Protocol C0221002

A PHASE 2, 12-WEEK, ADAPTIVE, OPEN LABEL, SEQUENTIAL COHORT TRIAL TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06730512 FOLLOWING MULTIPLE DOSES IN ADULT SUBJECTS WITH PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Statistical Analysis Plan (SAP)

Version: 3.0

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1. VERSION HISTORY

This CSR Statistical Analysis Plan (**SAP**) for study **C0221002** is based on **Protocol Amendment 5** dated **18-Aug-2021**.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 08 FEB 2023	5 18 Aug 2021	Updates to minor components of analysis due to recent FDA guidance, CCI	• CCI • further clarification on analysis and presentation of multiple dose levels; • inclusion of robust standard error estimation included in SAS code due to updated FDA guidance on controlling for covariates in randomized controlled trials; • update sample SAS code due to incorrect coding in previous version; • update to language on missing values being imputed by MMRM; • CCI
2 08 FEB 2023	5 18 Aug 2021	Changes needed based on Protocol Amendment 5	• Updated study objectives, study design and stiatistical methods to extend treatment duration from 12 weeks to 24 weeks, and to add an optional cohort (Cohort 3) to potentially explore a higher dose of PF-06730512 CCI in subjects with FSGS, based on emerging data from the study.
2 08 FEB 2023	4 12 Jun 2020	Changes needed based on emerging data to incorporate into IA1 and align with current IA Charter	• Included PPAS analysis into IA readouts due to emerging discontinuations in the study (Section 4.2, 6.1.1.2 and Appendix 1.1). • Added predictive probability table related to first morning void sensitivity analysis as was required based on IA Charter (version 1.0) (Section 6.1.1.2 and Appendix 1.1). • Added safety summaries that may be required at IA2 and/or IA3 due to potential need for internal business decision making or external briefing documents (Section 6.5). • Clarified definition of baseline UPCR in case of scenario where Week -1 values were missing (Section 3.1.1).

			• CCI [redacted] • Updated study objectives and study design to align with current protocol (Section 2.1.3 and 2.2) and removed any mention of "Part B". • Clarified minor points for individual profile plots (Section 6.1.1.1). • Updated demographic tables as required for IA readouts (Sections 6.4.2 and 6.4.3). • Note: Minor formatting issues were identified during QC performed after 22 Dec 2020 final draft version and were the only edits incorporated after database snapshot for IA1. • Included clinical output assessments, PK, ADA/Nab.

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol Amendment 5.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C0221002.

2.1. Study Objectives

2.1.1. Primary Objective

Primary Objective(s):	***Primary Endpoint(s):***
• *To evaluate the efficacy of PF-06730512 compared to baseline in the reduction of proteinuria following 12 weeks of treatment in patients with FSGS.*	• *Percentage change from baseline to Week 13 in Urinary Protein to Creatinine Ratio (UPCR), calculated from the 24-hour urine collection.*
Secondary Objective(s):	***Secondary Endpoint(s):***
• *To evaluate the safety and tolerability of PF-06730512 following up to 24 weeks of treatment in subjects with FSGS.* • *To evaluate the effects of PF-06730512 on proteinuria time course.* • *To evaluate the effect of PF-06730512 on renal function.* • *To evaluate the serum exposure of PF-06730512 in FSGS patients.* • *To evaluate the immunogenicity profile of PF-06730512.*	• *Adverse Events, Laboratory Safety Tests (Hematology, Clinical Chemistry, Urinalysis), Body Weight, Blood Pressure, Pulse Rate, Body temperature and Electrocardiogram (ECG).* • *Percentage change from baseline to Weeks 2, 5, 9, and beyond Week 13, as applicable, in UPCR.* • *Percentage change from baseline to Weeks 3, 5, 9, 13 and beyond as applicable, in estimated glomerular filtration rate (eGFR).* • *Serum concentration of PF-06730512.* • *Incidence of the development of anti-drug antibody (ADA) and neutralizing antibody (NAb).*
CCI [redacted]	[redacted]
[redacted]	[redacted]

2.2. Study Design

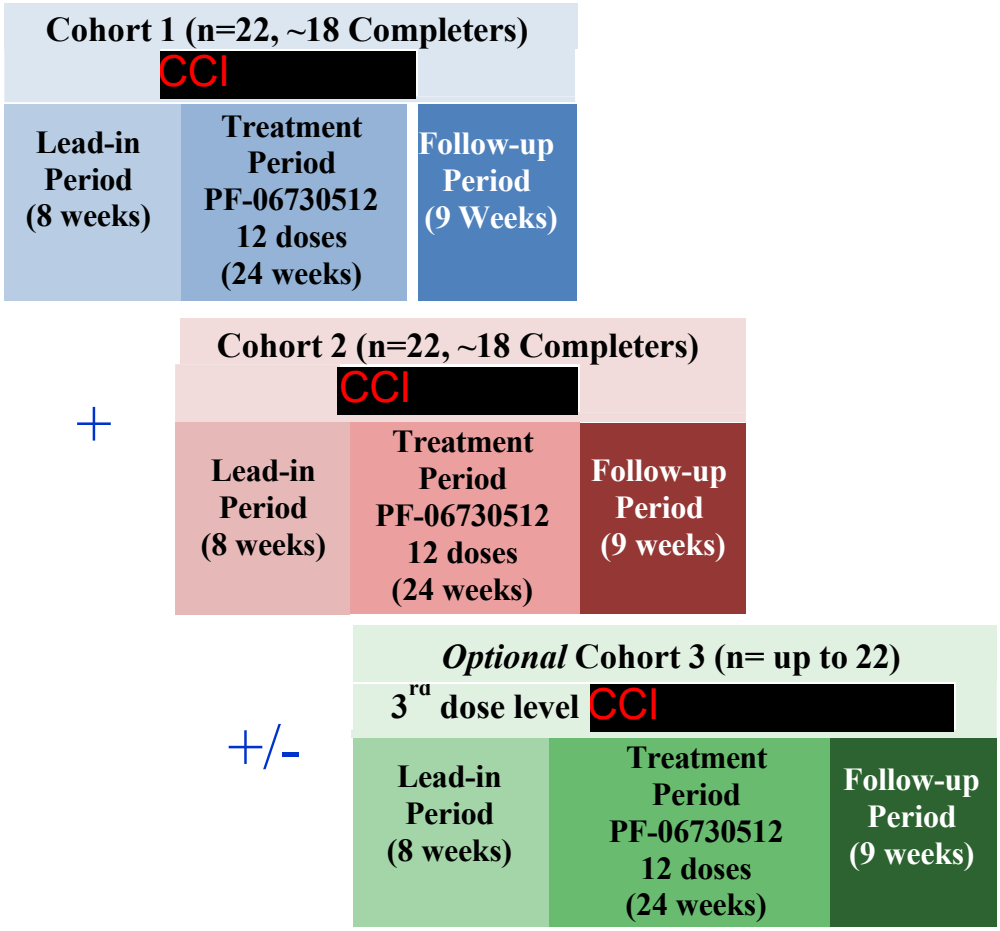
The adaptive study consists of a Screening Period of up to 43 days, an approximately 8-week Lead-in Period, an Investigational Treatment Period of up to 24 weeks during which subjects will receive PF-06730512 once every 2 weeks (Q2W), followed by an approximately 9-week

[redacted]

[redacted]

Follow-up Period. Delays to the beginning of Lead-in or Investigational Treatment Period (up to 1 week from visit window specified) due to pending primary or repeat laboratory results that are submitted for analysis within the protocol specified window, will not be considered protocol deviations.

Figure 1. Schematic of the Study Design



Upon commencement of active treatment with PF-06730512, subjects will be dosed intravenously Q2W for up to 24 weeks, but the primary endpoint result will be based on UPCR from a 24-hour urine collection at Week 13. There will be a maximum of 12 infusions of PF-06730512 within the 24-week Investigational Treatment Period. Subjects enrolled prior to Amendment 5 of the protocol will be dosed for 12 weeks with a maximum of 6 infusions of PF-06730512 within a 12-week Investigational Treatment period. *Telephone contact visits will be conducted the weeks in between dosing visits to check the subject's overall status, including new or worsening adverse events, changes to concomitant medications, compliance with appropriate contraceptive use, and reminders about upcoming urine collections, when applicable.*

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timepoints, according to the Schedule of Activities.

The duration of study participation will be up to approximately 11 months from Screening to the last post-treatment Follow-up Period visit. The durations of the study periods are listed below:

- *Screening Period up to 43 days;*
- *Lead-in Period: approximately 8 weeks;*
- *Investigational Treatment Period: up to 24 weeks (*up to 12 weeks for subjects enrolled prior to Amendment 5*);*
- *Follow-up Period: approximately 9 weeks (after last dose given at visit Week 11 or 23).*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

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3.1.1. Percentage change from baseline to Week 13 in Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection

The primary efficacy endpoint is the percentage change from baseline to Week 13 in the Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collections. UPCR will be calculated as urinary protein divided by the urinary creatinine value at the same collection time point. If a value of protein or creatinine is missing, UPCR will be missing for that respective value.

Baseline for the primary endpoint is defined as the Week -1 UPCR measurement that is based on the 24-hour urine collection. If the Week -1 24-hour UPCR value is not available, the nearest 24-hour UPCR measurement taken to the Week -1 visit will be used, provided it is pre-dose.

For sensitivity analyses utilizing first morning void UPCR assessments instead, the baseline is similarly defined as the Week -1 first morning void UPCR measurement. If the Week -1 first morning void UPCR value is not available, the nearest first morning void UPCR measurement taken to the Week -1 visit will be used, provided it is pre-dose.

Log-transformed change from baseline (i.e. the difference in $\log_e$-transformed values) will be the dependent variable in the analysis models. The results from the analysis models will be back-transformed to obtain the ratio to baseline. The percentage change from baseline will be derived by transforming the ratio using the following formula:

Percentage change from baseline = 100*([back-transformed LSMean] – 1)

For descriptive summaries, percentage change from baseline will be calculated as the Week 13 measurement minus the baseline value divided by the baseline value multiplied by 100.

3.2. Secondary Endpoint(s)

3.2.1. Percentage change from baseline to Weeks 2, 5, 9, and beyond Week 13, as applicable, in Urinary Protein to Creatinine Ratio (UPCR)

The secondary efficacy endpoints include percentage change from baseline to Weeks 2, 5 and 9 in UPCR based on both the 24-hour urine collections and the first morning voids. All analyses and descriptive summaries will report first morning void assesments and 24-hour urine assessments of UPCR separately. Descriptive statistics will be used to summarize UPCR by dose and timepoint for all timepoints in the Lead-in Period and the Investigational Treatment Period, as well as Week 13 data for subjects enrolled prior to amendment 5 and Week 25 data for subjects enrolled after amendment 5.

For descriptive summaries, percentage change from baseline will be calculated for each post-baseline measurement based on the respective urine collection, as that measurement minus the baseline value divided by the baseline value multiplied by 100.

3.2.2. Percentage change from baseline to Weeks 3, 5, 9, 13 and beyond, as applicable, in estimated glomerular filtration rate (eGFR)

The secondary efficacy endpoints of percentage change from baseline in estimated glomerular filtration rate (eGFR) include Weeks 3, 5, 9 and 13. Descriptive statistics will be used to summarize eGFR by dose and timepoint for all timepoints in the Lead-in Period and the Investigational Treatment Period, as well as Week 13 data for subjects enrolled prior to amendment 5 and Week 25 data for subjects enrolled after amendment 5.

The eGFR will be calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[1] (see Appendix 4).

[redacted]

[redacted]

Baseline is defined as the Week -1 measurement. If the Week -1 eGFR measurement is not available, the nearest eGFR measurement taken to the Week -1 visit will be used, provided it is pre-dose.

Log-transformed change from baseline will be the dependent variable in the analysis models. The percentage change from baseline will be calculated for each post-baseline measurement, as that measurement minus the baseline value divided by the baseline value multiplied by 100.

3.2.3. Serum concentration of PF-06730512

Blood samples (approximately 3 mL whole blood) to provide a minimum of 1 mL of serum for pharmacokinetic (PK) analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities section of the protocol.

Serum PK parameters will be derived, if data permits, *from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 1. Actual PK sampling times will be used in the derivation of PK parameters when available. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.*

Table 1. Serum PF-06730512 PK Parameters Definitions

Parameter	***Definition***	***Method of Determination***
AUC_{tau}	*Area under the concentration-time profile from time zero to time tau (the dosing interval)*	*Linear/Log trapezoidal method.*
$AUC_{tau}(dn)$	*Dose normalized AUCtau*	AUC_{tau}/*Dose*
C_{max}	*Maximum observed plasma concentration*	*Observed directly from data*
$C_{max}(dn)$	*Dose normalized maximum plasma concentration*	C_{max}/*Dose*
T_{max}	*Time to reach* C_{max}	*Observed directly from data as time of first occurrence*
$t_{½}$	*Terminal elimination half-life*	$Log_e(2)/k_{el}$, *where* k_{el} *is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.*
CL/	*Clearance*	*Dose/*AUC_{tau}
	Volume of distribution at steady state	*Dose/(*$AUC_{tau} \bullet k_{el}$*)*

- If data permits

[redacted]

[redacted]

3.2.4. Incidence of the development of antidrug antibody (ADA) and neutralizing antibody (NAb)

Blood samples (approximately 5 mL) to provide at least 2 mL of serum to detect ADA and NAb against PF 06730512 (~1 mL each of ADA and Nab) will be collected from subjects enrolled at the times specified in the Schedule of Activities.

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[redacted]

3.4. Safety Endpoints

3.4.1. Adverse Events (AEs)

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the Investigational Treatment Period and was not seen prior to the start of treatment (during the Lead-in Period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

Adverse events occurring during the Lead-in Period are considered non-treatment emergent. Events that occur during the Follow-Up Period will be counted as treatment emergent and attributed to the previous treatment taken.

A 3-tier approach for summarizing AEs will not be used for this study as a placebo or active comparator arm is not included in the design and there is a low number of subjects planned to be enrolled.

3.4.2. Laboratory Data

Safety laboratory tests (hematological, clinical chemistry (serum), urinalysis and other safety tests) will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline for all laboratory measurements will be defined as the pre-dose Day 1 (Week 1) measurement.

3.4.3. Vital Signs

Vital sign measurements (sitting blood pressure, pulse rate, and oral body temperature) will be taken as detailed in the Schedule of Activities given in the protocol.

Baseline is defined as the pre-dose Day 1 (Week 1) measurement. Changes from baseline for sitting systolic and diastolic blood pressure, pulse rate and body temperature will be

calculated for each post baseline measurement, as that measurement minus the baseline value.

3.4.4. Electrocardiogram (ECG)

A single standard 12-lead ECG (including QT, QTc, PR, QRS and heart rate) will be obtained at times detailed in the Schedule of Activities given in the protocol.

Baseline will be defined as the pre-dose Day 1 (Week 1) measurement. Change from baseline will be calculated for each post baseline measurement, as that measurement minus the baseline value.

3.4.5. Body Weight

Body Weight will be measured at times detailed in the Schedule of Activities given in the protocol.

Baseline will be defined as the pre-dose Day 1 (Week 1) measurement. Change from baseline will be calculated for each post baseline measurement, as that measurement minus the baseline value.

4. ANALYSIS SETS

4.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled subjects who have received at least one dose of study treatment and have at least one post-baseline measurement of UPCR based on 24-hour urine collection.

4.2. Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will be a subset of the FAS dataset. The primary analysis of the efficacy endpoints will be based on the FAS, with a sensitivity analysis conducted on the PPAS, which will include all subjects who were not major protocol deviators. Each deviation will be reviewed on a case by case basis to determine whether the subject should be excluded from the PPAS (based on Table 3).

Table 3 Potential reasons for exclusion of a subject from the PPAS

Exclusion of a subject	Responsibility	Action/Source	Required Listings from Programming
No valid primary efficacy measurement post-baseline (i.e. no readings in 24h UPCR at Weeks 5, 9 or 13)	Programmer/ Clinical/ Statistician	Programming check to highlight any subject with incomplete data, and those subjects with no primary efficacy readings at the scheduled time point. Listing will be reviewed by the clinician and statistician to determine if there is insufficient data.	Listing of whether primary efficacy reading was completed (including date/times of measurements).
Change in background treatment for FSGS (e.g. starting new immunosuppressant or increasing the dose of background steroids)	Programmer/ Clinical/ Statistician	Listing will be reviewed by the clinician and statistician to determine if subjects' change in background immunosuppressant medication (i.e. change of dosage or frequency) could have impact on efficacy	Listing of immunosuppressant medication (including dosage and frequency throughout study)
Falsely enrolled into study despite violating inclusion/exclusion criteria	Programmer/ Clinical/ Statistician	Review of all screening and baseline data listings.	Screening/Baseline data listings
Outside the visit window (±3 days) for the final primary endpoint time point (Week 13)	Programmer/ Clinical/ Statistician	Review of actual study day (collection date – first dosing date +1) for Week 13 visit. The window is 80~87.	Listing of actual study day for all subjects at Week 13.
Did not receive all specified doses of PF-06730512 as per protocol (i.e. missed dose not due to withdrawal from study)	Programmer/ Clinical/ Statistician	Programming check to highlight any subject who missed 1 or more dose of PF-06730512	Listing of study medication.

4.3. Safety Analysis Set

The Safety Analysis Set (SAS) is defined as all enrolled subjects who have received at least one dose of study treatment.

4.4. Other Analysis Sets

4.4.1. PK Concentration Analysis Set

The PK Concentration Analysis Set is defined as all enrolled subjects treated who received at least one dose of PF-06730512 and have at least 1 measureable concentration.

Subjects who experience events that may affect their PK profile (e.g. dosing error) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded from PK summaries if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

4.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all enrolled subjects treated who have at least 1 of the PK parameters.

4.4.3. Immunogenicity Analysis Set

The immunogenicity analysis population includes all treated subjects with at least 1 ADA sample (pre-dose or post-treatment) analyzed. If a subject only has pre-dose baseline data and no post-treatment immunogenicity data, this subject is not evaluable for subject-level ADA and NAb status and should not be included in subject-level data analysis (eg. overall ADA/NAb incidence, duration of ADA/NAb response).

5. GENERAL METHODOLOGY AND CONVENTIONS

The planned statistical methods and analyses for the primary and secondary endpoints are described in detail in Sections 6.1 and 6.2 below [redacted]

5.1. General Format

All tables, figures and listings for the final analyses will include titles/footnotes indicating the file in which the item is located and the date on which the item was produced as per Pfizer standards. All tables, figures and listings will also have a subtitle that will indicate the population on which the presentation is based.

5.2. Hypotheses and Decision Rules

No classical hypothesis testing will be done, as decisions will be based on Bayesian (posterior) probabilities. This Bayesian interpretation is based on the assumption that the model provides an adequate approximation to a Bayesian analysis with "vague" priors for all parameters in the model.

For final analysis, the decision criteria are given below and apply to each dose of PF-06730512 separately:

- *C1: At least **95%** confident that the PF-06730512 reduction **> 0%**;*

[redacted]

[redacted]

- *C2: At least **50%** confident that the PF-06730512 reduction **> 35%**.*

Interim Bayesian decisions, that is, the posterior predictive probability that at an interim analysis where less than the entirety of the cohort has been enrolled, that decisions C1 and C2 would be achieved once full enrollment has completed were performed at IA1 and IA3 for cohorts 1 and 3, respectively. Those probabilities will not be reproduced here. For the CSR, Table 14.2.1.1.7 and Table 14.2.1.1.6, Summary of Predictive Probabilities based on 24-Hour Urine Collection, at IA1 and IA3 using IA1 FAS and IA3 FAS may be used to present interim findings in the CSR.

5.3. General Methods

5.3.1. Summary Analyses for Continuous Data

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values. For endpoints to be analysed on the natural log scale, the geometric mean and geometric coefficient of variation will additionally be calculated.

5.3.2. Summary Analyses for Categorical Data

Categorical variables will be presented using summary statistics: number of observations, counts and percentages in each category.

5.3.3. Mixed Model Repeated Measures (MMRM)

The efficacy analyses over time will be based on the FAS and will use a mixed model repeated measures (MMRM) approach. The mixed effect repeated measures model will include baseline, week (as a factor), baseline*week interaction, and will use an unstructured covariance matrix for within-subject time-dependent correlation.

If convergence is not obtained or model fit is not adequate then other covariance structures will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters.

The probabilities for the decision criteria (listed in Section 5.2) for each of the doses (as required) will be calculated using the results of the MMRM (e.g. back-transformed LSmean estimate, standard error and degrees of freedom for Week 13).

The Least Squares Means (LSMeans) (back-transformed if $\log_e$ transformation is performed) together with 90% confidence intervals and standard errors will be obtained for each dose individually (if applicable) and week, and will be summarized in a table and a profile plot with a separate plot for each dose (if applicable).

Ratios in LSMeans (calculated by back-transforming modelled results if $\log_e$ transformation is performed), between doses at the different weeks, together with 90% confidence intervals and standard errrors, will also be obtained if applicable.

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5.4. Methods to Manage Missing Data

Missing values will not be imputed in the analysis. However, in the event of extensive missing data, alternative imputation methods may be explored.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Percentage change from baseline to Week 13 in Urinary Protein to Creatinine Ratio based on 24-hour urine collection (UPCR)

6.1.1.1. Primary Analysis

The primary analysis will be based on the FAS. A MMRM approach as specified in Section 5.3.3 will be fit to the post-dose 24-hour urine collection data on UPCR (i.e. Weeks 5, 9 and 13). All UPCR values (including baseline) will be $\log_e$-transformed prior to analyses. The primary analysis will include the change from baseline values of UPCR (on the $\log_e$-scale) as the dependent variable.

Absolute values and percentage changes from baseline in UPCR (based on 24-hour urine collection) will be summarized descriptively by dose (if applicable) and timepoint as described in Section 5.3.3. Tables will present all Lead-in Period, baseline and post-baseline time points where applicable. All 24-hour urine collection data will be included in the data listings.

The probabilities for the decision criteria for each of the doses (as required) will be calculated directly from the results of the MMRM. These are the probabilities that the reduction from baseline due to PF-06730512 (each dose level) is greater than (i) 0% and (ii) 35%. The LSMeans at Week 13 will be used to derive the posterior probabilities associated with the decision criteria.

A table showing the estimate of the mean of the posterior distribution for the percentage change from baseline for each dose of PF-06730512 (if applicable), the 90% credible interval and the posterior probabilities of passing the decision criteria will be produced (Appendix 3).

The following results from the above primary analysis will be plotted:

- Individual profile plots of the raw values (including all time points from Week -8, to Week 33) against time. Two plots per dose will be generated of absolute values and percentage changes from baseline. To distinguish between subjects enrolled before and after amendment 5, assessments from each individual's Follow-up Period will be interpolated with a different line style (e.g., a dashed line) than assessments from the Investigational Treatment Period.

- Profile plots of the back-transformed LSMeans (including 90% confidence intervals) over time, with a separate line included for each dose (if applicable).

No imputation of missing values will be conducted and all available data through Week 13 will be used in the MMRM models.

[redacted]

[redacted]

6.1.1.2. Sensitivity/Robustness Analyses

The following sensitivity analyses to the primary endpoint will be carried out:

- CCI [redacted]
- The primary efficacy endpoint will be analyzed for individual dose levels separately, and will follow the format described in section 5.3.3 and 5.3.4..
- The primary efficacy endpoint of % change from baseline in UPCR at week 13, and for all study weeks will be performed including the following potentially relevant covariates: GFR; disease duration (quantized into four categories);; and FSGS type, as measured by Columbia Classification consisteing of the following categories: PERIHILAR, CELLULAR, COLLAPSING, NOT OTHERWISE SPECIFIED. In the event the model does not converge due to sparseness in FSGS type, for example, a modified model excluding sparse covariates that impact model performance will be performed.
- CCI [redacted]
- CCI [redacted]
- The primary analysis MMRM model described in Section 6.1.1.1 will be repeated using the associated PPAS.

6.1.1.3. Statistical Model Diagnosis

The presence of outliers will be investigated for the primary analysis. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be generated of any subjects meeting these criteria for diagnostic purposes. The assumptions of normality will be verified graphically using residual plots.

If there are outliers or major deviations from normality then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses [redacted]

[redacted]

excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

6.2. Secondary Endpoint(s)

6.2.1. Percentage change from baseline to Weeks 2, 5, 9, and beyond Week 13, as applicable, in Urinary Protein to Creatinine Ratio (UPCR)

The analysis methodology for this secondary endpoint is summarized in Section 3.2.1.

For the CSR, an additional summary statistic table will be provided that is based on the respective SAS population.

6.2.2. Percentage change from baseline to Weeks 3, 5, 9, 13 and beyond, as applicable, in estimated glomerular filtration rate (eGFR)

The analysis for this eGFR endpoint will follow the same type of MMRM model and descriptive summary statistics as the primary analysis model (Section 6.1.1). Additional details regarding the handling of the eGFR endpoint can be found in Section 3.2.2.

6.2.3. Pharmacokinetics Analysis

The PK concentration population is defined as all enrolled subjects who received at least one dose of PF-06730512 and have at least 1 measurable concentration.

6.2.3.1. Serum and urine PK concentrations

Presentations for PF-06730512 concentrations for subjects in the Concentration Analysis Set (as defined in Section 4.4.1) will include:

- A listing of all concentrations sorted by dose level, subject ID, day, nominal time post-dose, actual times, and whether a subject was enrolled prior to or after protocol amendment 5. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by dose level and cohort, day, nominal time postdose, and enrollment prior to or after protocol amendment 5, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv%), minimum, maximum and the number of concentrations above the lower limit of quantification;

- Median concentrations time plots for timepoints

    - up to Week 13 predose (on both linear and semi-log scales) against nominal time post-dose by dose (all dose levels on the same plot per scale)

    - up to Week 13 predose (on both linear and semi-log scales) against nominal time post-dose by dose and ‘Baseline Nephrotic Range Proteinuria’ (see

Section 6.4; all dose levels and subgroups on the same plot per scale, using different line types to distinguish 'non-nephrotic' and 'nephrotic' range proteinuria at baseline)

- from Week 13 predose to last follow-up visit (on both linear and semi-log scales) against nominal time post-dose by dose and enrollment prior to or after protocol amendment 5 (all dose levels on the same plot per scale). Enrollment prior to, and after protocol amendment 5 will be distinguished with different line styles and/or symbols (e.g., solid vs dashed line)

- Mean concentrations time plots for timepoints
  - up to Week 13 predose (on both linear and semi-log scales) against nominal time post-dose by dose (all dose levels on the same plot per scale)
  - up to Week 13 predose (on both linear and semi-log scales) against nominal time post-dose by dose and 'Baseline Nephrotic Range Proteinuria' (see Section 6.4; all dose levels and subgroups on the same plot per scale, using different line types to distinguish 'non-nephrotic' and 'nephrotic' range proteinuria at baseline)
  - from Week 13 predose to last follow-up visit (on both linear and semi-log scales) against nominal time post-dose by dose and enrollment prior to or after protocol amendment 5 (all dose levels on the same plot per scale). Enrollment prior to, and after protocol amendment 5 will be distinguished with different line styles and/or symbols (e.g., solid vs dashed line)

- Individual concentration time plots by dose level and cohort (on both linear and semilog scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale). To distinguish between subjects enrolled before and after amendment 5, assessments from each individual's Follow-up Period will be interpolated with a different line style (e.g., a dashed line) than assessments from the Investigational Treatment Period.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06730512 concentration is quantifiable above the limit of quantification in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

6.2.3.2. Serum PK parameters

The serum PK parameters detailed in Section 3.2.3 will be listed and summarized descriptively by dose level, as data permit. Missing values will be handled as detailed in

Section 5.4.1. Each PK parameter will be summarized by dose level and will include the set of summary statistics as specified in Table 4.

Table 4. Serum PK Parameters to be Summarized Descriptively by Dose Level

Parameter	Summary Statistics
Day 1 and Day 71 AUC_{tau}, AUC_{tau}(dn), C_{max}, C_{max}(dn) CL, Vss	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
Day 1 and Day 71 T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Subject Disposition

Subject evaluation groups will show subject disposition and will show which subjects were analysed for efficacy (FAS) and safety (SAS). Frequency counts and percentages will be supplied for subject discontinuation(s) by dose.

6.5.2. Demographic Data

A summary of demographic data will be based on the respective SAS and provided for age, race, weight, body mass index and height. Baseline disease characteristics (duration of FSGS diagnosis, type of FSGS subtype and disease recurrence type) will be summarized in a further separate table.

Each will be summarized by sex at birth and 'All Subjects' for each dose separately.

6.5.3. Concomitant and Prior Medications

All prior and concomitant medication(s) will be reported and will be generated from the SAS. Three tables will be reported, one listing all concomitant medication(s), 1 restricted to treatments for FSGS and 1 restricted to antihypertensives and diuretics only.

6.5.4. Discontinuations

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarised by dose (if applicable) and will be based on the respective SAS.

6.6. Safety Summaries and Analyses

Safety summaries will be based on the SAS.

6.6.1. Adverse Events

Listings and summary tables of adverse events will be based on the SAS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by dose. Baseline is as defined in Section 3.5.2.

6.6.3. Vital Signs

Absolute values and changes from baseline in sitting systolic and diastolic blood pressure, pulse rate and body temperature will be summarized by dose. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

6.6.4. Electrocardiogram

Absolute values and changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by dose and time. Baseline is as defined in Section 3.5.4.

The number (%) of subjects with maximum postdose QTcF values and maximum increases from baseline in the categories specified in Appendix 5 will be tabulated by dose. In addition, the number of subjects with corrected and uncorrected QT values > 500 msec will be summarized and listed.

6.6.5. Body Weight

Absolute values and changes from baseline for body weight will be summarized by dose and time. Baseline is as defined in Section 3.5.5.

7. INTERIM ANALYSES

7.1. Introduction

The first interim analysis (IA1) and first committee meeting to review study data were scheduled after at approximately 50% of the planned subjects from the high dose cohort have completed the primary efficacy assessment. The second interim analysis (IA2) was conducted after all subjects from the high dose cohort completed the Week 13 visit or discontinued from the study. The third interim analysis (IA3) occurred after approximately 50% of the planned subjects from the low dose cohort completed the primary efficacy assessment. These details for IA1, IA2 and IA3 are summarised in Table 5.

[redacted]

[redacted]

Table 5 Timing of Interim Analyses

Name	Details of timing
IA1	After approximately 50% of the planned subjects from the high dose cohort have completed the primary efficacy assessment (expect ~9 completers)
IA2	After all subjects from the high dose cohort have completed the Week 13 visit or discontinued from the study
IA3	After approximately 50% of the planned subjects from the low dose cohort have completed the primary efficacy assessment (expect ~9 completers)

7.2. Interim Analyses

As this study is an open-label, Phase 2 non-pivotal study, a subset of the study team (hereafter referred to as "the committee") had continued access to the primary efficacy data throughout the conduct of the study oversaw the interim analyses, organized governance meetings, and ensured appropriate communications were conducted. CCI [redacted]

7.3. Ongoing monitoring of safety

This study will not use an external data monitoring committee (E-DMC). The study team and internal medical experts (eg, nephrologists) will review the accumulating safety data from this study on a regular basis. Additional details of the reviewing process are provided in the Charter for the safety review group.

Based on these reviews, there may be impact on the future conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed.

[redacted]

[redacted]

8. APPENDICES

Appendix 1. SUMMARY OF EFFICACY ANALYSES

Appendix 1.1. List of efficacy listings, figures and tables required

All plots produced may be used as in-text plots in the CSR and therefore need to be optimized for inclusion, i.e., legends, axis labels and titles should be clearly legible when inserted into one half of a page within the CSR.

Primary Analysis Output

Note for Table Type: L=listing, S=summary, SS=statistical summary, SA=statistical analysis (SAS Output is not needed form IA2), P=plot.

Table Type	Data Type	Analysis Set(s)	Title	Ref	Table Shell
L	UPCR	FAS	**Listing** of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection –FAS	1	16.2.6.1.1 in IA1 16.2.6.1.1.1 in IA2 & IA3
S	UPCR	FAS	**Summary** of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection –FAS	2	14.2.1.1.1 in IA1 14.2.1.1.1.1 in IA2 & IA3
SS	UPCR	FAS	**Statistical Summary** of **MMRM analysis** of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection –FAS	3	14.2.1.1.2 in IA1 14.2.1.1.2.1 in IA2 & IA3
SA	UPCR	FAS	**Statistical Analysis**: **Supporting Output** for MMRM analysis of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection – FAS	4	16.1.9.2.1
P	UPCR	FAS	**Individual Subject Data Plot** of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection –FAS	5	Figure 14.2.1.1.3, 14.2.1.1.4 in IA1, IA2 & IA3
P	UPCR	FAS	**LS Mean profile** (including 90% CI) plot for Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection –FAS	6	Figure 14.2.1.1.5 in IA1 Figure 14.2.1.1.5.1 in IA2 & IA3
SS	UPCR	FAS	Summary of **decision criteria** –FAS	7	Shell 1

					14.2.1.1.6 in IA1 14.2.1.1.7 in IA2 & IA3

Sensitivity Analysis to Primary Endpoint

- Outputs 1-6 & 8 to be repeated on MMRM analysis of first morning void UPCR.
- CCI [redacted]
- Outputs 3, 4 & 6 to be repeated on MMRM analysis of the PPAS.

Secondary Endpoints

Table Type	Data Type	Analysis Set	Title	Ref	Table Shell
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S	UPCR	FAS	Summary of Urinary Protein to Creatinine Ratio (UPCR) based on 24-hour urine collection by nephrotic-range proteinuria group –FAS	10	Shell 3 14.2.1.5.2 in IA1 14.2.1.1.1.3 in IA2 & IA3
L	eGFR	FAS	**Listing** of estimated Glomerular Filtration Rate (eGFR) - FAS	11	16.2.6.2.1 in IA2 & IA3
S	eGFR	FAS	**Summary** of estimated Glomerular Filtration Rate (eGFR) - FAS	12	14.2.2.1.1 in IA2 & IA3
SS	eGFR	FAS	**Statistical Summary of MMRM Analysis** of estimated Glomerular Filtration Rate (eGFR) - FAS	13	14.2.2.1.2 in IA2 & IA3
P	eGFR	FAS	**Individual Subject Data Plot** of estimated Glomerular Filtration Rate (eGFR) - FAS	14	Figure 14.2.2.1.3, Figure 14.2.2.1.4 in IA2 & IA3
P	eGFR	FAS	**LS Mean profile** (including 90% CI) plot for estimated Glomerular Filtration Rate (eGFR) - FAS	15	Figure 14.2.2.1.5 in IA2 & IA3

Appendix 2. STATISTICAL METHODOLOGY DETAILS

Appendix 2.1. Example SAS code for Statistical Analyses

Primary Analysis [Mixed Model Repeated Measures (MMRM)]:

Note: Loge_endpoint = log(UPCR at week x) – log(baseline)

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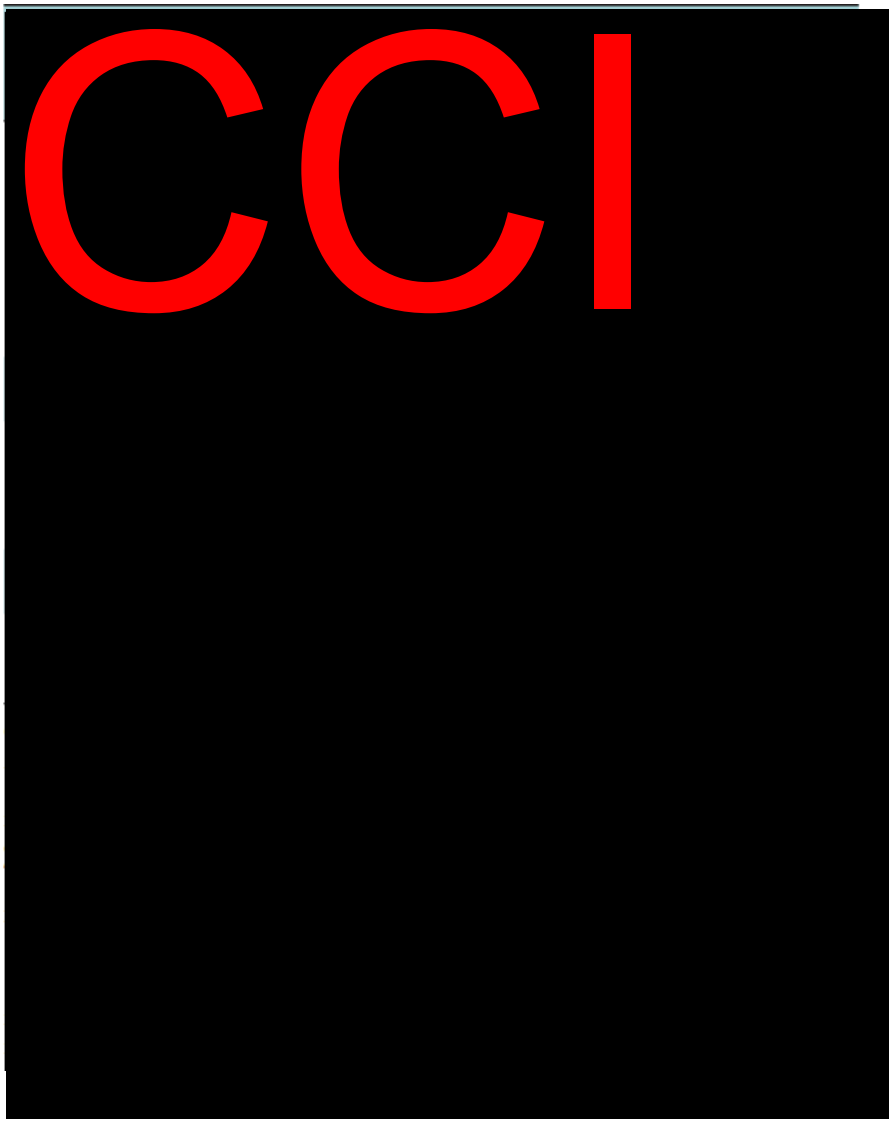

CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS OF POTENTIAL CLINICAL CONCERN

Categories for QTcF

QTcF (ms)	450< max. ≤ 480	480< max. ≤500	max. >500
QTcF (ms) increase from baseline	30< max. ≤60	max. >60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase	Baseline >200	Baseline ≤200 and

from baseline	and max. ≥25% increase	max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in the report.