A PHASE 2, 24-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 FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Investigational Product Number:	PF-06730512
Investigational Product Name:	Not Applicable (N/A)
US IND:	CCI
EudraCT Number:	2019-003607-35
Clinical Trials.gov ID	NCT03448692
Protocol Number:	C0221002
Phase:	2a

Document History

Document	Version Date	Summary of Main Changes and Rationale
Amendment 5	18 Aug 2021	The overall purpose of this amendment is to extend treatment duration from 12 weeks to 24 weeks, and to add an optional cohort to potentially explore a higher dose of PF-06730512. 1. Section 1.3. Rationale, Section 3. Study Design: Addition of an optional cohort (Cohort 3) to allow evaluation of a higher dose of PF-06730512 CCI [redacted] in subjects with FSGS, based on emerging data from the study. 2. Schedule of Activities: The SoA has been updated to incorporate extended treatment duration. Clarifications have been made to the table and footnotes to improve readability, redundancies have been removed and sections organized. Rows have been added to ensure appropriate timing and adequate data collection related to history of the disease under study (FSGS) and enrollment timing (non-randomized). 3. Schedule of Activities, Section 1.2.4. Nonclinical Safety, Section 1.3. Rationale, Section 3. Study Design, Section 6.3 Investigational Treatment Period: Extension of investigational treatment period from 12 weeks to 24 weeks to evaluate longer safety and durability of response to PF-06730512 in subjects with FSGS. Nonclinical safety data of the 6-month toxicity study conducted in rats were added to support extension of the treatment period. 4. Schedule of Activities, Section 6.2. Investigational Treatment Period: Additional telephone contact visits added in order to check on subject's overall status, including new, ongoing or resolved AEs or concomitant medications, contraceptive use and a reminder to

		the subject to collect the required urine samples and bring to the next study visit. 5. Schedule of Activities, Section 2. Study Objectives and Endpoints, Section 6.2. Investigational Treatment Period: Urine and blood sampling added to the Week 2 visit to enhance the understanding of pharmacokinetics (PK) profile and immunogenicity, as well as urine protein to creatinine ratio (UPCR), CCI 8. Section 1.2.5. Clinical Experience with PF-06730512: Removed TEAE tables and added reference to SRSD (the IB) to avoid redundancy between documents and streamline the protocol. 9. Protocol Summary, Section 2. Study Objectives and Endpoints: Endpoints with time duration (ie, up to Week 13) have been updated to encompass the extended duration of treatment, as applicable. CCI

		CCI [redacted] 10. Section 3.1 The Main Study to Assess PF-06730512, Section 6. Study Procedures: Delays in enrollment (up to 1 week) due to delayed laboratory test results will not be considered protocol deviations. This is to avoid requiring subjects to rescreen if the test results required for study entry are delayed due to circumstances out of the subject's or site's control, and the results are available within 1 week of the original screening window. 11. CCI [redacted] 12. Section 4. Subject Eligibility Criteria, Section 4.1. Inclusion Criteria: Specified in summary text that repeat testing is allowed to verify eligibility for Screening or Lead-in Period. Inclusion criterion #2. Clarified requirement for FSGS diagnosis includes a renal biopsy within the last 5 years, evaluated locally. Specific reference to number of glomeruli requiring segmental sclerosis has been removed. Inclusion criteria #4, 5 and 6 have been revised to provide clarity on the eligibility requirements related to the disease under study. 13. SoA, Section 4.1 Inclusion Criteria, Section 4.4.1 Reproductive Criteria: Specific requirements related to reproductive criteria and contraception requirements have been updated in Section 4.4.1. The language has been updated to reflect the current required guidance from Pfizer template, and to streamline the protocol. Repetitive information was removed from

		multiple sections, now referenced under Section 4.4.1. 14. Section 4.2 Exclusion Criteria: Clarifications provided; of note the context and content of criteria were not changed. Exclusion #11 added potential consultation with Sponsor to assist with interpretation of results, if needed. 15. Section 4.3 Criteria for Progression to Treatment on Day 1: Clarified the requirements for UPCR (from 24-hour urine) and eGFR results from Lead-in to confirm eligibility to progress to the Investigational Treatment Period, as not all eligibility criteria are required to be reconfirmed after Screening. 16. Section 5.8. Concomitant Treatments: Additional revisions have been incorporated to allow for investigator discretion for reasonable duration of prior and ongoing FSGS treatments, due to significant variability of treatment options and practice in each country. Further, the format has been revised from table to text for improved readability. Clarifications were also incorporated to allow for appropriate and adequate management of FSGS supportive medications during study conduct. 17. Appendix 3: Appendix 3 contained regional changes required by Health Authorities as part of Amendment 4 (eg, require use of condom for male participants). These changes have been applied to the study population, thus Appendix 3 which contained country-specific requirements for Japan and the EU is now incorporated into the main body of the protocol. 18. The administrative changes and clarifications from the 22 Dec 2020 Protocol Administrative Change Letter (PACL) have been incorporated, issued as PACL #1 for EU-specific regional Amendment 4 (June 2020) and as PACL #2 for global Amendment 3 (Jan 2020). Of note, PACL #1

		(12 June 2020) written under global Amendment 3 was incorporated in regional Amendment 4. 19. Minor corrections, clarifications to text, and correction of typographical errors have been made throughout the protocol to improve overall readability.
Amendment 4	12 June 2020	1. A region-specific change relevant only to sites in the European Union (EU) member states which participate in the Voluntary Harmonization Procedure (VHP) process, as well as any additional countries selected for study participation in the future, which revises language in Section 4.4.1. Contraception related to male subjects using a condom as protection from the potential risk of exposure via drug in the ejaculate which would pose a risk to a developing embryo/fetus in a women of childbearing potential (WOCBP). The section will now read: "In this study, male subjects are required to use a condom as protection from the potential risk of exposure via drug in the ejaculate which would pose a risk to a developing embryo/fetus in a WOCBP. This is purely precautionary as the calculated safety margin for PF-06730512 is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies". Rationale: This change in the form of a protocol amendment was requested by the VHP [grounds for non-acceptance (GNA) 31] and is applicable to sites in the EU member states which participate in the VHP process only and for any countries subsequently selected for trial participation. 2. Section 9.6 Interim Analysis. Added summarized details of the planned 3 interim analyses for this study, including the futility stopping criteria if applicable. Rationale: Details added to align with VHP request for a protocol amendment (GNA 48).

		3. Section 1.2.5.4 Benefit-Risk Assessment. Added text to clarify there are no important identified risks or important potential risks for PF-06730512, and based on the available safety and efficacy data for PF-06730512, the benefit-risk profile of the investigational medicinal product remains favorable. Rationale: Details added to align with VHP request for a Dear Investigator Letter or a protocol amendment (GNA 35). 4. Section 8.1.3 Withdrawal from the Study Due to Adverse Events and Section 8.4.3.1 Exposure During Pregnancy. Instructions added to clarify that withdrawal from the study due to an adverse event related to study drug is done at the discretion of the principal investigator and notification to the sponsor of the withdrawal must be accomplished immediately. In addition, pregnancy in a study participant must result in immediate cessation of study drug administration and study withdrawal. Rationale: Details added to align with VHP request for a Dear Investigator Letter or a protocol amendment (GNA 32). 5. Section 8.4.2 Potential Cases of Drug Induced Liver Injury (DILI). Instructions added to clarify that in case of potential DILI (Hy's law) events, the investigator must decide whether to interrupt or discontinue further administration of study drug. Rationale: Details added to align with VHP request for a Dear Investigator Letter or a protocol amendment (GNA 33). 6. Section 13.1 End of Trial in a Member State updated to clarify that the end of trial in all concerned countries is defined as last subject last visit (LSLV). Rationale: Details added to align with VHP request for a Dear Investigator Letter or a protocol amendment (GNA 34).

		7. Section 4.2 Exclusion criterion #21 added to clarify subjects with a history of hypersensitivity to the components of the study drug are not eligible to participate the study. Rationale: Additional exclusion criterion added at the request of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). 8. Appendix 3 Japan-Specific Requirements added to clarify country-specific subject selection criteria and highly effective contraception methods. Rationale: Incorporation of changes/clarifications made via Country (Japan) Level Protocol Administrative Changes and Clarifications (PACL) at the request of the PMDA. 9. SCHEDULE OF ACTIVITIES footnote e and f updated to clarify PK samples will be collected at Pre-dose (within 30 minutes prior to dosing) and at the end of infusion (within 6 minutes after the end of infusion) on Days 1 and 71 (Week 11), on Days 15, 29, 43, 57 at Pre-dose (within 30 minutes prior to dosing) only, and at follow up visits; Cytokines are collected at Pre-dose, 1hr, 2hr and 4hr post beginning of infusion within approximately ±15 minutes. Rationale: To provide clarification of the time window for PK and cytokine sample collection. 10. Section 4.4.1 Contraception footnote c updated to remove template instruction text and clarify acceptable contraceptive methods for females are limited to those which inhibit ovulation as the primary mode of action. Rationale: To remove protocol template instruction text and provide clarification. 11. Section 7.3.1 Serum for Analysis of PF-06730512 updated to clarify all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing and samples obtained within the time

		windows specified in the Schedule of Activity will not be captured as protocol deviations. Rationale: To provide clarification of the time window for PK sample collection.
Amendment 3	03 January 2020	Amendment 3 has become necessary mainly to allow for further changes in Inclusion and Exclusion Criteria. Main changes in Amendment 3 include the following: 1. Throughout the protocol, removed mention of primary FSGS and not explicitly excluding secondary FSGS. Rationale: This will allow inclusion of subjects with a diagnosis of secondary FSGS solely based on pathologic findings (percent foot process effacement) without evidence of a cause. 2. Section 4.1 Inclusion Criterion #5 updated to allow subjects treated with at least one, but no more than three prior immunosuppressant drugs. Rationale: Sequential use of drugs (alone or together) is standard of practice in treating FSGS. This will improve the study enrollment without impacting subject safety and the assessment of the study drug. 3. Section 4.1 Inclusion Criterion #6, Section 4.2 Exclusion Criterion #8 and Section 5.8 Concomitant Treatment updated to clarify that subjects are permitted to concomitantly take calcineurin inhibitors (CNIs) or mycophenolate mofetil (MMF) during the study provided they were on stable doses or serum levels prior to the start of the Lead-in Period. Rationale: This is consistent with standard of practice in treating FSGS. Clinicians hesitate to withdraw CNIs or MMF prior to entry into a FSGS protocol, especially when the only other drug is a reduced dose of corticosteroids.

		4. Section 4.2 Exclusion Criterion #3 updated to delete the subject eligibility assessment based solely on the HbA1c. Rationale: Poorly controlled diabetic subject will be excluded per investigator judgment. 5. Section 4.2 Exclusion Criterion #6 updated to increase the exclusionary Body mass index (BMI) from >40 kg/m^2 to >45 kg/m^2. Rationale: To include a wider range of patients with the rare disease FSGS. 6. Section 4.2 Exclusion Criterion #10 updated to increase the exclusionary blood pressure from ≥140/90 to ≥155/95 mmHg and allow repeat BP measurements on a different day. Rationale: This is consistent with the blood pressure status of patients with FSGS. 7. Section 4.2 Exclusion Criterion #18 and Section 6 STUDY PROCEDURES and Section 7.1.1 Laboratory Tests updated to delete the subject eligibility assessment based on the screening drug test of tetrahydrocannabinol (THC). Rationale: This is consistent with the evolving regulatory status of the cannabidiol products. Such products are now legal in many States and Countries. 8. Section 4.2 Exclusion Criteria updated to clarify that subjects with a known history of CMV disease, CMV mononucleosis, gammaherpesviral mononucleosis, parvovirus infection, or simian virus 40 infection, and subjects with a history of bilateral vesicoureteral reflux, or history of prior treatment with or use of interferon, lithium, pamidronate, mTOR inhibitors, testosterone/anabolic steroids, anthracycline (doxorubicin), heroin are not eligible to the study. Rationale: To exclude the majority of ineligible cases of secondary FSGS.

		9. PROTOCOL SUMMARY, Section 3.1 The Main Study to Assess PF-06730512, and Section 6.2 Screening and Lead-in Period Activities and Assessments updated to clarify that the Screening window is up to 39 days. Rationale: The protocol has inconsistent language regarding the screening window duration. The SCHEDULE OF ACTIVITIES table captures visit days for Screening to Lead-In Period to be up to 39 days. 10. Section 6 STUDY PROCEDURES and SCHEDULE OF ACTIVITIES updated to clarify that Screening procedures may be split into two visits if needed (however informed consent must be obtained prior to any study procedures taking place and at the beginning of the first Screening visit). Rationale: To improve compliance with procedures by increasing flexibility in screening visits. 11. CCI [redacted] CCI [redacted] 12. Changes addressed in Protocol Administrative Change and Clarification Letters (PACLs) issued prior to Amendment #3 have been incorporated. 13. Additional logistical, administrative and formatting changes have been made, discrepancies eliminated, and typographical errors corrected.
Amendment 2	10 June 2019	CCI [redacted] Main changes in Amendment 2 include the following:

		1. Inclusion and Exclusion Criteria have been broadened to be able to include a wider range of patients with the rare disease FSGS. Rationale: Over the past few years, there has been an increase of studies competing for FSGS patients. Without changing the eligibility criteria, it could be difficult to recruit 44 subjects in this competitive environment. 2. CCI  3. The Natural History part of the study (Part A) has been deleted. Rationale: The main study started recruiting after pre-planned Amendment 1 was in place; there was no time to perform the Natural History part. 4. Preliminary results of study C0221001 reported in Amendment 1 have been updated with final results. Rationale: The FIH study has been completed with the Clinical Study Report. 5. The content of several Protocol Administrative Clarification Letters (PACL A1#1 - #7) was added to Amendment 2. Rationale: PACLs became necessary over the past year to adjust several logistical study aspects to the real world. They were included to provide

		clarifications to the investigative sites and the clinical research associates. 6. Additional logistical, administrative and formatting changes have been made, discrepancies eliminated and typographical errors corrected.
Amendment 1	09 May 2018	Amendment 1 has been **pre-planned to** allow the overlap of C0221001 (FIH) study completion and start-up activities of C0221002 in order to reduce overall development time. The primary reason for this amendment was to insert the appropriate doses, dosing frequency and route of administration for PF-06730512, based on results from the FIH study. Main changes made in the amendment include the following: 1. Specifications for dose levels, dosing frequency and route of administration for PF-06730512 have been inserted. Rationale: Preliminary safety and pharmacokinetic data from the FIH study became available in April 2018 and allowed final selection of dose levels, dosing frequency and route of administration. 2. Section 1 has been updated with the most current information regarding safety and pharmacokinetics from the ongoing study C0221001 as well as with toxicology and EFD data from nonclinical studies. Rationale: Data from the clinical and nonclinical studies became available in April of 2018. 3. Randomization of subjects to the high versus the low dose has been removed. Instead, a sequential design has been implemented allowing Cohort 1 enrollment to complete prior to enrollment of Cohort 2. Rationale: The incorporation of an Interim Analysis for efficacy and safety made it necessary to collect data from the high dose in an adequate number of subjects for statistical analysis. The

		overlap of subjects assigned to each cohort was too small to warrant randomization. 4. The SOA has been revised to reflect Q2W instead of Q1W dosing. Any dosing frequency-related changes have also been corrected in Section 6 and 7. Rationale: Refer to item #1 above. 5. The requirements for contraceptive use have been modified for male study subjects. Rationale: Contraceptive (condom) use is no longer a requirement for male subjects in this study because the calculated safety margin is 100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. 6. Changes addressed in Protocol Administrative Change and Clarification Letters (PACLs) issued prior to Amendment #1 have been incorporated. 7. CCI [redacted] 8. Additional logistical, administrative and formatting changes have been made, discrepancies eliminated and typographical errors corrected.
Original protocol	09 October 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of regulatory authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

PF-06730512, a recombinant human Roundabout Guidance Receptor 2 (ROBO2) human immunoglobulin (Ig) G1 crystallized fragment (Fc) fusion protein that acts as a Slit Guidance Ligand (SLIT) neutralizing ligand trap, is currently being developed for the treatment of Focal Segmental Glomerulosclerosis (FSGS).

Proteinuria is a hallmark of podocyte injury in kidney disease, including FSGS, which is the most common glomerular disease leading to end stage renal disease in the United States. Features of FSGS include progressive scarring of glomeruli and diffuse podocyte effacement. Initially, scarring is focused on portions of specific glomeruli, and as the disease progresses, scarring worsens within glomeruli and the number of affected glomeruli increases. Podocyte injury leads to effacement of the podocyte foot processes and a breakdown of the glomerular filtration barrier.[1,2] Directly targeting podocyte effacement could slow disease progression of FSGS patients.

Roundabout Guidance Receptor 2 (ROBO2) is a receptor for Slit Guidance Ligand (SLIT) protein ligands.[3] ROBO2 is expressed at the basal surface of glomerular podocytes in the kidney and Slit Guidance Ligand 2 (SLIT2) is present in kidney glomeruli. Upon SLIT2 binding, ROBO2 forms a complex with nephrin in the glomerular filtration barrier and acts as a negative regulator to inhibit nephrin-induced actin polymerization. The loss of ROBO2 increases the actin polymerization in the podocyte and alleviates the abnormal podocyte structural phenotype found in nephrin-null mice.[4] Loss of ROBO2 also increases adhesion of podocytes to the glomerular basement membrane in mice.[5] PF-06730512 is a SLIT neutralizing ligand trap currently under development for the treatment of FSGS.

PF-06730512 consists of the first two immunoglobulin (Ig) domains of ROBO2 fused to a human immunoglobulin G1 crystallized fragment (IgG1 Fc) through a glycine serine linker. PF-06730512 contains three mutations in the Fc region to reduce effector function of the molecule. The mechanism of PF-06730512 is to bind SLIT and prevent its interaction with the ROBO2 receptor on podocytes, thereby improving the structural integrity of podocytes, and reducing proteinuria.

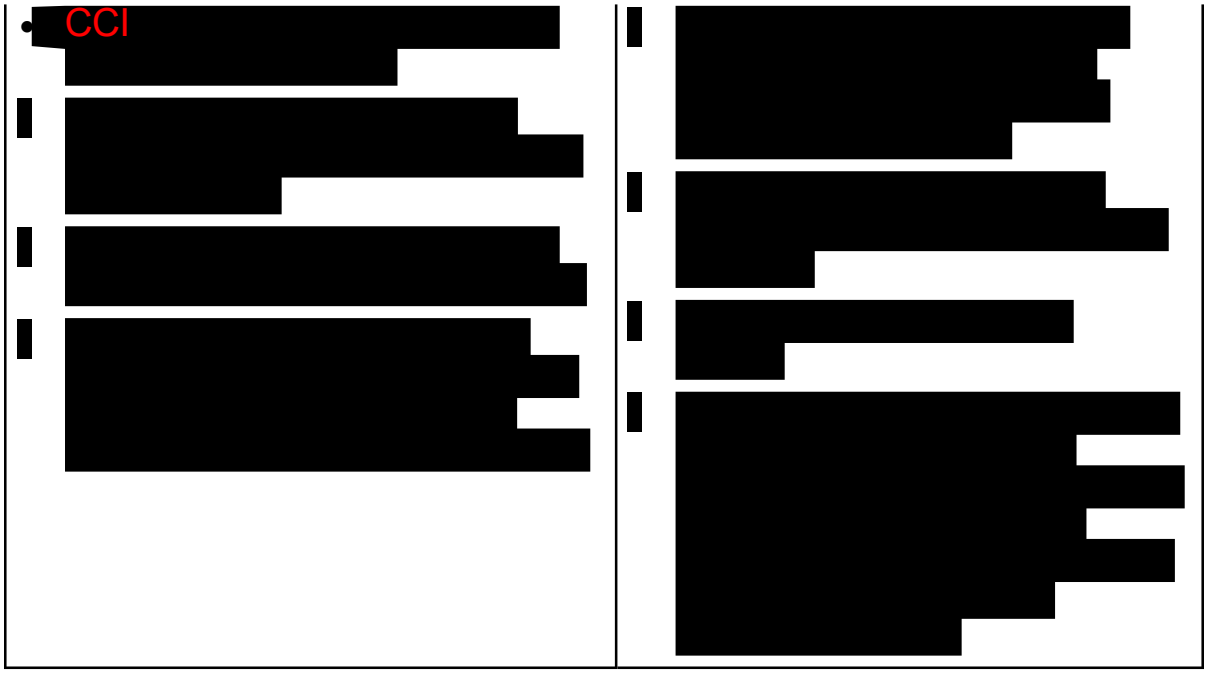
Study Rationale

An “Early Signal of Efficacy” (ESoE) design was chosen to enable the sponsor to relatively quickly identify if PF-06730512 is efficacious in the FSGS patient population prior to expanding the sample size and population to fully demonstrate efficacy and safety that is required for registration. Thus, although the purpose of this Phase 2 adaptive study is to evaluate the efficacy, safety, tolerability and pharmacokinetics of PF-06730512 following multiple intravenous administrations in adult subjects with FSGS, the primary intention is to obtain an early indication of efficacy. Up to 3 doses of PF-06730512 may be assessed in up to 3 separate cohorts.

All subjects will be required to complete an approximate 8-week Lead-in Period prior to receiving treatment with PF-06730512 in the Investigational Treatment Period. The Investigational Treatment Period will be 24 weeks in duration. Given the rarity of the disease and small sample size of the study, a placebo control is not being used. Adequate safety assessment will be feasible based on data obtained in the study's Lead-in Period in comparison to the Investigational Treatment Period and to historical data from previous clinical studies conducted in FSGS patients.

STUDY OBJECTIVES AND ENDPOINTS

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]



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 a 9-week Follow-up Period.

Subjects in the Lead-in Period will be eligible for transition to active treatment if at Week -1 the UPCR and eGFR meet eligibility criteria, as described in Section 4.3.

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. 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.

The study will investigate up to 3 doses of PF-06730512 in up to 3 cohorts, each consisting of up to approximately 22 subjects. CCI [redacted] All cohorts will collect the same procedures at the same timepoints, according to the Schedule of Activities. Interim analyses may be conducted

whilst the study is ongoing to determine futility of any evaluated dose, and to inform selection of next dose level to be evaluated (Section 9.6).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit days and Visit weeks are relative to first dosing day, Week 1 Day 1; listed days are the first days of the upcoming week.

Study Procedures Abbreviations in this Table may be found in Appendix 1: Abbreviations	**Screening Period**	**Lead-in Period**			**Investigational Treatment Period**													**Follow-up Period**				**Early Term**[i]
Visit Week[a]	**-12 to -9**	**-8**	**-4**	**-1**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**33**	
Visit Days[a]	**-90 to -57**	**-56**	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**225**	
Visit Window (days)	**-5**	**±5**	**±5**	**±5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±7**	
Informed Consent	X[b]																					
Demography (smoking, alcohol)	X[b]	X																				
Eligibility criteria	X	X[r]		X[r]																		
Medical history	X																					X
FSGS history; prior and ongoing FSGS treatment	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[d]	X	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]					[redacted]													[redacted]			[redacted]	
Contraception Check	X[b]	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring	X[b]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
12-lead ECG supine	X	X		X	X[c]		X		X		X	X		X[l]		X[l]		X			X	X
Vital Signs (BP, PR, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]		[redacted]		[redacted]				[redacted]				[redacted]						[redacted]			[redacted]	[redacted]
[redacted]		[redacted]	[redacted]				[redacted]				[redacted]						[redacted]			[redacted]		
Telephone Visit[k]							X	X	X	X	X	X	X	X	X	X	X					

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Visit Week[a]	**-12 to -9**	**-8**	**-4**	**-1**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**33**	
Visit Days[a]	**-90 to -57**	**-56**	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**225**	
Visit Window (days)	**-5**	**±5**	**±5**	**±5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±7**	
Study Treatment																						
Cohort Enrollment (non-randomized)					X[s]																	
PF-06730512 Administration[e]					X		X	X	X	X	X	X	X	X	X	X	X					
Infusion Site Reaction Assessment[e]					X		X	X	X	X	X	X	X	X	X	X	X					
Laboratory Assessments																						
Clinical Laboratory Tests (Section 7.1)	X	X	X	X	X[c]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Serum β-HCG (females of childbearing potential)	X	X		X	X[c,n]		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X		X	X	X
FSH (postmenopausal females), HBsAg, HBsAb, HBcAb, HCVAb, HIV	X																					
Lipid profile(post 8-hour fast)	X	X		X	X[c]			X		X		X		X		X		X			X	X
eGFR	X	X	X	X[s]	X[c]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
PF-06730512 PK					X[c,f]	X	X[g]	X[g]	X[g]	X[g]	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[f]	X	X	X	X	X
Cytokines[h]					X		X	X														
CCI					[redacted]																	
		[redacted]		[redacted]	[redacted]					[redacted]		[redacted]				[redacted]		[redacted]			[redacted]	
Immunogenicity (ADA, NAb)					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]	[redacted]																	[redacted]				[redacted]
Urine Collection																						
First Morning Void (FMV) (Subject to bring)	X[b,j]	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X		X	X
24-Hour Urine (Subject to bring)	X[j]	X		X		X		X		X		X		X		X		X	X		X	X
Urine for PK (20 mL from 24-hour urine collection)		X		X		X		X		X		X		X		X		X	X		X	X

Study Procedures Abbreviations in this Table may be found in Appendix 1: Abbreviations	**Screening Period**	**Lead-in Period**			**Investigational Treatment Period**													**Follow-up Period**				**Early Term**[i]
Visit Week[a]	**-12 to -9**	**-8**	**-4**	**-1**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**33**	
Visit Days[a]	**-90 to -57**	**-56**	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**225**	
Visit Window (days)	**-5**	**±5**	**±5**	**±5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±7**	
CCI		■		■		■		■		■		■		■		■		■	■		■	■
		■		■		■		■		■		■		■		■		■	■		■	■
		■		■		■		■		■		■		■		■		■	■		■	■
Urine reserve aliquot (10 mL from 24-hour collection)[p]		X		X		X		X		X		X		X		X		X	X		X	X
Urine drug test	X[m]																					
Urinalysis, including microscopy	X	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Urine Containers Distribution	X[b,j]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X		X		
Urine Collection Diary Distribution		X																				
Check Completion of Urine Collection Diary				X[o]		X		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]	X[o]		X[o]	X[o]

a. Visit day in study is relative to Day 1.

b. Subject written informed consent must be obtained prior to any study procedures taking place. The Screening process will require at least 2 site visits to accommodate at-home urine collection required to confirm eligibility (refer to footnote j). The subject must be provided with containers for urine collection and comprehensive instructions for the urine collection process at Screening Visit 1. For detailed collection procedures see Section 7.2.1.

c. All procedures and assessments should be done before dosing of PF-06730512, except for infusion site assessment, post-infusion electrocardiogram (ECG), and post-infusion PK and cytokine blood sampling (see footnotes f and h).

d. All physical examinations (full and brief examinations) must include edema assessment and weight. Full physical examination must be completed either at Screening or Week -8 Visit (first day of Lead-in Period); otherwise, brief examinations are performed if findings during previous examination or new/open AEs, at investigator discretion. Height is only measured once at Screening.

e. Investigational product (IP) administration will last approximately 60 minutes including the flush for the intravenous (IV) infusion. Post-infusion safety observation period of at least 3 hours is required after the first 3 doses of IP (Weeks 1, 3, and 5). The post-infusion observation period for all remaining IP administrations will be 1 hour (Weeks 7 – 23), provided no safety issues are observed.

f. Two PK samples will be collected: 1 sample at pre-dose (within 30 minutes prior to dosing), and 1 sample at the end of infusion (within 6 minutes after the end of infusion) on Days 1 and 71 (Week 11) and 155 (Week 23).

g. Only pre-dose PK samples will be collected on Weeks 3, 5, 7, 9, 13, 15, 17, 19, and 21 (within 30 minutes prior to dosing)

h. Cytokines are collected at pre-dose (within 30 minutes prior to dosing), and 1, 2 and 4 hours post beginning of infusion ±15 minutes. Extra blood samples for cytokine measurements should be taken immediately if a subject develops symptoms typical for an infusion reaction during the IP administration.

i. Subject who prematurely withdraws during Investigational Treatment Period (Week 1 through Week 24) should return for an Early Withdrawal/Termination visit and then enter into the Follow-up Period.

j. The 24-Hour and FMV urine collections are to be obtained from subject at follow-up Screening Visit (Screening Visit 2).

k. Telephone contact: Approximately 7 days after IP administration (±3 days at Weeks 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24) the subject will be contacted by telephone to discuss concomitant medications, contraceptive use and any new or changing adverse events. Subjects should also be reminded to collect urine samples as required and to bring the full containers back to site at the next visit (see footnote o below).

l. On IP administration days, 12-lead ECGs are done pre-dose and at the end of infusion, within an approximately 45-minute window.

m. The urine drug test at Screening is performed by the central lab.

n. Blood sample for serum β-HCG are collected for central lab testing (in females of child-bearing potential, Screening Visit 2, Weeks -8, -1, 25, 29 and 33). On all IP administration days, serum for pregnancy tests via test strip as a stat procedure performed locally at the site, with the negative result being available prior to the administration of IP (Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23).

o. Site personnel to call subject **prior to** the upcoming visit to remind the subject to perform FMV and a 24-hour urine collection, explain how to correctly collect and to bring the full FMV and 24-hour urine containers to the site at their scheduled study visit. ***This call is critical before Week -1, Week 13 and Week 25 and Week 33 Visits, or any Early Termination visits***. This call may be part of the Telephone contact calls, when applicable.

p. Prepare reserve 10-mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from main urine shipment, but on the same day. Any residual of this sample may also be used for exploratory purposes.

q. CCI

r. CCI

s. Prior to enrollment and first dose on Day 1, subjects must meet the eGFR and UPCR criteria outlined in Section 4.3.

t. A complete history of the subject's FSGS will be collected at screening, including initial diagnosis date, recurrence date if applicable, and prior and ongoing FSGS medications/treatments. Subjects will also be asked to provide their most recent diagnostic biopsy report. This request is optional and not required for enrollment. CCI

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06730512, a recombinant human Roundabout Guidance Receptor 2 (ROBO2)-human immunoglobulin (Ig) G1 crystallized fragment (Fc) fusion protein that acts as a SLIT neutralizing ligand trap, is currently being developed for the treatment of Focal Segmental Glomerulosclerosis (FSGS).

1.2. Background and Rationale

1.2.1. Rationale for Development of PF-06730512

Proteinuria is a hallmark of podocyte injury in kidney disease, FSGS, which is the most common glomerular disease leading to end stage renal disease. Features of FSGS include progressive scarring of glomeruli and segmental or diffuse podocyte effacement. Initially, scarring is focused to portions of specific glomeruli, and as the disease progresses, scarring worsens within glomeruli and the number of affected glomeruli increases. Podocyte injury leads to effacement of the podocyte foot processes and a breakdown of the glomerular filtration barrier.[1,2] Directly targeting podocyte effacement could slow disease progression of FSGS patients.

Roundabout Guidance Receptor 2 (ROBO2) is a receptor for Slit Guidance Ligand (SLIT) protein ligands.[3] ROBO2 is expressed at the basal surface of glomerular podocytes in the kidney and Slit Guidance Ligand 2 (SLIT2) is present in kidney glomeruli. Upon SLIT2 binding, ROBO2 forms a complex with nephrin in the glomerular filtration barrier and acts as a negative regulator to inhibit nephrin-induced actin polymerization. The loss of ROBO2 increases the actin polymerization in the podocyte and alleviates the abnormal podocyte structural phenotype found in nephrin-null mice.[4] Loss of ROBO2 also increases adhesion of podocytes to the glomerular basement membrane in mice.[5] PF-06730512 is a SLIT neutralizing ligand trap currently under development for the treatment of FSGS. PF-06730512 consists of the first two immunoglobulin (Ig) domains of ROBO2 fused to a human immunoglobulin G1 crystallized fragment (IgG1 Fc) through a glycine serine linker. PF-06730512 contains three mutations in the Fc region to reduce effector function of the molecule. The mechanism of PF-06730512 is to bind SLIT and prevent its interaction with the ROBO2 receptor on podocytes, thereby improving the structural integrity of podocytes, and reducing proteinuria.

CCI [redacted]

[redacted]

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CCI [redacted]

[redacted]

CCI [redacted]

1.2.5. Clinical Experience with PF-06730512

PF-06730512 was evaluated in a First-in-Human (FIH) study (C0221001) that has been completed and is being assessed in an ongoing Phase 2 study (C0221002).

1.2.5.1. Safety in Phase 1 C0221001 Study

In the FIH Study, C0221001, the safety of PF-06730512 was assessed in 79 (59 active and 20 placebo) healthy adult subjects. This study was a combined single ascending dose plus multiple ascending dose (SAD/MAD) study which was completed on 10 December 2018 with the Clinical Study Report. The study was a randomized, investigator- and subject-blinded (sponsor-open), placebo-controlled investigation of the safety, tolerability and PK of PF-06730512, following IV or SC administration (Cohorts 1-10). Additionally, an open label investigation of the safety, tolerability and PK of a single dose administration of PF-06730512 was conducted in healthy Japanese male subjects (Cohort 11). A total of 79 subjects were enrolled, with 6 subjects per cohort for Cohorts 1-3, 8 subjects per cohort for Cohorts 4-10 and 5 Japanese subjects in Cohort 11.

CCI [redacted]

There were no deaths, treatment-related Serious Adverse Events (SAEs), severe Treatment-Emergent Adverse Events (TEAEs) or infusion reactions. The majority of TEAEs were mild in severity and there was no clear dose-dependent increase in the frequency of TEAEs with increase in doses.

There were no clinically significant adverse safety laboratory changes or apparent adverse trends in the safety laboratory data. There were no dose-response relationships in fasting lipids identified in the study. No abnormalities in laboratory tests, vital signs, or ECGs were considered to be clinically significant or reported as AEs by the investigator.

CCI [redacted]

Complete safety information for this study can be found in the SRSD for PF-06730512, which for this study is the current Investigator Brochure.

1.2.5.2. Pharmacokinetics

In healthy non-Japanese subjects, C_{max} was observed shortly after the end of the infusion (median time for C_{max} [T_{max}] range of approximately 2.1 to 3.0 hours after the start of a 2-hour infusion) following single IV administration of PF-06730512 CCI [redacted] Serum concentrations post C_{max} exhibited a biphasic decline over time. Mean terminal halflife- ($t_{½}$) ranged from 5.3 to 13 days with a shorter $t_{½}$ observed at the lower doses, probably due to sensitivity limitation of the bioanalytical assay, ie, lack of quantifiable concentrations at later time points at lower doses. The geometric mean clearance (CL) values ranged between 0.034 to 0.054 L/hr across the doses and geometric mean volume of distribution at steady state (V_{ss}) values ranged from 9.3 to 14 L. CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

1.2.5.3. Immunogenicity

In the SAD part of Study C0221001, none of the 35 subjects who received PF-06730512 was confirmed positive for anti-drug antibodies (ADA). In the MAD part of Study C0221001, 2 of the 24 subjects CCI [redacted] who received PF-06730512 were confirmed positive for ADA, with 1 out of 24 subjects having positive neutralizing antibody (Nab). As the overall immunogenicity incidence was low, there was insufficient data to fully evaluate the effect of ADA/NAb on PK and safety. Evaluating the 2 subjects with positive ADA (and 1 of the 2 with NAb), no AEs, clinically significant findings or differences in PK were observed in relation to ADA/NAb.

There were no changes in cytokines considered to be clinically significant or reported as AEs by the investigator.

1.2.5.4. Safety in Phase 2 C0221002 Study

CCI [redacted] To date no adverse drug reactions have been identified from data collected.

1.2.5.5. Benefit-Risk Assessment

There are no adverse drug reactions identified from the nonclinical and clinical data collected. As such, there are no important risks or important potential risks for PF-06730512. Based on the available safety and efficacy data for PF-06730512, the benefit-risk profile of the medicinal product remains favorable.

1.3. Rationale

1.3.1. Study Rationale

An "Early Signal of Efficacy" (ESoE) design was chosen to enable the sponsor to relatively quickly identify if PF-06730512 is efficacious in the FSGS patient population prior to expanding the sample size and population to fully demonstrate efficacy and safety that is required for registration. Thus, although the purpose of this phase 2 adaptive study is to evaluate the efficacy, safety, tolerability and pharmacokinetics of PF-06730512 following multiple IV administrations in adult subjects with FSGS, the primary intention is to obtain an early indication of efficacy. Up to 3 doses of PF-06730512 may be assessed in up to 3 separate cohorts.

All subjects will be required to complete an approximately 8-week Lead-in Period prior to receiving treatment with PF-06730512 in the Investigational Treatment Period. The Lead-in Period is designed to:

1. Provide stable baseline data for proteinuria, as measured by urine protein to creatinine ratio (UPCR) and other laboratory and clinical markers of kidney function before subjects receive active treatment, thus enabling potential sensitivity analyses to the primary analysis using internal comparisons.

2. Assist in the interpretation of safety assessments by improving the differentiation of adverse events related to the course of FSGS under standard of care versus adverse events potentially related to investigational product during the Treatment Period.

The Investigational Treatment Period will be 24 weeks in duration.

Given the rarity of the disease and small sample size of the study, a placebo control is not being used. Adequate safety assessment will be feasible based on data obtained in the study's Lead-in Period in comparison to the Investigational Treatment Period and to historical data from previous clinical studies conducted in FSGS patients.

Safety monitoring will commence once the subject has provided informed consent. In the Lead-in Period, the focus will be on possible symptoms and complications of nephrotic syndrome including edema in peripheral (facial, extremity) and central (pleural effusion, ascites) locations, weight gain due to edema, ulcerations and infections in edema-dependent regions and worsening of hypertension. In addition, adverse events may occur due to thromboembolic complications related to FSGS which may manifest as renal venous thrombosis potentially extending to the inferior vena cava, deep venous thrombosis of the lower extremities and subsequent pulmonary embolism.[7] Adverse events may be related to side effects of previous or current FSGS therapy including cataracts, osteoporotic bone disease or avascular necrosis of the femoral head. A prolonged course of corticosteroids is associated with significant side effects, including diabetes, increased infection rates, osteoporosis, and weight gain. Nephrotoxicity is of great concern in the usage of calcineurin inhibitors in treatment of steroid-resistant FSGS with chronically impaired renal function.

[redacted]

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[redacted]

[redacted]

1.3.2. Dose Rationale

CCI [redacted]

CCI [redacted]

[redacted]

As there is currently no mechanistic biomarker that can provide the link to pathway modulation, PK/pharmacodynamic (PD) modeling approach was employed for projections of ROBO2-SLIT2 % reduction using a kidney site-of-action model. This incorporates preliminary PK modeling from study C0221001, ROBO2 and SLIT2 biomeasure from FSGS kidney samples, and in vitro binding data. The premise is translation of reduction in ROBO2-SLIT2 binding, and hence signaling, to efficacy ie, proteinuria reduction. CCI [redacted]

CCI [redacted]

Planned infusion duration in this study is approximately 1 hour, and the monitoring requirements post-infusion are detailed in Section 7.1.7.

2. STUDY OBJECTIVES AND ENDPOINTS

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]

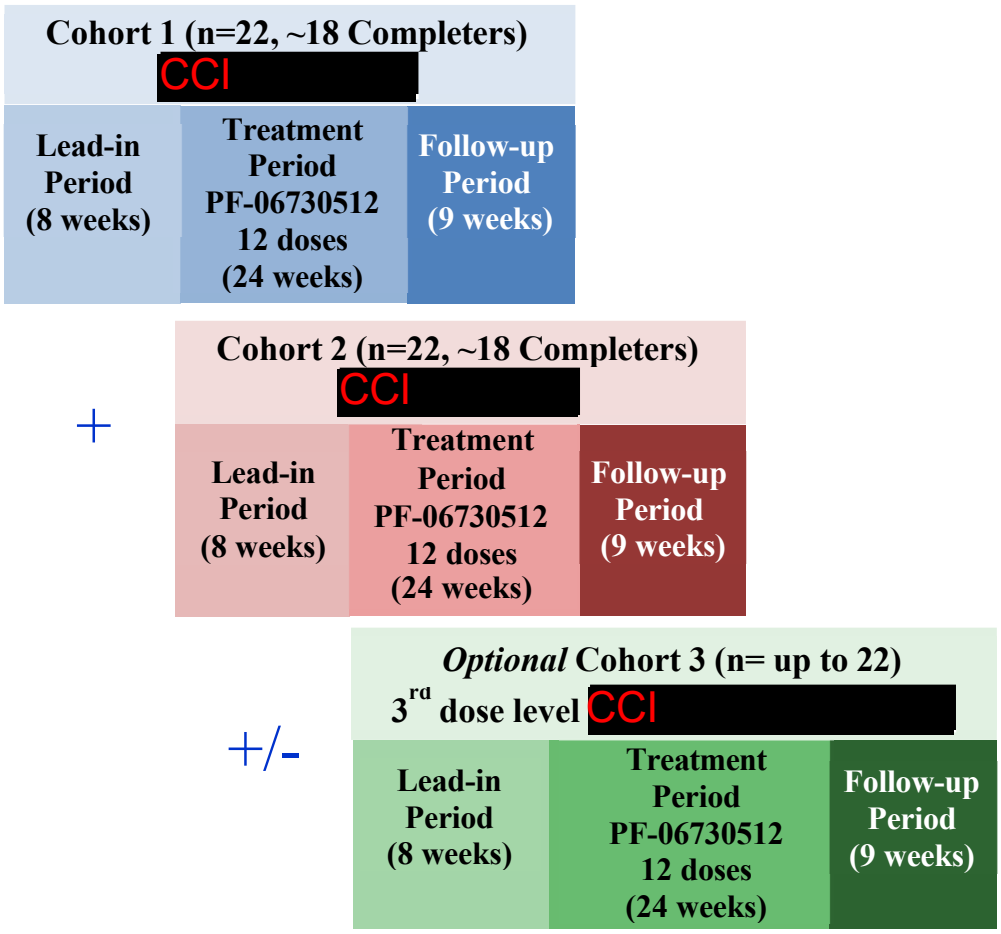
3. STUDY DESIGN

3.1. The Main Study to Assess PF-06730512

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 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. Any such delays should be documented and brought to the Sponsor's attention immediately.

whilst the study is ongoing to determine futility of any evaluated dose, as well as determine which dose level will be evaluated next (see Section 9.6). Cohorts will be enrolled in sequence, but depending on the timing and the results of the pre-specified formal interim analyses, as well as the status of enrollment, the optional Cohort 3 may be initiated prior to (or instead of) the start and/or completion of Cohort 2. Any change from one cohort to another will be communicated formally to all investigators, along with the specific dose of PF-06730512 for that given cohort.

Figure 1. Schematic of the Study Design



Subjects will be seen at Screening (2 Screening Visits) and at Weeks -8, -4 and -1 during the Lead-in Period prior to Day 1 (start of PF-06730512 treatment). Subjects in the Lead-in Period will be eligible for transition to active treatment if at Week -1 the UPCR and eGFR meet eligibility criteria, as described in Section 4.3.

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 (starting at Day 1/Week 1 and at Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 respectively). 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.

For this study, subjects with FSGS should have undergone a diagnostic biopsy within the past 5 years (see Section 4.1; Inclusion Criterion #2). For all sites, if possible and upon obtaining subject's written informed consent, the central renal histopathologist, will obtain a redacted copy of the subject's original, locally-read and anonymized FSGS diagnostic report for exploratory purposes only. Subjects who do not provide this optional diagnostic report are still eligible to participate in the study.

Finally, if emergent safety or PK data dictate, further dosing could be halted pending additional data evaluation. Safety assessments, including physical examination, vital signs, electrocardiogram (ECG) and laboratory parameters will be performed throughout the study.

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 (primary endpoint assessment at Week 13);
- Follow-up Period: approximately 9 weeks (after last dose given at visit Week 23).

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4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

NOTE: Screening and Lead-in laboratory results considered by the investigator to be transient and inconsistent with the subject's clinical condition may be repeated once during the respective period for confirmation of eligibility. The reason for repeating the assessment should be documented.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Male or female subject age ≥18 years must have a confirmed biopsy diagnosis of FSGS within 5 years prior (+3-month window) to Screening.

   - If a subject did not undergo a biopsy confirming the diagnosis of FSGS within the specified timeframe, a new renal biopsy would be required and read locally to assess this criterion.

3. Estimated glomerular filtration rate (eGFR) ≥45 ml/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

   - If eGFR is 30-45 ml/min/1.73 m^2, a recent biopsy (within 12 months prior to Screening) must demonstrate <50% tubulo-interstitial fibrosis. If a biopsy has not been performed within 12 months prior to Screening, a new renal biopsy would be required and read locally to assess this criterion.

4. UPCR >1.5 g protein/g creatinine at Screening.

5. Based on all previous treatment received for FSGS, subject is eligible if:

   a. Subject has been treated with an adequate course per investigator judgement of at least 1, and up to 3 classes of Immunosuppressants* either alone or in combination;

   OR

   b. Subject has a contraindication to any class of Immunosuppressant (may include steroids) or is considered to be intolerant to any class of Immunosuppressant (may include steroids) per investigator judgment.

   *Class of Immunosuppressants (one or more representatives of that same class). Single class examples: corticosteroids, CNIs, inosine monophosphate dehydrogenase (IMPDH) inhibitors (eg, mycophenolate mofetil [MMF], mizoribine), cytotoxic agents, rituximab.

6. Subjects on ongoing corticosteroid treatment must have received an adequate course and be on a stable dose for at least 4 weeks prior to the Lead-in Period and expected to remain stable throughout the study. The same requirements apply to ongoing treatment with CNIs and/or MMF so long as subjects have been receiving either or both of these treatments for at least 3 months prior to the Lead-in Period. Refer to Section 5.8.1 for additional information.

7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures including completion of daily diaries to record symptoms and urine collections.

8. Female subjects of non-childbearing potential will meet at least 1 of the reproductive criteria in Section 4.4.1. Females of childbearing potential and male subjects must agree to Contraception Methods in Section 4.4.2.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Diagnosis of collapsing FSGS.

2. Advanced chronic changes on renal biopsy as evidenced by >50% tubulo-interstitial fibrosis.

3. Evidence or history of clinically significant hematological, endocrine (including Type 1 diabetes mellitus), pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or hepatic disease, like cirrhosis or chronic active liver disease.

   Note the following:

   - Steroid-induced diabetes is not excluded.

   - Type 2 diabetes mellitus is not excluded if well-controlled and if a recent biopsy (within 12 months prior to Screening) shows no histological changes indicating diabetic nephropathy. If a biopsy has not been performed within 12 months prior to Screening, a new renal biopsy would be required and read locally to assess this criterion.

4. Organ transplantation.

5. History of any malignancy except for subjects who had a basal or squamous cell skin cancer which has been treated and fully resolved for a minimum of 5 years.

6. Body mass index (BMI) >45 kg/m^2 (based on an estimated dry weight as per judgment of the investigator, if applicable).

7. Treatment with rituximab within 6 months prior to start of the Lead-in Period.

   - If Rituximab treatment is longer than 6 months (prior to start of the Lead-in Period), subject is still excluded if no peripheral CD19+ B-cells are identified in the local laboratory prior to first study drug dosing.

8. The following immunosuppressant medications within the past 28 days prior to start of the Lead-in Period: azathioprine (Imuran), cytotoxic agents, acthar.

9. Excessive alcohol consumption that may impair the subject's ability to participate in the study per investigator judgment in accordance with national guidelines, if available.

10. Screening sitting blood pressure (BP) ≥155 mm Hg (systolic) or ≥95 mm Hg (diastolic), following at least 5 minutes of sitting rest. If BP is ≥155 mm Hg (systolic) or ≥95 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility. Repeat BP measurements on a different day are allowed to meet this eligibility criterion. Note: Repeat BP measurement should be done within designated screening window and may be considered as unplanned visit.

11. Active/serious infection including, but not limited to, Hepatitis B or C, human immunodeficiency virus (HIV). This includes subjects with a known history of cytomegalovirus (CMV), CMV mononucleosis, gammaherpesviral mononucleosis, parvovirus infection, or simian virus 40 infection. Note: Laboratory test results for these types of infections may require medical interpretation by the investigator and consultation with the Sponsor or designee.

12. Subjects with a history of bilateral vesicoureteral reflux.

13. Subjects with a history of prior treatment with or use of interferon, lithium, pamidronate, mTOR inhibitors (eg, sirolimus), testosterone/anabolic steroids, anthracycline (eg, doxorubicin), heroin.

14. Subjects with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a repeat test, if deemed necessary:

    a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level 1.5× upper limit of normal (ULN);

    b. Total bilirubin level 1.5× ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

15. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

16. Previous known participation in a study investigating PF-06730512.

17. Participation in other studies involving investigational drug(s) within 30 days (or as determined by the local requirement) or 5 half-lives prior to study entry and/or during study participation.

18. A positive urine drug test at Screening (except positive for tetrahydrocannabinol [THC]).

19. Pregnant female subjects; breastfeeding female subjects; lactating female subjects; male subjects and female subjects of childbearing potential who are unwilling or unable to use 1 highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 9 weeks (63 days) after the last dose of investigational product.

20. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

21. Subjects with a history of hypersensitivity to the components of the study drug.

4.3. Criteria for Progression to Treatment on Day 1

Subjects will be progressed to treatment on Day 1 of Week 1 of the Investigational Treatment Period if the following criteria are satisfied:

1. UPCR >1.5 g protein/g creatinine at Week -8 and Week -1 during the Lead-in Period based on 24-hour urine collections.

    - Subjects with substantial change in proteinuria during the Lead-in Period, defined as Week 1 UPCR value < 30% or >200% of the UPCR value at Week -8 (based on 24-hour urine collections), will not be permitted to progress into the Investigational Treatment Period.

2. eGFR must be maintained per the eligibility criteria:

    - eGFR ≥45 ml/min/1.73 m^2 based on the CKD-EPI formula at Week -8 and Week -1.

    - If eGFR at Week -1 is between 30-44 ml/min/1.73 m^2, subjects will only be eligible for the Investigational Treatment Period if a biopsy demonstrating <50% tubulo-interstitial fibrosis has been performed within 12 months prior to Screening.

- Clinical laboratory tests may be repeated to assess eligibility when appropriate in the medical judgment of the investigator. Any therapies or interventions to treat FSGS that are introduced or discontinued in the Lead-in or Investigational Treatment Periods should be discussed with the Sponsor to confirm that the subject may continue in the study (Section 5.8.1).

4.4. Lifestyle Requirements

It is important that subjects continue their typical dietary habits and physical activity throughout the study, ie, from Screening until the on-site follow-up visits. Subjects will be asked not to change their diet and macronutrient composition and/or their exercise routine.

4.4.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

- A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if she plans to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.4.2. Contraception

In this study, male subjects and female subjects who are of childbearing potential as applicable to the study will receive PF-06730512, which has been associated with suspected teratogenicity/fetotoxicity.

Female subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 1 method of highly effective contraception throughout the study and for at least 63 days after the last dose of PF-06730512. Highly effective methods of contraception are those that result in a failure rate of <1% per year when used consistently and correctly. The investigator or his/her designee, in consultation with the subject, will confirm that the female subject has selected 1 method of highly effective contraception for the individual subject and her partner(s) from the list below, and will confirm that the subject has been instructed in their consistent and correct use. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Male subjects are required to use a condom as protection from the potential risk of exposure via PF-06730512 in the ejaculate which would pose a risk to a developing embryo/fetus in WOCBP. This is purely precautionary as the calculated safety margin for PF-06730512 is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 1 highly effective method of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if the use of the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly Effective Methods That Are User Dependent

Items marked with an asterisk (*) denote contraceptives that are not approved for use in Japan.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.*

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral
    - Intravaginal*
    - Transdermal*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral*
    - Injectable*

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigator Site Master File.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is PF-06730512, a lyophilized powder for injection that requires reconstitution with sterile Water for Injection (WFI). This study does not include the use of placebo.

5.1. Allocation to Treatment

Subjects will be enrolled into Cohort 2 or Cohort 3 after approximately 22 subjects have been enrolled into Cohort 1. The sponsor will issue a formal communication to all sites upon transition from one cohort to the next. Allocation of subjects to the respective cohort (1, 2, or 3) will be conducted through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a cohort assignment, randomization number (enrollment), and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization (enrollment) number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Subject Compliance

Investigational Product, PF-06730512, will be administered once every two weeks by qualified investigator site personnel at visits indicated in the Schedule of Activities.

5.3. Investigational Product Supplies

CCI [redacted]

product is intended for intravenous administration. Details of the preparation and administration of the investigational product are outlined in the Investigational Product (IP) Manual.

5.3.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-06730512 lyophilized powder will be reconstituted using sterile WFI. The investigational product will be prepared at the investigational site or at a site-contracted qualified pharmacy by two operators; one of whom should be a licensed healthcare professional, preferably a qualified pharmacist. The operators must be fully trained and experienced in the reconstitution and preparation of sterile product solutions for intravenous administration. Dose preparation will be performed with locally accepted sterile handling technique.

5.4. Administration

PF-06730512 will be administered by qualified study site staff as an IV infusion over approximately 60 minutes using a calibrated infusion pump according to the IP Manual. The infusion line is flushed using a sufficient volume of Normal Saline (0.9% sodium chloride) that is greater than or equal to the hold-up volume of the infusion line/set. The flush solution should be administered at the same rate to ensure complete delivery of the dosing solution. The start and stop time of the infusion will be recorded on the case report form (CRF). The infusion stop time should be recorded as the time when the end of the saline flush is complete. The post-infusion observation period for each subject shall be 3 hours for the first 3 doses. The observation period can be decreased to 1 hour after the end of infusion for the subsequent doses, provided that no infusion reactions are noted.

If an arm is used for IV infusion, the opposite arm should be used for the pharmacokinetic/pharmacodynamic (PK/PD) blood sample collections, if possible. Premedication with an antihistamine and acetaminophen is optional and might be provided per investigator judgment. See the IP Manual for detailed instructions on how to administer the investigational product.

5.5. Infusion Discontinuation

If a subject experiences symptoms typical of anaphylaxis, the IP administration should be discontinued immediately and permanently.

If a subject experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever), the study drug infusion should be stopped. At the discretion of the Investigator, the infusion can be restarted at a slower rate if symptoms are resolved within 1 hour after the stop of infusion. If symptoms return, then the IP administration should be discontinued immediately and permanently.

In the event that there is an infusion interruption, the entire duration of the infusion, from the initial start of infusion to the completion of infusion, should not exceed 3 hours. Subjects will receive appropriate treatment at the discretion of the investigator.

5.6. Investigational Product Storage

Drug product vials of PF-06730512 shall be stored at 2 to 8°C. Refer to the IP Manual for the in-use stability of the prepared dosing solutions. The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Subjects will abstain from all prohibited medications that are listed in the Exclusion Criteria section and outlined in Section 5.8.2.

For blood pressure control, a systolic value below 155 mm Hg is recommended. If it is necessary, in the opinion of the investigator, to add an antihypertensive medication, this will be listed as concomitant treatment. While the doses of the renin–angiotensin–aldosterone system (RAAS) blockers are required to be stable during the entire Investigational Treatment Phase and Follow-up Period, blood pressure control can be further optimized by titrating diuretics and/or other anti-hypertensive medications, in addition to the stable doses of RAAS blockers.

Note: treatment with RAAS blockers is not mandatory.

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each visit.

Medications taken from Screening up to the first dose of study medication will be documented as ‘prior medication’. Medications taken after the first dose of study medication will be documented as ‘concomitant medication’.

5.8.1. Permitted FSGS Medications

All FSGS therapies administered prior to study should be captured on the CRF. FSGS therapies administered during the study period should adhere to the following guidelines below.

Dose adjustments and discontinuations are discouraged during the study (Lead-in, Investigational Treatment and Follow-up Periods), however doses may be adjusted or discontinued if a safety issue arises. Dose changes to therapies listed below during Lead-in or Investigational Treatment Period must be discussed with the Sponsor to evaluate study continuation for the subject. Dose changes and discontinuations during the Follow-up Period will be at the investigator's discretion but are discouraged for reasons other than subject safety concerns.

1. **RAAS blockers, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide 1 (GLP1) agonists:** Subjects receiving any of these therapies must be on stable dose approximately 4 weeks prior to beginning of the Lead-in Period and expected to remain on stable dose throughout the study.

2. **Corticosteroids:** Prior treatment with an adequate course of corticosteroid, per investigator judgment. Subjects on ongoing corticosteroid treatment must be on a stable dose 4 weeks prior to the initiation of the Lead-in Period.

3. **CNIs and/or IMPDH inhibitors** (eg, MMF**,** mizoribine [MZB]**)**:

    - Ongoing treatment is permitted, so long as initiated at least 3 months prior to Lead-in Period, and subject is on a stable dose for at least 4 weeks prior to start of the Lead-in Period.

    - CNIs and IMPDH inhibitors may be given standalone or in combination. CNIs can be monitored with whole blood levels, per investigative site standard of care. Any such dose adjustments should be discussed with the Sponsor to confirm that the subject may safely continue in the study.

Of note, discontinuation from any of the above listed therapies should occur no later than 4 weeks prior to the start of the Lead-in Period.

5.8.2. Prohibited Medications

- Prior or concurrent treatment with interferon, lithium, pamidronate, mTOR inhibitors (eg, sirolimus), testosterone/anabolic steroids, anthracycline (eg, doxorubicin), heroin.

- More than 3 prior regimens of immunosuppressive therapies.

- The following immunosuppressives must have been discontinued at least 4 weeks prior to the Lead-in Period and are not permitted during study participation, including:
  - azathioprine (Imuran)
  - cytotoxic agents
  - acthar
- Rituximab must have been discontinued at least 6 months prior to Lead-in Period and is not permitted during study participation.
- Any other investigational therapy within 4 weeks of Lead-in Period or during study participation.

6. STUDY PROCEDURES

6.1. Screening and Lead-in Period Activities and Assessments

Subjects will have up to 43 days for Screening procedures to be initiated before the Week -8 Lead-in Period Visit (refer to Schedule of Activities for details and visit windows). In addition, to prepare for participation into the study, subjects will be instructed on the Lifestyle Requirements, including Contraception Methods (Section 4.4.2) and Concomitant Treatments (Section 5.8). In particular, it is important that all prior FSGS treatments are stabilized or discontinued as described in the Concomitant Treatment(s) section of the protocol.

Please also refer to the Schedule of Activities and Section 7 for details of the study procedures**.**

A subject may be re-screened, after an agreement has been reached between the investigator and sponsor. If eligibility criteria are not met or evaluable within the Screening or Lead-in window, the subject will be Screen Failed. For subjects who consent to re-screen a new 8-digit study specific subject identification (SSID) number will be assigned and all screening procedures must be repeated. If eligibility confirmation for the Screening or Lead-in Period is delayed due to delayed primary or repeat laboratory results, the subject may enroll once eligibility is confirmed by test results provided the results are received within one week of the specified window.

Screening procedures may be split into 2 or more visits as recommended below. Alternatively, all procedures may be accomplished at one visit, with the exception of FMV and 24-hour urine collection. Subject written informed consent must be obtained prior to any study-specific procedures taking place.

Screening Visit 1

- Obtain informed consent from potential subject;

- Obtain potential subject's medical history, prior and ongoing medication details, demographic information and history of smoking and alcohol consumption);
- A complete history of the subject's FSGS will be collected at screening, including initial diagnosis date, recurrence date if applicable, and prior FSGS treatments administered, as well as capturing any contraindications or intolerance to these medications.
  - CCI [redacted]
- Review inclusion and exclusion criteria with subject to determine eligibility;
- Review contraceptive use with potential subject;
- Provide subject with container for urine collection and explain the urine collection process;
- Instruct subject to collect urine samples for 24-hour urine collection and first morning void (FMV) before next visit (Screening Visit 2);
- Renal biopsy if required for eligibility: a renal biopsy should be obtained and assessed locally to confirm the subject is eligible for study participation. May be collected at this visit or the next visit (Screening Visit 2), so long as there is sufficient time to confirm eligibility prior to the Lead-in Period.
- CCI [redacted] a renal biopsy may be obtained during Screening or Lead-in Phase, but must be collected prior to first dose of IP. CCI [redacted]

Screening Visit 2

- Verify potential subject's medical and medication history, including demographic information and history of smoking and alcohol consumption;
- Review inclusion and exclusion criteria with subject to verify eligibility;

- All full PE and Brief PEs must include edema assessment and weight measurement. Full physical exam must be completed either at Screening or Week -8 (first day of the Lead-in Period); otherwise, brief exams are performed, if no findings during previous exam or new or ongoing AEs, and if appropriate as per investigator's discretion;
- Height measurement is only performed once at Screening;
- Review contraceptive use with potential subject;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12 lead ECG;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Collect blood sample for HCG (female of child bearing potential);
- Collect blood sample for FSH (postmenopausal female);
- Collect blood sample for HBsAg, HBcAb, HCVAb, and HIV;
- Subject to bring container with FMV for CCI and UPCR;
- Subject to bring container with 24-hour urine collection for CCI and UPCR;
- Collect urine samples for urinalysis and drug test at the central lab;
- Provide subject with container for urine collection and explain the urine collection process.
  - Instruct subject to collect FMV and 24-hour urine before the next visit;
- CCI [redacted]

Study Week -8 Visit

- Review criteria for continuation to the Treatment Phase, as described in Section 4.3;
- Review concomitant medications;
- Review demographic information and history of smoking use and alcohol consumption;

- All full PE and Brief PEs must include edema assessment. Full physical exam must be completed either at Screening or Week -8; otherwise, brief exam is performed, if no findings during previous exam or new or ongoing AEs, if appropriate as per investigator's discretion. Height measurement is only performed once at Screening;
- Review contraceptive use as applicable;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG;
- Obtain vital signs (single PR, BP and body temperature);
- CCI [redacted]
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw - no food or drink except water);
- Collect blood sample for HCG (female of child-bearing potential);
- CCI [redacted]
- Subject to bring container with FMV;
- Subject to bring container with 24-hour urine collection;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]
- CCI [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- Provide subject with the Urine Collection Instruction and Diary;
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV for CCI and UPCR before next study visit.

Study Week -4

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use with subject;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI ;
- Collect blood sample for clinical laboratory test and eGFR;
- Subject to bring container with FMV for CCI and UPCR;
- Collect urine samples for urinalysis;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hr urine collection and FMV before next visit;
- Site personnel to call subject within **3 days** before Visit Week -1 to remind him/her to perform FMV and a 24-hour urine collection, explain how to correctly collect and to bring the urine containers for FMV and 24-hour urine collection to clinic site at Week -1.

Study Week -1

- Review criteria for continuation to the Investigational Treatment Phase, as described in Section 4.3;
- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use with subject;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI

- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Collect blood sample for HCG (female of child-bearing potential);
- CCI
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI UPCR;
- Subject to bring container with 24-hour urine collection for CCI UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV before next visit.

6.2. Investigational Treatment Period (Study Weeks 1 to 24)

Refer to the Schedule of Activities and Section 7 Assessments for the study procedures to be completed during the Investigational Treatment Period. The 24-week Investigational Treatment Period begins in Study Week 1 and continues through Study Week 24, and subjects will receive intravenous treatment with PF-06730512 every other week. In addition, subjects will be reminded on the use of the Lifestyle Requirements (Section 4.4) and Concomitant Treatment(s) of the protocol, in particular, protocol restrictions regarding other FSGS treatments as described in the Concomitant Treatment(s) section of the protocol.

The activities and assessments listed below are to be completed during the Investigational Treatment Period. Please refer to the Schedule of Activities for visit windows and Section 7 Assessments for the study procedures to be completed during this period.

If an intravenous catheter is placed for serial blood sample collections, ECGs and vital signs (PR, BP) assessments should be either collected prior to the insertion of the catheter or following a sufficient rest period after catheter insertion introduced to minimize impact of catheter placement on these assessments.

Study Week 1 - Day 1

- Review criteria for continuation to the Investigational Treatment Phase, as described in Section 4.3, to confirm eligibility;
- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- CCI
- Review contraceptive use with subject;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result confirmed prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA and NAb, and cytokines (within 30 minutes prior to dosing);
- Enroll the subject via IRT to allocate treatment as described in Section 5.1.
- Intravenously administer PF-06730512 per IP Manual;
- Collect blood sample for PK within 6 minutes after the end of infusion;
- Collect blood samples for cytokines at 1, 2 and 4 hours post beginning of infusion, within approximately ±15 minutes;
- Monitor subject for AEs and infusion site reaction for approximately 3 hours post end of infusion;

- CCI [redacted]
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Collect urine samples for urinalysis.
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hr urine collection and FMV before next visit.

Study Week 2 - Day 8

- Perform a physical exam including body weight and edema assessment;
- Review concomitant medications;
- Review contraceptive use with subject;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for pre-dose PK, ADA and NAb;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Subject to bring container with 24-hour urine collection for CCI [redacted] UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]
- [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI [redacted]
- Collect urine samples for urinalysis;
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV before next visit.

Study Week 3 - Day 15

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use with subject;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- CCI
- Collect blood sample for clinical laboratory test and eGFR;
- Collect blood sample for pre-dose PK, ADA and NAb, and cytokines;
- Intravenously administer PF-06730512 per IP Manual;
- Collect blood samples for cytokines at 1, 2 and 4 hours post beginning of infusion, within approximately ±15 minutes;
- Monitor subject for AEs and infusion site reaction for approximately 3 hours post end of infusion;
- Collect urine samples for urinalysis;
- Subject to bring container with FMV for CCI UPCR;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hr urine collection and FMV urine collection for CCI UPCR before next visit at Week 5.

Study Week 4 - Day 22 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as “how do you feel?”
- Review concomitant medications;

- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to next visit.

Study Week 5 - Day 29

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI [redacted]
- Collect blood sample for pre-dose PK, ADA and NAb, and cytokines;
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Intravenously administer IP per IP Manual;
- Collect blood samples for cytokines at 1, 2 and 4 hours post beginning of infusion, within approximately ±15 minutes;
- Monitor subject for AEs and infusion site reaction for approximately 3 hours post end of infusion;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Subject to bring container with 24-hour urine collection for CCI [redacted] UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]

- CCI [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from main urine shipment, but on the same day;
- CCI [redacted]

Study Week 6 - Day 36 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use.

Study Week 7 - Day 43

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG Pre-dose and at the end of infusion within an approximately 45--minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for pre-dose PK, ADA and NAb;
- Collect blood sample for clinical laboratory test and eGFR;
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Intravenously administer of IP per IP Manual;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Collect urine samples for urinalysis;

- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hour urine collection and FMV for CCI CCI UPCR before next visit.

Study Week 8 - Day 50 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to next visit.

Study Week 9 - Day 57

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA and NAb;
- CCI [redacted]
- [redacted]
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI [redacted] UPCR;

- Subject to bring container with 24-hour urine collection for CCI UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV for CCI UPCR before next visit.

Study Week 10 - Day 64 (Telephone Visit)

- Review concomitant medications;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Remind subject of FMV urine collection prior to next visit.

Study Week 11 - Day 71

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG Pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI
- Collect blood sample for clinical laboratory test and eGFR;

- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA and NAb;
- Intravenously administer IP per IP Manual;
- Collect blood sample for PK at the end of infusion, within 6 minutes after the end of infusion;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Collect urine samples for urinalysis;
- Subject to bring container with FMV for CCI UPCR;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hour urine collection and FMV for CCI UPCR before next visit.

Study Week 12 - Day 78 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to Week 13 Visit.

Study Week 13 - Day 85

- Site personnel to call subject **3 days** before Visit Week 13 to remind him/her to perform FMV and a 24-hour urine collection, explain how to correctly collect and to bring the urine containers for FMV and 24-hour urine collection to clinic site.

Reminder: Primary Endpoint (UPCR) and all other endpoints are collected and compared to baseline at Week 13

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;

- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG Pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- CCI
- Collect blood sample for pre-dose PK, ADA, NAb;
- Intravenously administer IP per IP Manual;
- Monitor subject for AEs and infusion site reaction for approximately 1-hour post end of infusion;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI UPCR;
- Subject to bring container with 24-hour urine collection for CCI UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI
- CCI
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV for CCI UPCR before next visit.

Study Week 14 - Day 92 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV urine collections prior to next visit.

Study Week 15 - Day 99

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test and eGFR;
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA, NAb;
- Intravenously administer IP per IP Manual;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Collect urine samples for urinalysis;
- Subject to bring container with FMV for CCI UPCR;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hour urine collection and FMV for CCI UPCR before next visit.

Study Week 16 - Day 106 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to next visit.

Study Week 17 - Day 113

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG Pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood samples for pre-dose PK, ADA, NAb;
- Intravenously administer IP per IP Manual;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI UPCR;
- Subject to bring container with 24-hour urine collection for CCI UPCR;

- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI [redacted]
- CCI [redacted]

Study Week 18 - Day 120 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use.

Study Week 19 - Day 127

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test and eGFR;
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of childbearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA and NAb;
- Intravenously administer IP per IP Manual;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;

- Collect urine samples for urinalysis;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hour urine collection and FMV for CCI UPCR before next visit.

Study Week 20 - Day 134 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to next visit.

Study Week 21 - Day 141

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG Pre-dose and at the end of infusion within an approximately 45-minute window;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood samples for pre-dose PK, ADA, NAb;
- CCI
- Intravenously administer IP per IP Manual;

- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI UPCR;
- Subject to bring container with 24-hour urine collection for CCI UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI
- CCI
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV for CCI UPCR before next visit.

Study Week 22 - Day 148 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV urine collections prior to next visit.

Study Week 23 - Day 155

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);

- CCI [redacted]
- Collect blood sample for clinical laboratory test and eGFR;
- Use serum for pregnancy test via test strip as a stat procedure performed locally at the site, in females of child-bearing potential, with the negative result being available prior to the administration of investigational product;
- Collect blood sample for pre-dose PK, ADA and NAb;
- Intravenously administer IP per IP Manual;
- Collect blood sample for PK at the end of infusion, within 6 minutes after the end of infusion;
- Monitor subject for AEs and infusion site reaction for approximately 1 hour post end of infusion;
- Collect urine samples for urinalysis;
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Provide subject with containers for urine collection and explain the urine collection process; request that subject perform 24-hour urine collection and FMV for CCI [redacted] UPCR before next visit.

Study Week 24 - Day 162 (Telephone Visit)

- Phone call to conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as “how do you feel?”
- Review concomitant medications;
- Review contraceptive use;
- Remind subject of FMV and 24-hour urine collections prior to next visit.

6.3. Follow-up Period Activities and Assessments (Study Weeks 25 to 33)

Following the conclusion of the Investigational Treatment Period, all subjects will enter the Follow-up Period for approximately 9 weeks from last dose of IP (Study Weeks 25-33).

The activities and assessments listed below are to be completed during the Follow-Up Period. Please also refer to the Schedule of Activities for the study procedures to be completed during this period and the associated visit windows.

Study Week 25 - Day 169

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- CCI [redacted]
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI [redacted]
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Collect blood sample for HCG (for women of child-bearing potential);
- CCI [redacted]
- Collect blood sample for PK, ADA, NAb;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Subject to bring container with 24-hour urine collection for CCI [redacted] UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]

[redacted]

- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI [redacted]

- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV and 24-hour collection for CCI UPCR before next visit;
- CCI [redacted]

Study Week 27 - Day 183

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- Collect blood sample for PK, ADA, NAb;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI UPCR;
- Subject to bring container with 24-hour urine collection for CCI UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]
- [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI [redacted]

Study Week 29 - Day 197

- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;

- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI
- Collect blood sample for clinical laboratory test and eGFR;
- Collect blood sample for HCG (for women of child-bearing potential);
- Collect blood sample for PK, ADA, NAb;
- Collect urine samples for urinalysis;
- Provide subject with container for urine collection and explain the urine collection process; request that subject perform FMV and 24-hour collection for CCI UPCR before next visit.

Study Week 33 – Day 225

- Site personnel to call subject **3 days** before Visit Week 33 to remind him/her to perform FMV and a 24-hour urine collection, explain how to correctly collect and to bring the urine containers for FMV and 24-hour urine collection to clinic site.
- Review concomitant medications;
- Perform a physical exam including body weight and edema assessment;
- CCI
- Review contraceptive use;
- Perform serious and non-serious adverse event monitoring;
- Perform single 12-lead ECG;
- Obtain vital signs (sitting single PR, BP and body temperature);
- CCI
- Collect blood sample for clinical laboratory test, eGFR and fasting lipid profile (subjects must be fasting at least 8 hours prior to blood draw with no food or drink except water);
- Collect blood sample for HCG (for women of child-bearing potential);

- CCI [redacted]
- Collect blood sample for PK, ADA, NAb;
- Verify subject's return/completion of Urine Collection Diary;
- Subject to bring container with FMV for CCI [redacted] UPCR;
- Subject to bring container with 24-hour urine collection for CCI [redacted] UPCR;
- Prepare urine for PK (20 mL from 24-hour urine collection);
- CCI [redacted]
- [redacted]
- Prepare reserve 10 mL urine aliquot from the 24-hour collection (for UPCR measurement) which is to be sent to the central lab with a shipment ***separate*** from the main urine shipment, but on the same day;
- CCI [redacted]

6.4. Subject Withdrawal/Early Termination

Please refer to the Schedule of Activities for additional guidance on the procedures.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record)]. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests as noted in Table 1 are performed at times defined in the Schedule of Activities section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns and/or to confirm eligibility to participate in the study.

If an intravenous catheter is placed for serial blood sample collections, ECGs and vital signs (PR, BP) assessments should be either collected prior to the insertion of the catheter or following a sufficient rest period after catheter insertion introduced to minimize impact of catheter placement on these assessments.

Table 1. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Absolute and %) Eosinophils (Absolute and %) Monocytes (Absolute and %) Basophils (Absolute and %) Lymphocytes (Absolute and %)	BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Prothrombin time - INR	pH Glucose (qualitative) Protein (qualitative) Blood (qualitative) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Specific Gravity Microscopy[a] CCI UPCR	FSH;[b] Serum pregnancy test Urine drug screening[c] Hepatitis B surface antigen[d] Hepatitis B surface antibody[d] Hepatitis B core antibody[d] Hepatitis C core antibody[d] Human immunodeficiency virus[d] Lipid profile (***post 8 h fast***) Cytokines:[e] TNF-α, IL-6 and IFN-γ
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. At Screening only once in females amenorrheic ≥12-months.

c. The urine drug test at Screening is performed by the central lab. If the Screening drug test is positive for drugs other than THC, subjects are excluded. The minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines. Subjects may undergo random urine drug testing at the discretion of the investigator.

d. At Screening only once.

e. Extra blood samples for cytokine measurement should be taken immediately if a subject develops symptoms typical for infusion reaction during the IP administration. CCI [redacted]

7.1.2. Pregnancy Testing

One form of appropriate contraception must be used *from* Screening onward and continued throughout the Investigational Treatment and Follow-Up Phases. Serum pregnancy tests (HCG) are performed throughout the study as indicated in the Schedule of Activities. Pregnancy tests will also be done whenever one (1) menstrual cycle is missed, if applicable; during the Investigational Treatment and Follow-up Phases and when potential pregnancy is otherwise suspected and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

All serum pregnancy tests used in this study must have a sensitivity of at least 25 mIU/mL. Serum pregnancy tests will be done locally by the site on all dosing days during the Investigational Treatment Period, as indicated in the Schedule of Activities, with a negative result required prior to the administration of investigational product. All other serum pregnancy tests, which are required at the Screening, Lead-in and Follow-up Periods (or Early Termination visit) will be submitted to the certified central laboratory.

7.1.3. Physical Examinations

The physical examinations will be administered at times specified in the Schedule of Activities. Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

- A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.

- The brief physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as toward subject reported symptoms.

Both, the full and brief physical examination should include presence/absence of edema and any changes in edema from one visit to the next. Leg edema, for example of the ankle or in the pretibial area, should be graded according to a scale from 'Trace' to 1+, 2+ or 3+ pitting edema.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.4. Vital Signs (Blood Pressure, Pulse Rate and Body Temperature)

Vital sign measurements (sitting BP, PR, and body temperature) will be performed at all time points as indicated in the Schedule of Activities. Additional collection times, or changes to collection times of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Qualified staff members will perform the BP measurement with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg, while the subject is sitting. The same arm (preferably the dominant arm) will be used throughout the trial. If possible, blood pressure measurements will be taken from the same arm (opposite the arm that is used for blood sample collection). If there is a clinically important change in blood pressure from the previous recording, measurements will be repeated immediately to confirm the change.

All scheduled BP and PR measurements should be performed after the subject has rested quietly for at least 5 minutes. The same size blood pressure cuff, which has been properly sized, will be used to measure blood pressure each time. The use of automatic devices for measuring BP, PR, and respiratory rate are acceptable, although, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

Based on his or her judgment, the investigator makes the decision whether collecting orthostatic data is clinically meaningful. If deemed necessary, the procedure for collecting orthostatic data will be as follows:

- Assess BP after subject is in supine position for a minimum of 5 minutes;
- Stand subject up for 2 minutes;
- Assess BP after subject is in the standing position for 2 minutes.

Orthostatic hypotension is defined as a decrease of ≥20 mmHg for systolic blood pressure or ≥10 mmHg for diastolic blood pressure 2 minutes after standing from a supine position.

Body temperature should be measured per the instructions provided with the thermometer. The temperature will be reported in degrees Celsius.

7.1.5. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the section of this protocol; additionally, please note that ECG is performed Pre-dose and at the End of Infusion (approximately 45 minute window from end of infusion) during the visits in the Investigational Treatment Period, as indicated in the Schedule of Activities.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. A single standard 12-lead ECG will be performed at the Baseline (Day 1 pre-dose). A single standard 12-lead ECG will be performed at time points as indicated in the Schedule of Activities.

Interpretation of ECGs will be performed locally by the site, and ECG data as well as any clinically important findings (eg, suspected QTc prolongation) will be recorded on the appropriate CRF. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval, and assessment of rhythm and morphology.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine read states QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

CCI [redacted]

7.1.7. Infusion Site Reaction

Infusion site reactions will be assessed according to the Schedule of Activities. Infusion site reactions may include but are not limited to: erythema, induration, ecchymosis, pain and pruritus. The size and severity of infusion site reactions will be assessed and documented.

7.2. Efficacy

7.2.1. Urine Protein:Creatinine/:CCI [redacted] (UPCR/CCI [redacted])

UPCR represents the primary endpoint of the study and therefore, it is very important to generate reliable and accurate data for UPCR. The collection procedures by the subject, the handling of the FMV and the 24-hour collections by the site and the shipping as well as the receiving and analytical processes by the central lab have to be extremely carefully performed to avoid any errors or mishaps along the way.

Depending on the visit, subjects will be instructed to bring a FMV for a "spot" urine assessment or a full 24-hour urine collection or both collections to the scheduled clinic visit.

A detailed explanation will be provided to the subject on the method of collection, together with receptacles, and storage containers for urine collections. Subjects are advised to complete collection of their FMV and 24-hour samples within 24 to 48 hours prior to attending their scheduled clinic visit.

At home, subjects are advised to collect the FMV in the morning within 24-48 hours before their visit at the clinic; the FMV should be collected into a small container, separate from the 24-hour urine collection container. Immediately after obtaining the FMV, the 24-hour collection starts with the next urine void and includes all subsequent voids, up to and including the first morning urine void on the following day. All of these urine voids must be collected to obtain the full 24-hour urine collection, and must be placed into the large split urine container. The small FMV and the large containers have to be brought to the clinic.

Both the FMV and the 24-hour collection urine will be used to measure urine protein to creatinine ratio (UPCR) and CCI [redacted] At the subject's home while collecting the urine and in the clinic, all urine containers must be stored in the refrigerator or in an insulated cooler or cooler bag with frozen refrigeration packs provided by the central lab to maximize stability of the samples.

Subjects will receive Urine Collection Instructions and a Urine Collection Diary in which they will fill in the dates of their urine collection, the time they collected the FMV and the time they began and ended the 24-hour period of collecting. Subjects will enter the time of each urine void during the 24 hours.

Site personnel will call the subject approximately **3 days** before each visit that urine containers are collected from the subject, to remind the subject to perform the FMV and the 24-hour urine collections according to the Schedule of Activities, explain again how to correctly collect and to bring the urine containers for FMV and 24-hour urine collections to the clinic site. In addition, when the performing the telephone visits the site personnel reminds the subject of the urine collections for the upcoming visits.

A repeat of 24-hour urine collection is allowed, for example in case the subject forgot to fill one or more of the voids into the container.

It is of great importance that the site completes the Requisition Form for shipment to the central laboratory in accordance to the central laboratory manual, including the following data:

- Total volume of the 24-hour urine collection
- Date of urine collection
- Time of start and end of urine collection

A 10 mL reserve urine aliquot is prepared from the 24-hour collection urine which is to be sent to the central lab with a shipment separate from the main urine shipment, but on the same day. Any urine aliquots not used for the purposes described above will be considered exploratory biomarker urine samples in accordance with Section 7.3.3.

A 20 mL aliquot of the 24-hour urine samples collected from the Investigational Treatment and Follow-up Periods may also be used for exploratory PK analysis (Section 7.3.2).

CCI [redacted]

7.3. Pharmacokinetics

7.3.1. Serum for Analysis 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.

The actual sampling times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the time windows specified in the Schedule of Activity will not be captured as protocol deviations.

In addition to samples collected at the scheduled times, an additional blood sample for determination of PF-06730512 PK may be collected from subjects experiencing unexpected and/or serious AEs. The date and time of the blood sample collection and of the last dosing prior to PK collection will be documented in the CRF.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

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7.3.2. Urine for Analysis of PF-06730512

A 20 mL aliquot of the 24-hour urine samples from the Investigational Treatment and Follow-up Periods will be collected. As part of understanding the PK of the investigational product, the samples may be used for evaluation of the bioanalytical method, CCI [redacted]

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7.4. Immunogenicity

7.4.1. Immunogenicity Analyses

Blood samples (approximately 5 mL) to provide at least 2 mL of serum to detect ADA and NAb against PF-06730512 (~1 mL each for ADA and NAb) will be collected from subjects enrolled at the times specified in the Schedule of Activities. Samples will be analyzed using a validated analytical method in compliance with Pfizer/vendor standard operating procedures (SOPs). Samples determined to be positive for ADA may be further characterized for NAb.

Subjects with positive results at the conclusion of the study may be requested to return for additional follow-up for up to approximately 3 months after the last scheduled follow-up visit. An additional immunogenicity sample will be collected and the information recorded as an unscheduled visit.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

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biospecimens will be stored for many years (no time limit) to allow for research in the future,

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7.7. Blood Volume

The total blood sampling volume for individual subjects is approximately 560 mL for participating in the study. The blood volumes increase by approximately 72 mL in WOCBP due to serum pregnancy tests; the blood volumes increase by 5 mL in women of non-child-bearing potential due to FSH measurement.

The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by the Sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF. Withdrawal from the study due to an adverse event that is related to study drug is done at the discretion of the principal investigator. Notification to the sponsor of the withdrawal must be accomplished immediately. Pregnancy in a study participant must result in immediate cessation of study drug administration.

When a subject withdraws from or is withdrawn from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 70 ±7 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.** The investigator then must decide whether to interrupt or discontinue further administration of study drug because of the potential DILI.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy;

- If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

If a subject becomes pregnant during treatment with the investigational product, administration of the product must immediately cease and the patient must be withdrawn from further treatment. Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product;

- Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

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9.2. Efficacy Analysis

Baseline for the primary endpoint is defined as the Week -1 UPCR measurement that is based on the 24-hour urine collection. The Week 13 value for the primary endpoint is also based on the 24-hour urine collection.

Baseline for the secondary endpoints related to UPCR based on the 24-hour urine collection or estimated glomerular filtration rate (eGFR) will be based on the Week -1 measurement; otherwise, the Week 1 value will be used.

9.2.1. Analysis of the Primary Endpoint

The primary analysis will be based on the full analysis set (FAS), which will be defined to be all enrolled subjects who have received at least one dose of study treatment and have at least one post-baseline measurement of UPCR. A mixed effects model of repeated measures (MMRM) will be fitted to the post-dose 24-urine collection data on UPCR (ie, Weeks 5, 9 and 13) using data through Week 13. The model will include treatment (if more than one dose), baseline, week (as a factor), baseline*week interaction and the week*treatment (if more than one dose) interaction, with week fitted as a repeated effect, and subject as a random effect. An unstructured correlation matrix will be used to estimate the variances and covariance within subject across time points. 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 percentage change from baseline to Week 13 treatment effect(s) will be the primary comparison(s) of interest.

The probabilities for the decision criteria for each of the doses (as required) will be calculated using the results of the MMRM.

The back-transformed Least Squares Means (LSMeans) together with 90% confidence intervals will be obtained for each dose (if applicable) and week.

Ratios in LSMeans (calculated by back-transforming modelled results), amongst the doses at the different weeks, together with 90% confidence intervals, will also be obtained if applicable.

All values for UPCR (including baseline) will be $\log_e$-transformed prior to analyses, where analysis of changes from baseline will be performed. 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)

Plots will be produced including:

- The treatment back-transformed LSMeans (including confidence intervals) for each dose (as required) over time.

Missing values will be imputed as part of the MMRM model assumptions.

As a sensitivity to the primary analysis, an analysis of covariance (ANCOVA) model including the Week 13 measurement as the dependent variable, with treatment included as a fixed effect and baseline as a covariate will be performed, using last observation carried forward (LOCF) for missing data. The same MMRM model to the primary analysis will also be fitted to the single morning void assessments of UPCR only as a further sensitivity

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A Per-Protocol (PP) analysis set will also be defined to be all subjects in the FAS with any post-baseline efficacy data who were not major protocol deviators. As a supportive analysis, the primary analyses may be repeated based on the PP analysis set. Full details of the primary analysis will be provided in the SAP.

9.2.2. Analysis of Secondary Endpoints

The secondary endpoints of percentage change from baseline in UPCR over time post-treatment will come from the same MMRM model used for the primary analysis using post-treatment data, including time points beyond Week 13 as applicable. Estimates of percentage changes from baseline to weeks post-treatment will be derived from a model similar to the primary MMRM model.

Changes from baseline to Weeks 3, 5, 9, 13 and beyond as applicable, in eGFR over time post-treatment will be analyzed using an approach similar to that used for the primary endpoint. This will also be analyzed on the $\log_e$ scale.

Full details of these and all other secondary efficacy analyses will be included in the SAP.

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9.3. Pharmacokinetic Analysis

9.3.1. Analysis Population

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. PK concentrations will be summarized and presented with summary statistics, and if appropriate, non-compartmental PK parameter estimates will be provided. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately.

Data permitting, the relationship between exposure and clinical responses (efficacy and safety) may be explored using either observed or predicted exposures from the PK model. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

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9.5. Safety Analysis

Adverse events, ECGs, body weight, BP, PR, body temperature and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

Any clinical laboratory, ECG, BP and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular format and summarized descriptively, where appropriate.

Medical history and physical and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and neurological examinations conducted after the administration of the first dose of investigational product will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/ exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

Immunogenicity (ADA, NAb) results will be listed (including titers) and summarized by treatment group and time points. Effect of positive ADA and neutralizing immune response on safety, PD and PK may be assessed, if appropriate. Full details of analyses will be given in the SAP.

9.5.1. Electrocardiogram (ECG) Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum post-dose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Table 2. Safety QTcF Assessment

	Borderline (msec)	**Prolonged (msec)**
Absolute Value	>450 - ≤480	>480
Absolute Change	30 - ≤60	>60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

9.6. Interim Analysis

Interim analyses will be performed to assess efficacy and safety after at intervals wherein half of the planned subjects for each cohort, ie, approximately 9 subjects, have completed the primary efficacy assessment.

Up to five interim analyses are currently planned for this study, which are summarized below, but where more details (such as internal business decisions regarding future study planning based on interim results) will be documented and approved in a charter and an Interim Analysis SAP. Up to two such analyses per cohort may be performed. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, stopping for early success, advancing to a new cohort, or conducting a sample size re-estimation. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per Pfizer's SOPs will be documented and approved in a charter and an Interim Analysis SAP or final SAP (as applicable). These documents will be finalized before any interim analysis is instigated and may modify what is outlined below; however, any major modifications will also be reflected in a protocol amendment. The first interim analysis (IA1) will be conducted after at least 50% of the planned subjects from Cohort 1 (ie, approximately 9 subjects) have completed the primary efficacy assessment.

The second interim analysis (IA2) will be conducted after the remaining 50% of subjects from Cohort 1 (ie, approximately 18 subjects) have completed the primary efficacy assessment or discontinued from the study. Direct advancement to the optional Cohort 3 may also be determined at this IA2.

A third interim analysis (IA3) will be conducted after at least 50% of the planned subjects from the next cohort (ie, approximately 9 subjects) have completed the primary efficacy assessment. Enrollment of the rest of the cohort or advancement to the next, optional cohort will be recommended based on the totality of the data from both doses, including observed efficacy and safety and a multitude of qualitative factors listed in the charter.

Should it be considered necessary for the future development of the compound, further interim analyses may also be undertaken, as specified in the IA charter and/or SAP. The purpose of these interim analyses would be to give an early read out for the primary efficacy endpoint to enable efficient decision-making for this study, as well as for the entire project.

9.7. Data Monitoring Committee

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. Decisions or outcomes which may impact the future conduct of the study will be forwarded to sites and regulatory authorities, as appropriate. Additional details of the reviewing process are provided in the safety review plan.

Based on these reviews, there may be impact to 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.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of

Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process, any subject recruitment materials, and any subject-facing materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Thus end of trial in all concerned countries is the same: last subject last visit (LSLV). Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06730512 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs/data collection tools (DCTs) completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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17. APPENDICES

17.1. Appendix 1: Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BBS	biospecimen banking system
BMI	body mass index
BP	blood pressure
bSAP	biomarker statistical analysis plan
BUMC	Boston University Medical Center
BUN	blood urea nitrogen
C1q	complement protein 1q
CDC	complement-dependent cytotoxicity
C_{eff}	human efficacious concentration
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
C_{max}	maximum plasma drug concentration
CNI	calcineurin inhibitor
CCI	[redacted]
CO_2	bicarbonate
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
%CV	coefficient of variation
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DCT	data collection tool
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee

Abbreviation	Term
EDP	exposure during pregnancy
EU	European Union
eGFR	estimated glomerular filtration rate
ESoE	early signal of efficacy
ETS	exploratory toxicity study
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
Fc	crystallized fragment
FcγR	fragment crystallizable gamma receptor
FIH	first in human
FMV	first morning void
FPW	foot process width
FSGS	focal segmental glomerulosclerosis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GNA	grounds for non-acceptance
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin hormone
HCV Ab	hepatitis C antibody
HIV	human immunodeficiency virus
HRQL	health-related quality of life
HTRF	homogenous time resolved fluorescence
IA	interim analysis
IB	Investigator Brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IFN-*y*	interferon gamma
Ig	immunoglobulin
IgG1 Fc	immunoglobulin G1 crystallized fragment IgG1 Fc
IgGl	immunoglobulin G1
IL-6	interleukin-6
IMPDH	inosine monophosphate dehydrogenase inhibitors
IND	investigational new drug application
INR	International Normalised Ratio
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee

Abbreviation	Term
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
Kg	Kilogram
LFT	liver function test
LOCF	last observation carried forward
LSLV	last subject last visit
LSMeans	least squares mean
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMF	mycophenolate mofetil
MMRM	mixed effects model of repeated measures
CCI	[redacted]
N/A	not applicable
NAb	neutralizing antibody
NOAEL	no observed adverse effect level
PACL	Protocol Administrative Changes and Clarifications
PCD	primary completion date
PD	pharmacodynamics(s)
PGIS	Patient Global Impression of Severity
PI	principal investigator
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
PR	pulse rate
Prep B1	K2EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis
Prep D1	dipotassium edetic acid
PT	prothrombin time
q.o.d.	every other day
Q2W	every 2 weeks
QTc	Corrected QT Interval
QW	every week
RAAS	renin–angiotensin–aldosterone system
RBC	red blood cell
RNA	ribonucleic acid
ROBO2	roundabout guidance receptor 2
SAD	single ascending dose
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SC	subcutaneous
SF-12	12-Item Short Form Survey
SIQ	Symptom Impact Questionnaire
SLIT	slit guidance ligand
SLIT2	slit guidance ligand 2
SLIT2-N	slit guidance ligand 2, N-terminal fragment SLIT2-N
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
Sym-D	symptom diary
TBili	total bilirubin
TEAE	treatment-emergent adverse events
TNF-α	tumor necrosis factor-alpha
CCI	[redacted]
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VHP	Voluntary Harmonization Procedure
Vz/F	apparent volume of distribution
WBC	white blood cell
WFI	water for injection
WOCBP	women of child-bearing potential

CCI

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4. INCLUSION AND EXCLUSION CRITERIA

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