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

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Statistical Analysis Plan
v1.0

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1. Overview

DESIGN:

- Multicenter, double-masked, placebo-controlled, parallel-group
- N=40 total number of participants

STUDY POPULATION:

- Individuals with type 1 diabetes and early to moderate diabetic kidney disease (eGFR in the 40 to 99.9 ml/min/1.73 m^2 range) at high risk of further kidney function decline based on AER=100-5000 mg/24 hrs or ACR=100-5000 mg/g, or previous evidence of iGFR or eGFR decline ≥3 ml/min/1.73 m^2/year and micro- or macro-albuminuria during the PERL allopurinol trial.
- Full inclusion and exclusion criteria are listed in the protocol.

STUDY TREATMENTS:

- Oral fenofibrate (145 mg daily, decreased to 48 mg daily if the GFR falls below 30 ml/min/1.73 m2) or placebo for 76 weeks followed by an 8-week drug wash-out.
- A subset of participants underwent an abbreviated protocol aimed at addressing Aim 1, according to which they were treated with oral fenofibrate or placebo for only 8 weeks.

PRIMARY OUTCOME MEASURES:

- Aim 1: Baseline-adjusted iohexol GFR (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 at the end of the drug-wash-out period (week 84).

2. Schema

Figure 2.1. Fenofibrate Pilot Study Schema

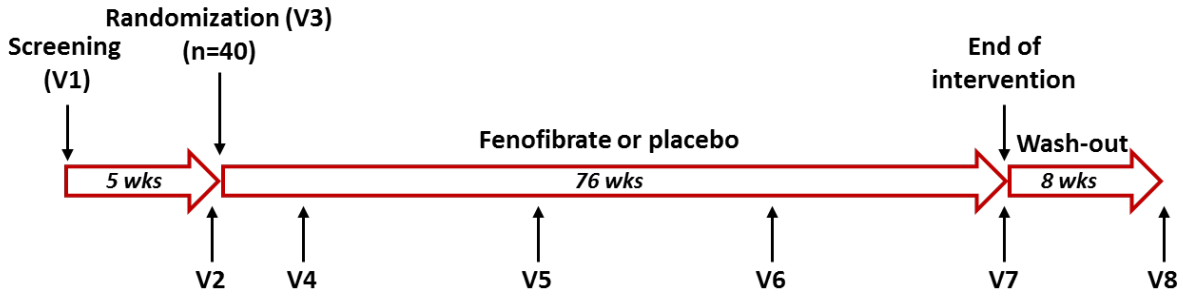
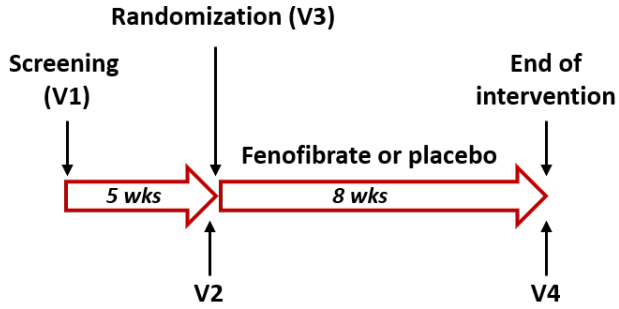


Figure 2.2. Fenofibrate Abbreviated Pilot Study Schema



3. Study Aims

The overall goal of this pilot study is to gain essential information to design a larger study investigating the hypothesis that fenofibrate, an inexpensive generic drug with an excellent safety profile, may slow or prevent GFR decline in persons with T1D. The objectives of this study are:

1. Define the nature of the acute effect of fenofibrate on kidney function. At this time, it remains unclear whether the acute, reversible reduction in eGFR observed with fenofibrate treatment (GFR dip)[1,2] 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)[3,4] – 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[5,6] 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 outcomes, we aim 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.[7] 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.

4. Study Estimands

This section describes the primary and secondary estimands for corresponding endpoints and variables of interest. We follow ICH-E9 (R1) recommendations and specify estimands in terms of five attributes defining the treatment effect of interest:

A1. **Treatment condition** of interest and treatment to be compared
A2. **Target population**
A3. **Variable (or endpoint)** to be obtained for each patient that is required to address scientific question of interest
A4. **Strategies for addressing intercurrent events**
A5. **Population-level summary for the variable (endpoint)** that provides a basis for a comparison between treatment conditions.

In Table 4.1, we include various intercurrent events that may have occurred in the pilot study and divide them into three groups, based on their implications for subsequent data collection of the endpoint of interest.

Table 4.1. Groups of potential intercurrent (IC) events

Group of IC events	IC event		Implications for Post-IC data

Group A	Non-adherence to study drug schedule		Post-IC data are collected, but their interpretation may be affected depending on the estimand of interest
	Permanent discontinuation of study drug		
	Use of prohibited medication		
	Missed scheduled visit		
Group B	Treatment of kidney failure (chronic dialysis or transplant)		Post-IC data do not contain any relevant information about estimands of interest and for this reason they are not collected
Group C	Early discontinuation from the study		Post-IC data cannot be collected
	Terminal event, i.e. death not related to kidney failure		

4.1. Primary estimands

4.1.1. Aim 1 Primary Estimand (Baseline-adjusted iGFR at 8 weeks after randomization).

This estimand concerns the acute effect of fenofibrate on kidney function (GFR dip), without confounding by any spurious effect that this drug may have on the metabolism of endogenous filtration markers such as serum creatinine. The five attributes of this estimand are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: The primary endpoint is the iGFR at the end of 8 weeks of treatment. iGFR after 8-week of treatment is measured by plasma iohexol disappearance.[3,4] 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.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest, in this case iGFR values, collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly

measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since the latter would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effect on iGFR at the end of 8 weeks of treatment adjusted by the baseline iGFR.

4.1.2. Aim 2 Primary Estimand (Baseline-adjusted iGFR at the end of the drug-wash-out period [week 84]).

This estimand concerns the longer-term effect of fenofibrate on kidney function. The five attributes of this estimand are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: The primary endpoint is the iGFR at the end of an 8-week washout after 76 weeks of treatment (Week 84). The rationale of measuring the Aim 2 primary outcome at the end of the wash-out period is to (1) evaluate treatment effects without the bias resulting from the potential reversible GFR reduction (GFR dip) induced by fenofibrate, and (2) test the durability of any treatment benefits. Furthermore, for the same sample size, the baseline-adjusted GFR at the end of the study provides greater power than other possible indices of DKD progression such as GFR slope over the treatment period (expressed as mL/min/1.73 m^2/year) or time to ≥ 40% GFR loss

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest, in this case iGFR values, collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since the latter would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effect on iGFR at the end of an 8-week drug-wash-out period following 76 weeks of treatment (week 84) adjusted by the baseline iGFR.

4.1.3. Aim 3 Primary Estimands (Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug-wash-out period [week 84]).

These related estimands concern the effect of fenofibrate on a panel of 21 biomarkers (so called Joslin Kidney Panel or JKP) identified by the Joslin group as predictors of high ESKD risk in persons with T1D.[7] The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: biomarkers of ESKD risk, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: The primary endpoint is the serum level of each of the 21 biomarkers at the end of an 8-week washout after 76 weeks of treatment (Week 84). Biomarkers are measured by an Olink multiplex assay. The rationale of measuring the Aim 3 primary outcome at the end of the wash-out period is to evaluate subclinical effects of treatment that are durable rather than reversible.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest, in this case biomarker values, collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on serum biomarkers of ESKD (kidney failure) at the end of an 8-week drug-wash-out period following 76 weeks of treatment (week 84) adjusted by the baseline biomarker values.

4.2. Secondary estimands

4.2.1. Aim 1 Secondary Estimands (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).

These related estimands concern the acute effects of fenofibrate on eGFR estimated from endogenous filtration markers (rather than directly measured) and other kidney function variables. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: eGFR-SCr (eGFR estimated from serum creatinine by means of the CKDEPI 2021 equation,[8] eGFR-CysC eGFR estimated from serum cystatin C by means of the CKDEPI 2012 equation,[9] uAER (albumin excretion rate measured through timed overnight urine collections), creatinine clearance (measured through timed overnight urine collections), ERPF (measured by PAH clearance) and afferent and efferent arteriolar resistances, estimated glomerular hydrostatic pressure and filtration pressure (estimated from ERPF, iGFR, blood pressure, total plasma proteins, and hematocrit by means of the Gomez equations[10-13]) at week 8.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variables of interest collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since the latter would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on eGFR-SCr, eGFR-CysC, uAER, creatinine clearance, ERPF, renal hemodynamic indices at the end of 8 weeks of treatment adjusted by their baseline values.

4.2.2. Aim 2 Secondary Estimand Group #1 (Baseline-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the drug-wash-out period [week 84]).

These estimands concern longer-term effects of fenofibrate on eGFR estimated from endogenous filtration markers (rather than directly measured) and on urinary albumin excretion rate. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: eGFR-SCr (CKDEPI 2021), eGFR-CysC (CKDEPI 2012), and uAER at the end of an 8-week drug-wash-out period following 76 weeks of treatment (week 84. The rationale of measuring these outcomes at the end of the wash-out period is to (1) evaluate treatment effects without the bias resulting from the potential reversible GFR reduction (GFR dip) induced by fenofibrate, and (2) test the durability of any treatment benefits. Furthermore, for the same sample size, the baseline-adjusted GFR at the end of the study provides greater power than other possible indices of DKD progression such as GFR slope over the treatment period (expressed as mL/min/1.73 m^2/year) or time to $\geq$ 40% GFR loss.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on eGFR-SCr, eGFR-CysC, and uAER at the end of an 8-week drug-wash-out period following 76 weeks of treatment (week 84) adjusted by their baseline values.

4.2.3. Aim 2 Secondary Estimand Group #2 (Baseline-adjusted iGFR, eGFR-SCr, eGFR-CysC, and uAER at the end of treatment [week 76])

These estimands concern the net effects (including acute and longer-term effects) of fenofibrate on eGFR estimated from endogenous filtration markers (rather than directly measured) and on urinary albumin excretion rate. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: iGFR, eGFR-SCr (CKDEPI 2021), eGFR-CysC (CKDEPI 2012), and uAER. The rationale of measuring these outcomes at the end of the treatment period, with adjustment for their baseline values, is to estimate the net effect (including acute and longer-term effects) of fenofibrate on eGFR and uAER.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on eGFR-SCr, eGFR-CysC, and uAER at the end of 76 weeks of treatment adjusted by their baseline values.

4.2.4. Aim 2 Secondary Estimand Group #3 (Week 8-adjusted iGFR, GFR-SCr, eGFR-CysC, and uAER at the end of treatment [week 76]).

These estimands concern the longer-term effects of fenofibrate on eGFR estimated from endogenous filtration markers (rather than directly measured) and on urinary albumin excretion rate. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: iGFR, eGFR-SCr (CKDEPI 2021), eGFR-CysC (CKDEPI 2012), and uAER. The rationale of measuring these outcomes at the end of the treatment period, with adjustment for their values at week 8, is to obtain an estimate of the longer-term benefit of fenofibrate on kidney function, avoiding the negative confounding of acute, reversible GFR changes induced by this drug.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on eGFR-SCr, eGFR-CysC, and uAER at the end of 76 weeks of treatment adjusted by their values at 8 weeks.

4.2.5. Aim 2 Secondary Estimand Group #4 (eGFR-SCr and eGFR-CysC trajectories from week 8 to week 76).

These estimands concern the effect of fenofibrate on the rate of kidney function decline during the treatment period, after the acute eGFR reduction induced by fenofibrate has occurred. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: kidney function, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: eGFR-SCr (CKDEPI 2021) and eGFR-CysC (CKDEPI 2012) values obtained between week 8 and week 76.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons are automatically addressed by the analytical method that is employed for these outcomes (mixed linear effect regression), which considers all available measures up to the time of study discontinuation.

A5. **Population summary to compare treatments**: Population-average treatment effects on rates of eGFR-SCr and eGFR-CysC decline expressed as ml/min/1.73m^2/year.

4.2.6. Aim 3 Secondary Estimand Group #1 (Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]). These estimands concern the net effect (including acute and longer-term effects) of fenofibrate on 21 biomarkers (so called Joslin Kidney Panel or JKP) identified by the Joslin group as predictors of high ESKD risk in person with T1D. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: biomarkers of ESKD risk,, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: The primary endpoint is the serum level of each of the 21 JKP biomarkers at the end of the drug treatment period [week 76]. JKP biomarkers are measured by an Olink multiplex assay. The rationale of measuring these outcomes at the end of the treatment period, with adjustment for their baseline values, is to estimate the net effect (including acute and longer-term effects) of fenofibrate.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest, in this case biomarker values, collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on serum biomarkers of ESKD (kidney failure) at the end of the drug treatment period [week 76]. adjusted by the baseline biomarker values.

4.2.7. Aim 3 Secondary Estimand Group #2 (Week 8-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]). These estimands concern the longer-term effects of fenofibrate on 21 biomarkers (so called Joslin Kidney Panel or JKP) identified by the Joslin group as predictors of high ESKD risk in person with T1D. The five attributes of these estimands are as follows:

A1. **Treatment condition** of interest and treatment to be compared: biomarkers of ESKD risk, fenofibrate (experimental therapy) and matching placebo (control group).

A2. **Target population**: Type 1 diabetes patients with early to moderate diabetic kidney disease at high risk of further kidney function decline.

A3. **Variable (or endpoint)**: The primary endpoint is the serum level of each of the 21 JKP biomarkers at the end of the drug treatment period [week 76]. JKP biomarkers are measured by an Olink multiplex assay. The rationale of measuring these outcomes at the end of the treatment period, with adjustment for their values at 8 weeks, is to obtain an estimate of the effect of fenofibrate on ESKD risk biomarkers, avoiding the confounding of acute changes induced by this drug.

A4. **Strategies for different groups of IC events**: Depending on IC event group membership (see Table 4.1), the variable of interest, in this case biomarker values, collected after an IC event will be considered as follows:

- Group A: the variable outcome will be considered as directly interpretable. Effectively, IC events in this group are ignored, which is consistent with the ITT principle.
- Group B: No kidney failure (ESKD) events were observed in the study.
- Group C: No discontinuations due to death were observed in the study. Discontinuations due to other reasons will be addressed by using a complete-case approach, in which only participants in whom the outcome variable was directly measured are included in the analysis. Given the small size of the study, its pilot nature, and the likely non-informative missingness, this approach was deemed preferable to imputing missing outcome variables, since this other approach would have added complexity without clear benefits.

A5. **Population summary to compare treatments**: Population-average treatment effects on serum biomarkers of ESKD (kidney failure) at the end of the drug treatment period [week 76]. adjusted by the week 8 biomarker values.

5. Analytical Strategy

The initial data analysis will be performed to detect any differences in distributions of characteristics measured at each study visit between treatment groups. 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, interquartile ranges) will be estimated from the data for continuous variables. Frequency distributions will be provided for categorical data. This preliminary analysis step will provide us

with insight into data, distributions of the variables considered, and will allow us to find additional invalid values not detected earlier during data validation.

No formal interim analyses of the primary endpoint will be conducted (see Section 11.3.7 of the Study Protocol). Given this and the pilot nature of the study, a nominal α level of 0.05 will be used for all the analyses of primary and secondary outcomes.

5.1. Study Populations

Multiple study populations will be defined for the purpose of data analysis:

- ***Intention to Treat (ITT):*** The ITT analysis set consists of all participants enrolled in SUGARNSALT, randomized to study medication.
- ***Per Protocol (PP):*** A per protocol analysis sets will be defined for each primary and secondary outcome as the subset of the ITT population with observed data for that outcome.
- ***Safety:*** The safety analysis set consists of all randomized participants who received at least one dose of study medication.

5.2. Blinded Data Review

Prior to unmasking the study and starting any formal analysis, data will be reviewed in a blinded fashion by computing summary statistics for primary and secondary outcomes. This will allow the identification of unusual values and/or patterns of missing values for key variables that need to be queried. All decisions will be made and documented in this SAP document prior to database lock and unblinding.

5.3 Baseline Covariates

The following baseline covariates will be used in the various analyses outlined in the remainder of Section 5:

- Study site with two levels (Joslin and Michigan)
- Treatment group with two levels (Sotagliflozin, Placebo)

In the study protocol, we proposed to also include a categorical indicator of whether the individual had previously participated in the PERL allopurinol trial. However, after observing that only five randomized subjects had previously participated in the allopurinol trial, we decided to omit this covariate from all analyses.

5.4 Missing Values

Given the small size of the study, its pilot nature, and the likely non-informative missingness (no outcome data were missing due to kidney failure or death), we decided to use a complete-case approach for each outcome, in which only participants with available data for that outcome and for covariates are included in the analyses. This approach was deemed preferable to imputing missing variables, since the latter would have added complexity without clear benefits.

5.5. Analyses for Primary Estimands

In this Section, we describe analyses of the primary estimands defined in Section 4.1.

5.5.1. Aim 1 Primary Estimand (Baseline-adjusted iGFR at 8 weeks after randomization).

The goal of the analysis is to test the null hypothesis of the difference in means between treatment arms in the primary endpoint (baseline-adjusted iGFR at the end of 8 week of

treatment) being equal to zero. This will be accomplished by means of the following analysis of covariance (ANCOVA) model:

M1: iGFR at 8 weeks ~ treatment group + Study site indicator + iGFR at baseline

Results of the analysis will be expressed in terms of the point estimate and its corresponding 95% confidence interval (CI) for the treatment effect at the end of 8 weeks of treatment and will be accompanied by the corresponding p value.

We decided to adjust the dependent variable for its value at baseline to reduce both error variance and regression to the mean effects. The research by Tu et al. (2005) confirms that this ANCOVA based approach provides higher statistical power compared to using change in the dependent variable as an outcome. This effect is especially prominent if the correlation between pre- and post-treatment dependent variable values is moderate.

Estimand	Aim 1 Primary estimand defined in Section 4.1.1 (Baseline-adjusted iGFR at 8 weeks after randomization).
Analysis Set	Per Protocol Population for Week 8 iGFR
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	iGFR at the end of 8 weeks of treatment (week 8)
Model	Fixed effects: • Treatment group • Study site • Baseline iGFR
Results	• Least square iGFR means at the end of 8 weeks of treatment • Estimate of treatment effect at the end of 8 weeks of treatment adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.5.2. Aim 2 Primary Estimand (Baseline-adjusted iGFR at the end of the drug-wash-out period [week 84]).

The goal of the analysis is to test the null hypothesis of the difference in means between treatment arms in the primary endpoint (baseline-adjusted iGFR at the end of 8-week washout following 76 weeks of treatment) being equal to zero. This will be accomplished by means of the following analysis of covariance (ANCOVA) model:

M1: iGFR at the end of washout~ treatment group + Study site indicator + iGFR at baseline

Results of the analysis will be expressed in terms of the point estimate and its corresponding 95% confidence interval (CI) for the treatment effect at the end of 8 weeks of treatment and will be accompanied by the corresponding p value.

As with the primary estimand for Aim 1, we decided to adjust the dependent variable for its value at baseline as this ANCOVA based approach provides higher statistical power compared to using change in the dependent variable as an outcome.

Estimand	Aim 2 Primary estimand defined in Section 4.1.2 (Baseline-adjusted iGFR at the end of the drug-wash-out period [week 84])
Analysis Set	Per Protocol Population for Week 84 iGFR
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	iGFR at the end of washout (week 84)
Model	Fixed effects:

	• Treatment group • Study site • Baseline iGFR
Results	• Least square iGFR means at the end of the drug washout (week 84) • Estimate of treatment effect at the end of the drug washout (week 84) adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.5.3. Aim 3 Primary Estimands (Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug-wash-out period [week 84]).

The goal of the analysis is to test the null hypothesis of the difference in means between treatment arms in the primary endpoints (baseline-adjusted JKP biomarker levels at the end of 8-week washout following 76 weeks of treatment) being equal to zero. This will be accomplished by means of the following analysis of covariance (ANCOVA) model:

M1: JKP biomarker level at the end of washout~ treatment group + Study site indicator + JKP biomarker at baseline

Results of the analysis will be expressed in terms of the point estimate and its corresponding 95% confidence interval (CI) for the treatment effect at the end of 8 weeks of treatment and will be accompanied by the corresponding p value.

As with the primary estimands for Aims 1 and 2, we decided to adjust the dependent variable for its value at baseline as this ANCOVA based approach provides higher statistical power compared to using change in the dependent variable as an outcome.

Estimand	Aim 3 Primary estimand defined in Section 4.1.3 (Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug-wash-out period [week 84])
Analysis Set	Per Protocol Population for Week 84 biomarkers
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	JKP biomarker level at the end of washout (week 84)
Model	Fixed effects: • Treatment group • Study site • Baseline JKP biomarker level
Results	• Least square iGFR means at the end of the drug washout (week 84) • Estimate of treatment effect at the end of drug washout (week 84) adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6. Analyses for Secondary Estimands

5.6.1. Aim 1 Secondary Estimands

Estimand	Aim 1 Secondary estimand defined in Section 4.2.1 (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).
Analysis Set	Per Protocol Populations for week-8 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)

Dependent Variable	GFR-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
Model	Fixed effects: • Treatment group • Study site • Baseline outcome variable
Results	• Least square means of the outcome variables at the end of 8 weeks of treatment • Estimate of treatment effect at the end of 8 weeks of treatment adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.2. Aim 2 Secondary Estimand Group #1

Estimand	Aim 1 Secondary estimand Group #1 defined in Section 4.2.2 (Baseline-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the drug-wash-out period [week 84])
Analysis Set	Per Protocol Populations for week-84 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	eGFR-SCr, eGFR-CysC, and uAER at the end of the drug-wash-out period [week 84]
Model	Fixed effects: • Treatment group • Study site • Baseline outcome variable
Results	• Least square means of the outcome variables at the end of the drug washout (week 84). • Estimate of treatment effect at the end of the drug washout (week 84) adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.3. Aim 2 Secondary Estimand Group #2

Estimand	Aim 2 Secondary estimand Group #2 defined in Section 4.2.3 (Baseline-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the treatment period [week 76]
Analysis Set	Per Protocol Populations for week-76 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	eGFR-SCr, eGFR-CysC, and uAER at the end of the treatment period [week 76]
Model	Fixed effects: • Treatment group • Study site • Baseline outcome variable
Results	• Least square means of the outcome variables at the end of 76 weeks of treatment • Estimate of treatment effect at the end of 76 weeks of treatment adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.4. Aim 2 Secondary Estimand Group #3

Estimand	Aim 2 Secondary Estimand Group #3 defined in Section 4.2.4 (Week 8-adjusted eGFR-SCr, eGFR-CysC, and uAER at the end of the treatment period [week 76])

Analysis Set	Per Protocol Populations for week-76 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	eGFR-SCr, eGFR-CysC, and uAER at the end of the treatment period [week 76]
Model	Fixed effects: • Treatment group • Study site • Week-8 outcome variable
Results	• Least square means of the outcome variables at the end of 76 weeks of treatment • Estimate of treatment effect at the end of 76 weeks of treatment adjusted for baseline covariates and week 8 outcome variable level. • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.5. Aim 2 Secondary Estimand Group #4

Estimand	Aim 2 Secondary Estimand Group #4 defined in Section 4.2.5 (eGFR-SCr and eGFR-CysC trajectories from week 8 to week 76.
Analysis Set	Per Protocol Population for week-8 secondary outcomes
Methods	Linear mixed-effects model for longitudinal eGFR.
Dependent Variable	eGFR measures from week 8 to week 76
Model	Fixed effects associated with: • Study site • Treatment group • Time since randomization (in years) • Time by treatment group interaction Subject-specific random effects • Random intercept for eGFR • Random slope for eGFR
Results	• eGFR slope estimates and 95% CIs by treatment group • Estimate of a treatment effect measured as a difference between average eGFR time slopes for allopurinol and placebo groups adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.6. Aim 3 Secondary Estimand Group #1

Estimand	Aim 3 Secondary estimand Group #1 defined in Section 4.2.6 (Baseline-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]).
Analysis Set	Per Protocol Populations for week-76 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	Serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]).
Model	Fixed effects: • Treatment group • Study site • Baseline outcome variable
Results	• Least square means of the outcome variables at the end of treatment period (week 76)

	• Estimate of treatment effect at the end of 76 weeks of treatment adjusted for baseline covariates • 95% confidence interval for treatment effect • P-value for treatment effect

5.6.7. Aim 3 Secondary Estimand Group #2

Estimand	Aim 3 Secondary Estimand Group #2 defined in Section 4.2.7 (Week 8-adjusted serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]).
Analysis Set	Per Protocol Populations for week-76 secondary outcomes
Methods	Analysis of Covariance (ANCOVA)
Dependent Variable	Serum levels of biomarkers of increased ESKD risk at the end of the drug treatment period [week 76]).
Model	Fixed effects: • Treatment group • Study site • Week 8 outcome variable
Results	• Least square means of the outcome variables at the end of 76 weeks of treatment • Estimate of treatment effect at the end of 76 weeks of treatment adjusted for baseline covariates and week 8 outcome variable level. • 95% confidence interval for treatment effect • P-value for treatment effect

5.8 Other Analyses

5.8.1. Effect of GFR estimation method

Additional analyses will be done to assess whether the effects of fenofibrate on GFR varies according to whether GFR is estimated from serum creatinine or serum cyststatin C or is measured by iohexol plasma disappearance (iGFR). This question will be addressed by means of mixed effect linear regression using a dataset including three observations for each participant, one for each of the three methods of GFR measure/estimation. All GFR measurements will be included as a single "GFR" variable along with an indicator of the GFR estimation/measure method that was used for each observation. Differences in the effect of fenofibrate according to the GFR estimation method will be assessed by including a treatment x GFR method interaction term. A schematic description of this analysis is provided below.

Analysis Set	Per Protocol Populations for week-8 iGFR and eGFR
Methods	Linear mixed-effects model
Dependent Variable	GFR at the end of 8 weeks of treatment (week 8) measured by iohexol plasma disappearance (iGFR) or estimated from serum creatinine (eGFR-SCr) or serum cystatin C (eGFR-CysC).
Model	Fixed effects associated with: • Study site • Baseline iGFR • Treatment group • GFR method • GFR method by treatment group interaction Subject-specific random effects

	• Random intercept for GFR
Results	• Least square means of the outcome variable at the end of 8 weeks of treatment by treatment and method of GFR estimation. • Estimate of treatment effect at the end of 8 weeks of treatment adjusted for baseline covariates by method of GFR estimation. • Estimate of the differences between treatment effects estimated using eGFR-SCr or eGFR- CysC and treatment effect estimated using iGFR. • 95% confidence interval for treatment effect • P-value for treatment effect

5.8.2. Subgroup analyses

To investigate the possible presence of heterogeneity in the response to fenofibrate, subgroup analyses (based on the primary efficacy analysis described in **Section 5.5**, with the inclusion of an interaction term of the treatment group by the subgroup variable) will be performed. The pre-specified groups include:

- age (≤40 and >40 years)
- gender (male and female)
- HbA1c at Visit 4 (≤8.0 and >8.0%)
- eGFR at screening (≤40 ml/min and >40 ml/min/1.73m^2)
- UAER at baseline (≤500 and >500 mg/24 hr)
- Below and above median baseline value of each JKP biomarker

5.8.3. Analyses of safety outcomes

Safety during the post-randomization period will be summarized as follows:

- Percentage of participants with and number of SAEs during the treatment and washout period by MedDRA System Organ Class and by relatedness to study medication.
- Percentage of participants with and number of non-SAEs during treatment and washout period by MedDRA System Organ Class and by relatedness to study medication.
- Percentage of participants with and number of permanent discontinuations of study medication because of adverse effects during treatment period.

For dichotomous safety outcomes, the proportion of participants experiencing adverse outcomes (AEs, SAEs) will be summarized by treatment group and compared by means of odds ratios and 95% CIs. This analysis will employ the safety analysis set. No imputation for missing data will be used. No inferential analyses will be performed.

5.8.4 Analyses of other measures

In addition to primary, secondary, and safety measures, the following additional outcomes may be analyzed to help with the interpretation of study results:

- Descriptive statistics for body weight, blood pressure, eGFR, and HbA1c, and their changes from baseline, by treatment group in the ITT or PP populations. No imputation for missing data will be employed.
- Percentage of participants receiving adequate study medication exposure (i.e., fenofibrate or placebo) independent of adverse events. This is defined as the actual total dose during the 76-week dosing period, as determined from the dispensed dosage and pill counts, divided by the expected total dose, without consideration for temporary or permanent discontinuations or reductions owing to adverse events.

The proportion of participants receiving the presumed adequate study medication exposure is defined as the number of participants who had at least 80% and no more than 120% of the intended study medications during the entire dosing period, independent of adverse events, among all randomized participants. No imputation for missing data will be employed.

5.9. 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 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 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.

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