this pilot study is crucial for the design of a pivotal trial testing the hypothesis that fenofibrate can halt or slow down GFR decline in T1D subjects. If we can eventually prove this hypothesis, we will provide a simple, safe, and inexpensive intervention to prevent or delay kidney failure in T1D. It is difficult to overstate how significant this finding would be, both from the perspective of public health and that of persons with diabetes. Thus, risks to subjects are deemed to be reasonable in relation to the knowledge to be gained with this study.

12.6. Incentives/remuneration

If allowed by local regulations, participants will be reimbursed for the time and effort associated with participating in this study. Reimbursement amounts will be decided locally. Payments will be made at each visit. Participants with financial hardships deriving, for example, from loss of income or child care costs, may be reimbursed for such costs on a case by case basis. Participants who do not complete the study will only be reimbursed for the visits they completed. Transportation costs (e.g., parking or public transportation) may be reimbursed according to local policies. Remote site participant costs associated with travel to a Main Site will be reimbursed according to Federal travel, hotel, and per diem rates (gsa.gov).

12.7. Institutional Review Board

The protocol and informed consent forms and subsequent modifications will be reviewed and approved for compliance with applicable standards/regulations by the Joslin Committee on Human Studies (CHS), which will serve as single IRB for the entire study.

13. DATA AND SAFETY MONITORING PLAN

13.1. Adverse event reporting

13.1.1. Definitions

An Adverse Event (AE) is any untoward medical occurrence in a study participant regardless of its relationship to study treatment. A treatment-emergent AE is an adverse event occurring during the period between the first dose and 30 days after the final dose of the study medication. A Serious Adverse Event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability, or is a congenital anomaly/birth defect. Important medical events that do not fall into the above categories may also be considered an SAE when, based on medical judgment, such events may jeopardize the patient's safety and require medical/surgical intervention to prevent one of the outcomes listed in the SAE definition. The term SAE is not intended as a measure of severity or intensity. All AE's/SAE's that occur after the time of informed consent will be reported.

A Suspected Adverse Reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies less certainty about causality than adverse reaction, which means any adverse event caused by a drug. An Unexpected Adverse Event or Unexpected Suspected Adverse Reaction is an adverse event or suspected adverse reaction that is not listed in the investigator brochure or is not listed

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at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected", as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. An Expected Adverse Event or Expected Adverse Reaction is any adverse experience that has been identified in nature or severity in the current investigator brochure and/or protocol.

13.1.2. Adverse Events Reporting

All AEs will be reported on the Adverse Events form that will be completed by the study staff, who are masked as to study treatment assignment, at each regular follow-up visits. This will insure that AEs are ascertained in an unbiased manner using the same standardized methodology for participants in both treatment arms. Forms will include standardized questions relating to specific events of import in diabetic patients on either of the study treatment arms as well as any significantly abnormal physical finding identified on examination and any significantly abnormal laboratory results obtained on the patient between visits or at the time of the visit. AEs reported or ascertained between clinic visits will be captured and reported at the time of the next schedule visit. Pre-existing conditions (that is, any condition that was known to be present prior to the signing of informed consent or was identified during the screening procedures at Visit 1) will not be considered or recorded as AEs unless the condition worsens in intensity or frequency after Visit 1. Likewise, continuing AEs will not be reported as AEs at subsequent visits unless they increase in severity or frequency between visits, they results in criteria for a SAEs, and/or they resolve between visits. SAE will be reported according to the following procedures:

- All SAEs as defined previously will require expedited event notification within 72 hours of occurrence or identification to the CC.
- An independent physician not involved in the study will serve as the Medical Safety Officer, reviewing all SAEs promptly after being reported in the database by the clinical sites. The Medical Safety Officer will prepare a final SAE narrative report for each SAE, which will be distributed to the PI's and DSMB Chair. In addition, the DSMB will review all AEs during their regularly scheduled meetings, or on an expedited basis as determined by the Chair of the DSMB.
- Once the SAE is resolved, a final report will be generated by the Medical Safety Officer. The final report will be sent to the clinical site PI to review for accuracy and completeness of the report. Following review by the clinical site PI, the Medical Safety Officer will send the final report to the PIs, the clinical site director, and the Project Manager. All SAE reports will be forwarded to the DSMB for review during their regularly scheduled meetings. The FDA definitions and requirements for expedited reporting will be used to determine if any individual SAE warrants expedited notification to the IRB.

13.1.3. Assessment of Causality and Severity

The seriousness of adverse events will be ascertained by the study staff according to the criteria listed in **13.1.1** and the need for further evaluation, follow-up, or referral. The relationship between study participation and AEs will be determined according to the following criteria:

A. Not related – temporal relationship of the onset of the event, relative to study participation, is not reasonable or another cause can by itself explain the occurrence of the event.

B. Possibly related – temporal relationship of the onset of the event, relative to study participation, is reasonable but the event could have been due to another, equally likely cause.

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C. **Probably related** – temporal relationship of the onset of the event, relative to study participation, is reasonable and the event is more likely explained by the study treatment than by another cause.
D. **Definitely related** – temporal relationship of the onset of the event, relative to study participation, is reasonable and there is no other cause to explain the event.

13.2. Data and safety monitoring

13.2.1. Data Safety Monitoring Board (DSMB)

A DSMB including outside experts in the design and conduct of clinical trials and in diabetic nephropathy will be established in coordination with NIDDK. The purpose of the DSMB is to assure independent review as to whether study patients are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity The DSMB will receive detailed data from the Coordinating Center (CC) as frequently as deemed appropriate by the board, including summary tabulations and narratives of adverse events, and will have periodic teleconferences/ webinars with the Study Investigators and the CC personnel. They will have full access to all data, and their recommendations and input will be given high priority and will be incorporated into the study protocol. To this end, the DSMB will meet separately in closed sessions with the CC staff, excluding Dr. Doria, the co-PI, to review all adverse event data in relation to the randomized treatment groups in order to detect any increased frequency of significant adverse events which could be study drug related, and decide whether continuation of the trial is warranted.

13.2.2. IRB monitoring

The conduct of the study will be monitored by the Joslin IRB (Joslin Committee on Human Studies [CHS]), which will serve as single IRB for the Joslin and U. Michigan sites. All AE's will be reported to the Joslin IRB according to its AE reporting policy and procedures.

13.2.3. Clinical monitoring

Periodic monitoring visits will be conducted during the trial to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow monitors direct access to source documents to perform this verification. In the first year, site initiation visits will be conducted remotely to review the protocol, verify that the Site Director and his/her collaborators receive all necessary trial documents for a proper trial conduct, and review the procedures related to CRFs completion and query resolution. Investigators will be instructed about the importance of recording accurate and clean data, avoiding protocol deviations/violations, and retaining subjects in the study. Follow-up monitoring visits will involve the verification of source documents and reporting of adverse events. Monitors will also verify that an informed consent form is on file for each subject screened, with appropriately dated signatures and all pages present, that all of the inclusion and exclusion criteria were met for each subject enrolled into the study, and that all the withdrawals and dropouts of enrolled subjects from the trial are reported and explained in the appropriate CRFs. Accrual and retention rates will also be monitored and if these fall appreciably below the projected levels, attempts will be made to identify the reasons. At the end of each monitoring visit, a clinical monitoring report will be prepared by the monitor and sent to the site directors with recommendations to correct problems and/or improve the trial quality.

13.2.4. Statistical monitoring

Clinical monitoring will be complemented by statistical central monitoring, as described by Venet et al.[60] Such statistical approach to central monitoring relies on assessing the clinical data for departures from expected patterns (e.g., baseline variables in our randomized trial should be comparable between treatment arms for each site; visit days should be randomly distributed over the week), and assessment of a greater number of data values than those associated with site performance metrics. The statistical monitoring plan will be incorporated into the larger data management plan, and will identify the specific descriptive statistics, graphical presentations, and formal hypothesis tests to be performed and at what

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frequency. Pattern recognition may require a sufficient number of subjects followed for a sufficient amount of time in order to be valid.

13.2.5. Laboratory quality monitoring

The Central Laboratory at the U. of Minnesota uses internal quality control methods to assess assay precision and drift as well external quality control (e.g., proficiency testing) to assess accuracy. The laboratory is well versed in both aspects and adheres to rigid performance standards. For all analytes, enough commercial lyophilized control material is typically purchased prior to beginning the study, so that a single control pool lot can be used throughout. Control pool mean and between-day SD's for each analyte are routinely established at a minimum of two different analyte concentrations on a minimum of one hundred different analytical batches. In the unlikely event that a new control pool lot becomes necessary during the study, both the new and old control pool lots will be run for a minimum of 20 days to establish a target mean for the new pool. The target SD's are not changed if the new and old lots of control material are the same "matrix" (e.g., lyophilized human serum). An in-house control pool is also typically prepared from the exact same specimen type (e.g., 0.5-mL aliquots of pooled serum or EDTA-plasma from several individual donors), kept at -70°C, and incorporated as an internal control in all analytical batches throughout the study. This sort of control is very useful since occasionally the commercial pools of lyophilized serum have matrix effects that make assessment of the true accuracy of the given assay difficult to assess. Accuracy is assessed by comparison of external quality control proficiency testing results. For most of the assays, the laboratory participates in either the College of American Pathologists' Surveys Program (creatinine, ALT, glycosylated hemoglobin, urine albumin, urine creatinine) or by sample exchange in a survey program with another laboratory (iohexol). The laboratory is CLIA certified. PAH will be measured in Dr. Davor Brinc's Laboratory at University Health Network in Toronto, Canada. Calibration for PAH testing is performed using 6 standards prepared from a stock standard solution. No commercial quality control products are available for this assay. Daily quality control consists of measurement of two levels of pooled urine and two levels of pooled serum. The values for these pooled levels are determined through repetitive assays. The Westgard 1-2s rule is followed when determining the validity of results produced. Quality control material is assayed before the first patient sample and after the clearance sets.

13.3. Miscellaneous provisions

- When collecting data on participants, adequate safety levels will be set for flagging test results. When these levels are reached, the Coordinating Center will notify the appropriate clinical site that an abnormal result has been received. Detailed follow-up procedures will be set in the Manual of Operations that will be followed by the clinic when any abnormal results are received.
- Bi-weekly conference calls will be scheduled for the Executive Committee (EC) and the Trial Coordinators. Subject participation and compliance will be discussed in detail during these calls.
- The PERL-Fenofibrate Drug Monitoring Committee (DMC) consisting of the Dr. Mauer, the Directors of the two clinical sites, and Dr. David Cherney (U. Toronto), will hold conference calls regarding any serious medication related problem that a participant may have. Changes in study medication dose, medication discontinuation and medication re-institution will be discussed during these calls.

14. STUDY ADMINISTRATION

15.1. Organization

The major organizational components of the study are:

- The *PERL Steering Committee* is responsible for the design of the study and provides guidance to its execution. Members are the co-Chairs of the PERL Consortium (Drs. Mauer and Doria), the Directors of the PERL Clinical Sites, the Directors of the PERL Data Coordinating Center (Drs. Galecki and Spino), and the Director of the PERL Central Laboratory (Dr. Karger).

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- The *Fenofibrate Pilot Executive Committee* will consist of the two PIs (Drs. Doria and Mauer), the two Fenofibrate Pilot Clinical Site Directors (Drs. Rosas and Pop-Busui), the Lead Biostatistician (Dr. Galecki), the Project Manager, and the Lead Clinical Coordinator. The EC will have at least monthly conference calls to discuss the overall conduct of the study and set the agendas for the Clinical Coordinators and Steering Committee conference calls. The EC will be responsible for the overall quality of the study, the setting of broad policy directions, and will address major budgetary issues, including, if necessary, reallocation of funds based on developed parameters of need and performance.
- The *Fenofibrate Pilot Drug Monitoring Committee* is responsible for the oversight of the study drug administration during the trial. Members are Dr. Mauer, the Directors of the two clinical sites, and Dr. David Cherney (U. Toronto).
- The *Fenofibrate Pilot Clinical Sites* are located at the Joslin Diabetes Center and the University of Michigan.
- The *Fenofibrate Pilot Coordinating Center (CC)* is based at the Joslin Diabetes Center, is directed by Dr. Doria and is responsible for managing the trial on a day-to-day basis, monitoring enrollment, retention, and protocol adherence and for collecting, monitoring, and cleaning data from the Clinical Sites.
- The *Fenofibrate Pilot Statistical Team* is based at the University of Michigan, is directed by Dr. Galecki, and is responsible for the final data analyses.
- The PERL *Central Laboratory*, located at the University of Minnesota, is directed by Dr. Karger, and is responsible for all blood and urine tests.
- The *Fenofibrate Pilot Data Safety Monitoring Board (DSMB)* will be composed of to-be-named outside experts in the design and conduct of clinical trials and in diabetic nephropathy. The board will be responsible for reviewing the study documents, monitoring study progress and participant safety.

Monthly conference calls will be scheduled for the PERL Steering Committee and the trial coordinators to discuss subject participation and compliance.

15.2. Protocol Deviations, Violations, and Amendments

A Protocol Deviation is defined as any change, divergence, or departure from the approve study protocol that does not affect the participant's safety, rights, welfare or the integrity of the study and its resultant data. A Protocol Violation is defined as a protocol deviation that may affect the participant's rights, safety, or wellbeing and/or the completeness, accuracy, and reliability of the study data. Deviation will be reported to the IRB at the time of continuing review whereas violations will be reported as soon as study personnel are aware of the event. Dr. Doria, one of the PIs, will keep an internal protocol deviation and violation log at the Coordinating Center that will be forwarded to the IRB at the time of continuing review. Adoption of protocol amendments will require three-fifths majority approval by members of the Steering Committee. The amended protocol is resubmitted to the IRB.

15.3. Financial Disclosure

On an annual basis or whenever there is a significant change in status, participating investigators will be required to disclose any financial or related interest that could present an actual conflict of interest or could be perceived as presenting a conflict of interest. The Steering Committee will determine (1) if the disclosed interest could directly and significantly affect the performance of study responsibility and, (2) the management, reduction, or elimination of the conflict.

15.4. Publications

It is anticipated that this research may lead to oral and written presentations including one or more jointly authored publications. The contribution of investigators will be acknowledged in accordance with scientific custom in all published and oral communications concerning this study and its results.

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PERL-Fenofibrate Pilot Protocol Change Log

Date	08/16/21	
Previous Version	2.0	
New Version	3.0	
Changes		
Location	**Change**	**Rationale**
General Info. P6	Inclusion of clinicaltrial.gov and IND #	Study entered into clinicaltrial.gov, IND submitted and approved
Exclusion criteria – Protocol summary, subject population and Section 5.2 Exclusion Criteria	Addition of exclusion criteria 7.Elevated blood pressure (SBP>150 and/or DBP >95 mmHg) at screening;	Uncontrolled blood pressure may interfere with the kidney hemodynamic results.
Section 6.1.5 Dispensing Procedures	Include option to return meds at next visit to study center	Some participants may find it easier to return unused meds the next time the come to the study center
Section 8.1 Schedule of Events	Addition of urine ACR to local labs at screening	Provides faster turnaround to determine eligibility
Table 1. Schedule of events	Removed study drug prescription from V7.	Medications are not prescribed at V7 as this is the beginning of washout.
	Added Biomarkers of increased risk of ESDK to V4	Correction of grid to include planned biomarkers collection at V4.
	Include HbA1c at local lab for all visits with HbA1c at Central	Central will provide bulk data downloads, having it done locally will allow us to better monitor their health, as well as provide results to the participant.
	Addition of urine ACR to local labs at screening	Provides faster turnaround to determine eligibility
	Inclusion of optional repeat visit 2 (visit 2a)	See rationale below (section 8.3)
Section 8.3 Screening (Visit 1)	Option for one urine rather than two at screening. Clarification of spot urine collection "in the days preceding the visit"	If candidates already have one urine in their medical history, we may request only one to capture the 2 values needed to determine eligibility. Urines should be collected preceding screening.
Section 8.4 Enrollment in the study and Baseline Assessment (Visit 2)	Inclusion of the option to repeat visit 2 if a valid iGFR cannot be obtained at that visit	Reduces the risk of ineligibility due to procedural errors/qc failure of the iGFR procedure.
Section 8.6 Treatment Period (Visits 4, 5 and 6) and Section 8.7 End of Intervention (Visit 7)	Inclusion of "if not already sent by mail,"	Accounts for the option of returning study meds via pre-stamped envelope

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Section 8 heading numbers	Correction of number increment from 8.5 – 8.16	Heading number 8.4 duplicated for visit 3 and Visit 4.
12.1.2. Sources of Materials	Central RepositoryStored →Central Repository. Stored bio-	Correction of typo
12.2.2.2. Specific	Correction of bullet letters a-f → g-l	Typo in bullet letters, a-f were repeated, updated to g-l.
12.2.3.3. Handling of Specimens	Include Joslin Diabetes Center for storage of bio-specimens	For long term storage the samples may be held at PERL Central Lab or the Joslin Diabetes Center

PERL-Fenofibrate Pilot Protocol Change Log

Date	11/1/21	
Previous Version	3.0	
New Version	4.0	
Title Page	Version and date	Increment version and date
Table of Contents and protocol summary	IND # corrected, 156937	Correction of typo in IND number
Protocol Summary, Inclusion criteria and 5.1. Inclusion Criteria	Inclusion of estimated glomerular filtration rate (eGFR) as inclusion for PERL participants	Including eGFR as a determinant for kidney function decline allows for the screening of more PERL participants and prevents the exclusion of participants who may have missed iGFR procedures.
	Expansion of kidney decline review from previous 2 to previous 3 years	Due to the COVID-19 pandemic the number of in person visits over the past ~2 years was significantly reduced. As such, lab tests were reduced, expanding the time frame to 3 years, allows us to capture information reflecting more typical times.
6.1.3. Randomization Procedures	Removed Previous PERL participation as stratum for randomization	Due to the small number of participants enrolled in the study and even smaller number of possible PERL participants joining the study, this stratum has been removed from the blocked randomization strategy, in order to prevent the occurrence of unfilled randomization blocks.
6.1.4 Masking procedures	Removed Dr. Doria from masked personnel	Change reflects the need for Dr. Doria to have access to treatment assignment in his role as Coordinator Center Director.
	Revised unmasking procedures	Previous language was a remnant of the PERL Allopurinol Study protocol. Change reflects the actual procedures that will be used in the present study.
6.1.5. Dispensing Procedures	Revised Dispensing procedures to reflect lack of access to GFR by Study Coordinators.	In order to prevent potential unmasking, study coordinators will not calculate or have access to GFR after Visit 2. The Pharmacy will access eGFR to determine dose by accessing a dedicated database made available by the Coordinating Center.
8.1. Schedule of Events and 13.2.5. Laboratory quality monitoring	Update of location for PAH testing to Dr. Petter Bjornstad's lab	The PAH testing methodology is being transferred from Dr. Nelson's laboratory to the laboratory of Dr. Petter Bjornstad
8.1. Schedule of Events and	Removal of Dr. Doria from DMC	Dr. Doria has been added to the unmasked personnel and as such cannot be part of the DMC.

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13.3. Miscellaneous provisions		
8.2. Location of study visits, Remote Biospecimen Collections	Addition of HbA1c, AP, Bilirubin and Sodium to local lab tests	To accurately reflect Visit grid and prevent any confusion induced from not having the complete list detailed.
8.10. Para-aminohippurate (PAH) estimated renal plasma flow (ERPF) measurement	Blood sampling timeline adjustment from 30', 60' and 120' to 60', 90', and 120'	After reviewing several protocols it was determined that 60', 90', and 120' were the optimal timepoints from which to collect blood to measure PAH clearance as it aligns with the blood draws for iohexol disappearance, thereby reducing the amount of blood drawn from the participant during the study visit.
	PAH bolus changed from "8 mg/kg" to "8-16 mg/kg depending on GFR"	Change reflects the updated PAH protocol received from Drs. P. Bjornstad and R. Nelson
11.3. Effectiveness analysis	Data analysis timeline added.	Change is to allow for Aim 1 data analysis before completion of study.

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Date	01/20/22	
Previous Version	4.0	
New Version	5.0	
Location	**Change**	**Rationale**
Title Page and header	Version and date	Increment version and date
General Information	Update Dr. Mauer's contact info	
Throughout protocol	Grammatical and spelling error corrections	Several grammatical and/or spelling errors, were updated throughout the protocol. All are tracked.
Protocol Summary, Inclusion criteria and 5.1. Inclusion Criteria	Expansion of timeframe for presence of Microalbuminuria in PERL participants to include values collected after participation in the PERL clinical trial	PERL allopurinol trial participants were originally considered to be eligible for the present study if they had significant GFR decline accompanied by evidence of increased urinary albumin excretion (microalbuminuria) during the trial. The proposed expansion of the time frame for the detection of microalbuminuria will identify additional PERL allopurinol study participants who have been experiencing progression of diabetic kidney disease after completion of the trial
Protocol Summary	Protocol Date	Updated to newest version date
	Reduction of ACR for Inclusion for all other subjects from 300 to 200	This change is due to the fact that we are requiring participants to be on RASB therapy, which is known to decrease urinary albumin levels. Therefore the previous criterion was overly restrictive.
Table 1. Schedule of Events	Remove Central Lab tests from Screening Visit (V1)	As the baseline study visit is visit 2 and study outcomes will be analyzed from baseline, test results used for that purpose are not need prior to V2. Screening visit tests are used to determine eligibility and can therefore be all completed at the local lab. Turnaround will be faster and likewise determination of eligibility.
	Move HbA1c from Central to Local Lab tests	HbA1c is a valuable clinical result which should be received by the participants immediately after each study visits. As it is a routine test, this will be run at the local lab for faster turnaround and reporting purposes.
	Move ACR from Central to Local Lab tests at Screening Visit	As ACR is only required at the Screening Visit to determine eligibility and given that it is a routine test, this will be completed at the local lab. Turnaround

		will be faster and likewise determination of eligibility.
	NA/K labs optional	Sodium and Potassium labs were remnants from the previous PERL allopurinol trial, in which they were utilized to monitor renin/angiotensin system blocker (RASB) therapy started during the study. Since participants are required to be on RASB before enrolling in the present study, NA/K should be monitored as part of their routine care. Additionally, Fenofibrate is not known to affect NA/K levels. Thus, Na/K levels does not need to be measured as part of the trial unless they have not been measured in the past six months as part of the participants' clinical care.
	Update ALT, AP, Bilirubin labs to "LFT" with optional additional testing	ALT, AP, and bilirubin are often run as part of a larger liver function test panel. This panel is commonly less expensive than running ALT, AP, and bilirubin separately and is more comprehensive, including tests such as Albumin, Globulins, and AST.
8.6 Treatment Period (Visits 4, 5, and 6)	Addition of DNA and RNA to stored samples collected during visits	Clarifying that all stored specimen types are collected at iGFR visits. Outlining each specimen type for consistency
8.7 End of Intervention (Visit 7)	Addition of DNA and RNA to stored samples collected during visits	Clarifying that all stored specimen types are collected at iGFR visits. Outlining each specimen type for consistency
8.8 End of Wash-out Period (Visit 8)	Addition of DNA and RNA to stored samples collected during visits	Clarifying that all stored specimen types are collected at iGFR visits. Outlining each specimen type for consistency

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Date	04/05/2022
Previous Version	5.0
New Version	6.0

Location	**Change**	**Rationale**
Title Page and header	Version and date	Increment version and date
8.10 Para-aminohippurate (PAH) estimated renal plasma flow (ERPF) measurement	Addition of collection time point 150 minutes	The current protocol calls for PAH measurements at 60, 90, and 120 minutes. Initial data indicated that the PAH concentration had not yet reached steady state, required for appropriate calculation of ERPF. RNI160 was approved to test the addition of a collection at 150 minutes. Data from this collection validated that some individuals do not reach steady state until after the 120 minute mark. Therefore, we will proceed with an amendment to the protocol to include an additional time point at 150 minutes.
8.1 Schedule of Events And 13.2.5 Laboratory Quality Monitoring	PAH testing laboratory changed to Dr. Davor Brinc's Laboratory at University Health Network in Toronto, Canada	Transition of PAH testing from Dr. David Cherney's laboratory to Dr. Petter Bjornstead's laboratory is not complete. As there is not an established timeline for when this assay will be available, we are transitioning testing to the lab at UHN, which is currently set up and has been running PAH assays.
11.3.5 Model Assumptions	Lower ACR eligibility threshold to 200 mg/ml	Residual from the protocol amendment to ver 5.0. This section was missed in the previous submission. Updating to match lowered ACR threshold criteria of 200 mg/ml

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Date	07/28/2022	
Previous Version	6.0	
New Version	7.0	
Location	**Change**	**Rationale**
Title Page and header	Version and date	Increment version and date
Protocol Summary, Inclusion criteria And 5.1 Inclusion Criteria	Decrease of threshold of albuminuria for inclusion in the study from ACR 200 mg/g or 100 mg/g or AER 200mg/24hr or 100 mg/24hr	The current ACR criterion (uACR >200 mg/g on at least two occasions in the past three years) was considered too restrictive given that participants are on renin-angiotensin blockers, which decrease uACR, and that participants in the previous PERL study having baseline uACR values in the 100-200 mg/g range had a rate of GFR decline that was similar to that of participants with baseline uACR in the 200-300 mg/g. On this basis, the Executive Committee, decided to reduce the ACR eligibility threshold from 200 to 100 mg/g.
Protocol Summary, exclusion criteria And 5.2 Exclusion Criteria	Addition of exclusion criteria "10. History of cholelithiasis unless gallbladder has been removed."	As gallstones can be common in the population, it was decided that, although covered in exclusion #5 as a contraindication to fenofibrate, it should be outlined as an explicit exclusion criteria as to not overlook a history or presence of gallstones during screening.
	Adjustment of hepatic disease exclusion criteria, History of clinically significant hepatic disease has been changed and expanded to include the following; 12. Current or past history of decompensated cirrhosis (defined as variceal bleeding, ascites, or hepatic encephalopathy and/or diagnosis of cirrhosis based on liver biopsy, imaging, or elastography and/or aspartate or alanine aminotransferase (AST or ALT) >2 times the upper limit of normal at screening and/or total bilirubin >1.3 times the upper limit of normal at screening (in the case of Gilbert syndrome, direct bilirubin >1.5 times the upper limit of normal at screening)..	After reviewing the exclusion criteria of history of clinically significant hepatic disease with an expert hepatologist and the study medical safety monitor, it was determined that this criteria is overly restrictive as it may lead to the exclusion of individuals who do not have active liver disease and for whom fenofibrate is not contraindicated. Participants with a previous history of Hepatitis infection but no evidence of active liver disease are not at increased risk of liver injury due to fenofibrate treatment. As such we have taken the recommendation of the expert hepatologist (Dr. Anna Lok - U. of Michigan) to clarify that those with a history of cirrhosis and/or elevated liver enzymes who may be at increased risk of liver injury due to treatment with fenofibrate will be excluded from the study.

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Protocol Summary, Date and version of protocol	Version date and number	Increment version and date
Abbreviations	PAH: Para-amino hippurate	Oversight that this commonly used abbreviation was not annotated in the list
6.1.7.1 Reasons for discontinuation	Correction of reference section regarding drug discontinuation as a result of pregnancy or breastfeeding	Incorrect section referenced (5.5.2), updated to appropriate section (6.1.7.2)
6.1.7.1 Reasons for discontinuation	Addition of "Develops an AE that is deemed to be related or possibly related to the study drug" as reason for discontinuation of study med	Clarifying that any event that may be related to study drug should escalate the site to immediately stop treatment with the study drug. After resolution of the AE, study drug can be resumed with DMC approval.
6.1.7.2 Handling of study drug discontinuations	Addition language to address resuming study med after AE, "If the study drug is discontinued due to an AE reported as related or possibly related to the study drug, the possibility of resuming the study drug will be evaluated by the Drug Monitoring Committee once the AE has resolved (e.g. If cholelithiasis is reported as an AE and the gall bladder has been removed, the DMC may approve resumption of study drug)."	If the event that was determined to be related or possibly related to study drug has been resolved, resumption of study drug can occur after DMC approval.
8.1 Schedule of Events	Expansion of study visit window for Visit 2 from -1 week / +2 weeks to -1 week / +8 weeks	We are expanding the window for Visit 2 in order to reduce out of window visits due to the short timeframe between screening and Visit 2. Visit 2 is a baseline visit and occurs prior to the treatment interval. As all parameters which may change during this timeframe will be drawn at each visit, the expansion of this visit window will not impact participation or data integrity. Visit windows for all other visits will not change.
Potential Risks, 112.1.3.3. Risks associatioed with fenofibrate treatment	Addition of percentage of people whom develop cholelithiasis during treatment with fenofibrate	Indicating percent risk associated with the known risk of gallstones as we have done other possible risks.
Protection against risks; 12.2.2.2. Specific	Clarification of clinically significant hepatic disease based on the newly structured exclusion criteria listed above	Included language to specify when individuals are excluded due to hepatic disease/injury. Newly clarified exclusion

		criteria used as a basis for this language (note above change to exclusion criteria)
11.3.5. Model assumptions and alternative analyses	Correction of subgroup analysis from AER at baseline above and below 200 to above and below 300	Correction of typo

Date	02/02/2023
Previous Version	7.0
New Version	8.0

Location	**Change**	**Rationale**
Title Page and header	Version and date	Increment version and date
8.1 Schedule of Events	Remove AER/ACR from Central Lab testing for V5 and V6	The outcomes in the statistical analysis plan do not utilize urine AER/ACR results from Visit5 and Visit6, therefore we are removing those collections to reduce burden on study participants

Date	02/22/2023
Previous Version	8.0
New Version	8.1

Location	**Change**	**Rationale**
Title Page and header	Version and date	Increment version and date
Title Page, Header, & Protocol Summary Version Number and Date	Increment of 8.1 and date 02/23/2023	Version 8.0 was missing increments to version number and date in document header and in the protocol summary section. Updating to ver 8.1 to correct these errors with updated version and date.

PERL-Fenofibrate Pilot Protocol Change Log

New Version	9.0	
Previous Version	8.1	
Date	8/29/2023	
Changes		
Location	**Change**	**Rationale**
Title Page	Version 9.0 and date	
Header	Version 9.0 and date	Version and date increment
Section: Protocol Summary	Version number and date increment	Version and date increment
Section 8. Study Procedures, 8.1 Schedule of Events	• Addition of subsection: 8.1.1 Abbreviated protocol (visits 1-4) • Update to schedule of events to include annotation for abbreviated protocol, addition of physical exam and ECG to occur at V4, and additional column for a repeat V4 (V4a), if V4 iGFR returns invalid results.	Due to the stringent enrollment criteria for this trial, recruitment has become increasingly challenging. Even with the addition of 3 satellites sites, enrollment remains below the goal of 40 participants. In an effort to complete enrollment we have shortened the protocol to include those study procedures that occur from Visit 1 to Visit 4, Visit 4 being the study endpoint for the first Aim of the grant, "define the nature of the acute effect of fenofibrate on kidney function", the aim for which the study was powered. By shortening the protocol, we hope to enroll individuals who expressed interest, but did not have the time commitment for the full trial. Shortening the period of participation from 89 weeks to 13 weeks will also allow additional people to enroll and complete the study before the end of the funding period.
Section 8.6 Treatment period	• Addition of ECG and physical exam at V4 for participants enrolled in abbreviated protocol • Addition of directions for study medication after visits 4 for pariticpants enrolled in abbreviated protocol.	

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New Version	10.0	
Previous Version	9.0	
Date	10/28/25	
Changes		
Location	**Change**	**Rationale**
Title Page	Version 10.0 and date	
Header	Version 10.0 and date	Version and date increment
Section: Protocol Summary	Version number and date increment	Version and date increment
12.2.3.2. Data security	Description of digitization of participant binders	Due to limited storage space available as part of the Joslin re-location project, participant binders will be scanned and stored digitally