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SYNOPSIS

Study Title: 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)

Study Number: C0221002 (PODO)

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT: 2019-003607-35

ClinicalTrials.gov ID: NCT03448692

Study Phase: 2a

Name of Study Intervention: PF-06730512

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (LPLV date) Version 1.0; 25 September 2023

Number of Study Center(s) and Investigator(s):

This study was conducted at 31 sites that enrolled participants in the US (12 sites), Canada (3 sites), Spain (3 sites), Japan (3 sites), Slovakia (2 sites), UK (2 sites), Poland (2 sites), Germany (1 site), Czech Republic (1 site), Italy (1 site), and Mexico (1 site).

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Beck LH Jr, Berasi SP, Copley JB, et al. PODO: Trial Design: Phase 2 Study of PF-06730512 in Focal Segmental Glomerulosclerosis. Kidney International Reports 2021;6(6):1629-1633.

Study Period:

The first participant first visit (FPFV) was 15 October 2018, and the last participant last visit (LPLV) was 14 February 2023. The study was terminated.

Rationale:

Although the purpose of this Phase 2 adaptive study was to evaluate the efficacy, safety, tolerability and pharmacokinetics (PK) of PF-06730512 following multiple intravenous (IV) administrations in adult participants with focal segmental glomerulosclerosis (FSGS), the

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primary intention was to enable the sponsor to identify if PF-06730512 would be efficacious in the FSGS patient population prior to expanding the sample size and population to fully demonstrate efficacy and safety required for registration. Up to 3 doses of PF-06730512 were to be assessed in up to 3 separate cohorts.

All participants were required to complete an approximate 8-week Lead-in Period prior to receiving PF-06730512 in a 12-week, later amended to 24-week Investigational Treatment Period. Given the rarity of the disease and the small sample size of the study, a placebo control was not included in the design. Adequate safety assessment would be feasible based on data obtained in the study's Lead-in Period in comparison to the Investigational Treatment Period.

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Objectives, Endpoints, and Statistical Methods:

Type	Objectives	Endpoints
	Primary	
Efficacy:	• 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 urine protein to creatinine ratio (UPCR), calculated from the 24-hour urine collection.
	Secondary	
Safety:	• To evaluate the safety and tolerability of PF-06730512 following up to 24 weeks of treatment in subjects with FSGS.	• Adverse events (AEs), laboratory safety tests (hematology, clinical chemistry, urinalysis), body weight, blood pressure, pulse rate, body temperature and electrocardiogram (ECG).
Efficacy:	• To evaluate the effects of PF-06730512 on proteinuria time course. • To evaluate the effect of PF-06730512 on renal function.	• 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).
PK:	• To evaluate the serum exposure of PF-06730512 in FSGS patients.	• Serum concentration of PF-06730512.
Immunogenicity:	• To evaluate the immunogenicity profile of PF-06730512.	• Incidence of the development of anti-drug antibody (ADA) and neutralizing antibody (NAb).

Methodology:

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The adaptive study consisted 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 participants received PF-06730512 every 2 weeks (Q2W), followed by a 9-week Follow-up Period. Participants in the Lead-in Period would be eligible for transition to active treatment if at Week -1, the UPCR and eGFR met eligibility criteria.

The study was designed to investigate up to 3 doses of PF-06730512 in up to 3 cohorts, each consisting of up to approximately 22 participants. Participants in Cohort 1 were to receive PF-06730512 at 1000 mg Q2W IV. The planned dose level for Cohort 2 was PF-06730512 300 mg Q2W IV, and based on emerging data the dose could be adjusted up to 1000 mg Q2W IV. A 3rd optional cohort (Cohort 3) could be enrolled to evaluate an additional high dose of PF-06730512 up to 2500 mg Q2W IV, based on cumulative safety, efficacy, and PK data from Cohorts 1 and/or Cohort 2. All cohorts were to collect the same procedures at the same timepoints. Interim analyses were to be conducted to determine futility of any evaluated dose, and to inform selection of next dose level to be evaluated.

Number of Participants (planned and analyzed):

A total of 47 participants were enrolled into the study. All these participants received at least 1 dose of the study intervention. Of the 47 treated participants, 10 discontinued the study intervention, including 1 in Cohort 1 (due to AE), and 9 in Cohort 2, none of which were due to AEs and 5 were due to study termination. Except for per-protocol analysis set (PPAS) which included 18 evaluable participants, all 47 participants were included in full analysis set (FAS), safety analysis set (SAS), PK analysis sets and immunogenicity analysis set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were adult participants with a renal biopsy-confirmed diagnosis of FSGS, having eGFR ≥45 mL/min/1.73 m^2 (or eGFR 30-45 mL/min/1.73 m^2, accompanied by a recent biopsy within the past 12 months demonstrating <50% tubule-interstitial fibrosis) and UPCR >1.5 g/g at Screening. And it should be noted that in the most recent protocol amendment 5:

1. Secondary FSGS was allowed in the study;
2. Single class to three classes of FSGS treatments were allowed during the study;
3. Stable dose of corticosteroid dose criteria ≤7.5 mg per day (or 15 mg every other day) or other steroids equivalent was allowed during the study;
4. Stable dose of calcineurin inhibitors (CNIs) and/or mycophenolate mofetil (MMF) was allowed during the study.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Participants were dosed Q2W IV (infusion over approximately 60 minutes) for up to 12 weeks, receiving a maximum of 6 infusions (Day 1/Week 1 and at Weeks 3, 5, 7, 9 and

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11, respectively) or 24 weeks, receiving a maximum of 12 infusions of PF-06730512 (Day 1/Week 1 and at Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23, respectively) based on the informed consent that the participants consented to.

The manufacturing lot numbers for the study intervention dispensed in this study are provided in Table S1.

Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
PF-06730512 Powder for Solution for Injection, 120 mg/vial	20-DP-00258	20-003403	120 mg	Lyophile
PF-06730512 Powder for Solution for Injection, 120 mg/vial	Not Applicable (NA)	16-005034	120 mg	Lyophile

Duration of Study Intervention:

Participants received study intervention for up to 12 weeks or 24 weeks.

Summary of Results:

Demographic and Other Baseline Characteristics:

Of the 47 participants, most were white (76.6%); gender distribution was overall balanced (male: 53.2%, female: 46.8%); more than half of participants (55.3%) were aged 18 to <45 years old. The median (range) age in Cohort 1 (47.0 [21, 59] years old) was numerically higher than that in Cohort 2 (39.0 [21, 75] years old). The median (range) body mass index (BMI) of the 47 participants at Baseline was 27.770 (11.69-44.60) kg/m^2.

The average (standard deviation [SD]) duration of disease (years) in Cohort 1 (3.72 [4.04]) was less than that in Cohort 2 (5.72 [7.60]); the average (SD) baseline UPCR (g/g) based on 24-hour urine collection in Cohort 1 (5.42 [4.11]) was lower than that in Cohort 2 (6.03 [3.51]), so was the average (SD) baseline eGFR ($mL/min/1.73\ m^2$) (63.12 [18.86] in Cohort 1 and 69.25 [24.83] in Cohort 2).

Exposure:

All 47 participants received at least 1 dose of their assigned study intervention:
10 participants (1 in Cohort 1 and 9 in Cohort 2) discontinued the study intervention; a total of 24 participants (18 in Cohort 1 and 6 in Cohort 2) completed 12-week Investigational Treatment Period; and a total of 13 participants (4 in Cohort 1 and 9 in Cohort 2) completed 24-week Investigational Treatment Period.

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Two participants (both in Cohort 1) did not receive the planned 1000 mg dose and instead received 1080 mg at 3 visits, which were recorded as important protocol deviations (IPDs) and medication errors. Additionally, 5 participants (1 in Cohort 1 and 4 in Cohort 2) had study intervention interruption due to AEs, and in 4/5 participants the interruption was due to treatment-emergent AEs (TEAEs).

Efficacy Results:

All the efficacy analyses were performed based on the FAS, except for one of the sensitivity analyses for the primary efficacy endpoint that was based on the PPAS.

Primary Efficacy Endpoint: Percent Change From Baseline (%CFB) in UPCR to Week 13 - 24-hour Urine Collection

Primary Analyses

Based on 24-hour urine collection, the least squares mean (LS mean) %CFB in UPCR at Week 13 was -12.283% (90% confidence interval [CI]: -26.096%, 4.112%) and -0.045% (90% CI: -9.528%, 10.432%) in Cohort 1 and Cohort 2, respectively.

The posterior probability of being at least 95% confident that the UPCR reduction >0% at Week 13 was 89.74% and 50.30% in Cohort 1 and Cohort 2, respectively. The posterior probability of being at least 50% confident that the UPCR reduction >35% at Week 13 was <1% in both cohorts.

Sensitivity Analyses

Five (5) sensitivity analyses to the primary endpoint were performed and the results are summarized as below:

- **Primary analysis mixed effects model of repeated measures (MMRM) model using first morning void (FMV)**: based on FMV, similar results to that based on 24-hour urine collection were observed in Cohort 1. The LS mean %CFB in UPCR at Week 13 was -14.451% (90% CI: -29.209%, 3.384%) and 7.413% (90% CI: -7.120%, 24.221%) in Cohort 1 and Cohort 2, respectively. The posterior probability of being at least 95% confident that the UPCR reduction >0% was 90.27% and 54.65% in Cohort 1 and Cohort 2, respectively. The posterior probability of being at least 50% confident that the UPCR reduction >35% was <1% in both cohorts.

- **Primary analysis MMRM model based on PPAS**: based on 24-hour urine collection, the LS mean %CFB in UPCR at Week 13 for the PPAS was -2.976% (90% CI: -17.288%, 13.812%) and -3.058% (90% CI: -16.443%, 12.470%) in Cohort 1 and Cohort 2, respectively.

- **Alternative MMRM model taking into account all information from the Lead-in Period**: based on 24-hour urine collection, the LS mean %CFB in UPCR at Week 13

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using alternative MMRM analysis that considered all information from the Lead-in Period, was -12.675% (90% CI: -25.856%, 2.849%) and 2.777% (90% CI: -6.999%, 13.581%) in Cohort 1 and Cohort 2, respectively.

- **Primary analysis MMRM model with potentially relevant covariates being added to the model:** When relevant covariates were added, based on 24-hour urine collection, the LS mean %CFB in UPCR at Week 13 was -10.886% (90% CI: -24.151%, 4.699%) and -1.455% (90% CI: -11.082%, 9.215%) in Cohort 1 and Cohort 2, respectively.
- [redacted]

Secondary Efficacy Endpoints

%CFB in UPCR to Weeks 5 and 9 - 24-hour Urine Collection and FMV

For the secondary endpoint "%CFB in UPCR to Weeks 2, 5, and 9", the number of participants who had Week 2 visit was too small to successfully run the statistical model, and therefore LS mean %CFB results were not provided at Week 2 for the endpoint.

Based on 24-hour urine collection, the LS mean %CFB in UPCR:

- at Week 5 was 6.250% (90% CI: -7.035%, 21.433%) and -3.788% (90% CI: -11.344%, 4.411%) in Cohort 1 and Cohort 2, respectively; and
- at Week 9 was -11.335% (90% CI: -20.746%, -0.807%) and -2.354% (90% CI: -11.069%, 7.215%) in Cohort 1 and Cohort 2, respectively.

Based on FMV, the LS mean %CFB in UPCR:

- at Week 5 was 8.509% (90% CI: -3.471%, 21.976%) and 0.917% (90% CI: -10.167%, 13.369%) in Cohort 1 and Cohort 2, respectively; and
- at Week 9 was 6.803% (90% CI: -8.049%, 24.054%) and 0.423% (90% CI: -9.177%, 11.036%) in Cohort 1 and Cohort 2, respectively.

%CFB in eGFR to Weeks 3, 5, 9, and 13

From Week 3 through Week 13, the LS mean %CFB in eGFR:

- at Week 3 was 5.657% (90% CI: -0.722%, 12.446%) and -0.180% (90% CI: -4.179%, 3.987%) in Cohort 1 and Cohort 2, respectively;

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- at Week 5 was 2.174% (90% CI: -3.012%, 7.637%) and -2.038% (90% CI: -8.008%, 4.319%) in Cohort 1 and Cohort 2, respectively;
- at Week 9 was -1.536% (90% CI: -15.575%, 14.838%) and -5.017% (90% CI: -11.596%, 2.052%) in Cohort 1 and Cohort 2, respectively; and
- at Week 13 was 2.892% (90% CI: -6.096%, 12.740%) and -12.217% (90% CI: -18.831%, -5.063%) in Cohort 1 and Cohort 2, respectively.

Safety Results:

Treatment-Emergent AEs (TEAEs)

AEs described here are all treatment-emergent, and those started before the first dose of study intervention, ie, during the Lead-in Period were not included.

Brief Summary of Adverse Events

A total of 124 all-causality and 24 treatment-related TEAEs were reported in 37 (78.7%) and 15 (31.9%) participants, respectively. The majority of the TEAEs were mild or moderate in severity. Serious AEs (SAEs) and severe TEAEs were reported in 4 (8.5%) and 3 (6.4%) participants, respectively, and none of these were treatment-related. There was 1 participant (in Cohort 1) who discontinued the study intervention due to non-treatment-related TEAE. No participant in Cohort 2 discontinued the study intervention due to TEAE. A total of 4 participants (1 in Cohort 1 and 3 in Cohort 2) underwent dose reduction or treatment interruption due to TEAEs, and for 1 of them the TEAEs were treatment-related. Incidence of all-causality TEAEs was higher in Cohort 1 compared to Cohort 2 (87.0% vs 70.8%). Incidences of SAEs (8.7% vs 8.3%), treatment-related TEAEs (30.4% vs 33.3%), and severe TEAEs (4.3% vs 8.3%) were similar between the 2 cohorts.

The most frequently reported TEAEs in the study (in ≥5% of participant in total) included fatigue and headache (10.6% each), coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test positive, and diarrhoea (8.5% each), and vomiting and acute kidney injury (6.4% each). The TEAEs reported in ≥2 participants in Cohort 1 included fatigue in 3 participants, and diarrhoea, vomiting, pyrexia, viral infection, SARS-CoV-2 test positive, dehydration, headache, insomnia, acute kidney injury, and cough (each in 2 participants); those in Cohort 2 included COVID-19 and headache (each in 3 participants), and diarrhoea, fatigue, oedema, nasopharyngitis, urinary tract infection, infusion related reaction, SARS-CoV-2 test positive, flank pain, muscle spasms, and dizziness (each in 2 participants).

Treatment-related TEAEs reported in ≥2 participants in Cohort 1 included fatigue and headache (each in 2 participants); those in Cohort 2 included fatigue, infusion related reaction, and headache (each in 2 participants), all others were reported in single participants.

Clinical Laboratory Evaluation, ECG, and Vital Signs

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There were no clinically important trends in lab values. There were no notable changes from baseline in ECG parameters, or vital signs.

Pharmacokinetic Results:

Following multiple IV infusions of PF-06730512 at doses of 300 mg Q2W and 1000 mg Q2W in adult participants with FSGS, maximum serum concentration during the dosing interval (C_{max}) was observed shortly after the end of the 1-hour infusion (median time for C_{max} [T_{max}] range of approximately 1.1 to 1.2 hours). Serum PF-06730512 Day 71 C_{max} and area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where tau = 336 hours for Q2W dosing (AUC_{τ}) increased approximately proportionally from 300 mg Q2W to 1000 mg Q2W.

At steady state (Days 71 and 155), geometric mean clearance for IV dosing (CL) was 0.043 L/h and 0.029 L/h and geometric mean volume of distribution at steady state for IV dosing (V_{ss}) was 6.5 L and 5.4 L for 300 mg and 1000 mg doses, respectively. Mean terminal half-life ($t_{½}$) was 224 hours and 252 hours for 300 mg and 1000 mg doses, respectively.

Participant variability in PF-06730512 exposure based on geometric percent coefficient of variation (CV%) for AUC_{τ}, and C_{max} ranged between 31% to 41% on Day 1 and 70% to 134% on Day 71. On Day 155, variability was low for the 1000 mg dose group (geometric CV% for AUC_{τ} and C_{max} was 15% and 21%, respectively), while for the 300 mg dose group variability was high with geometric CV% for AUC_{τ} and C_{max} at 226% and 361%, respectively.

In participants with baseline UPCR ≥3 g/g (nephrotic group), median trough serum concentrations were generally 30-60% of that in participants in the non-nephrotic group (baseline UPCR <3 g/g), in both the 1000 mg and 300 mg IV Q2W dose cohorts.

Immunogenicity Results:

Of the 47 participants evaluated for ADA and NAb, the overall incidence of positive ADA during the study treatment was 2.1%, and the overall incidence of positive NAb was 0%. The positive ADA, which was detected in only 1 participant in Cohort 1, was treatment-induced and transient in duration.

Conclusions:

PF-06730512 was in general safe and tolerable, with no clinically significant safety signals being identified. The study failed to meet the primary efficacy endpoint of percent reduction from baseline in UPCR at Week 13 based on 24-hour urine collection at both tested doses of PF-06730512 1000 mg and 300 mg IV Q2W.

Efficacy

UPCR: In Cohort 1 (1000 mg IV Q2W), UPCR results were similar based on 24-hour urine collection and FMV: the LS mean %CFB in UPCR at Week 13 was -12.283% (90%

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CI: -26.096%, 4.112%) based on 24-hour urine collection and -14.451% (90% CI: -29.209%, 3.384%) based on FMV. In Cohort 2 the %CFB in UPCR at Week 13 was -0.045% (90% CI: -9.528%, 10.432%) based on 24-hour urine collection and 7.413% (90% CI: -7.120%, 24.221%) based on FMV.

The posterior probability of being at least 50% confident that the UPCR reduction >35% at Week 13 was <1% in both cohorts based both on 24-hour urine collection and FMV.

The posterior probability of being at least 95% confident that the UPCR reduction >0% at Week 13 in Cohort 1 was 89.74% and 90.27% based on 24-hour urine collection and FMV, respectively; and in Cohort 2 was 50.30% and 54.65% based on 24-hour urine collection and FMV, respectively.

eGFR: At Week 13 LS mean %CFB in eGFR was 2.892% (90% CI: -6.096%, 12.740%) in Cohort 1 and -12.217% (90% CI: -18.831%, -5.063%) in Cohort 2.

Safety

- During the study, treatment-emergent SAEs, severe AEs, and discontinuation from the study intervention due to AEs were reported in limited number of participants (8.5%, 6.4%, and 2.1%, respectively), and none were related to the study intervention.
- Incidence of all causality TEAEs was higher in Cohort 1 than that in Cohort 2 (87.0% vs 70.8%), while the incidence of treatment-related TEAEs was similar across Cohorts 1 and 2 (30.4% vs 33.3%, respectively).
- The most frequently reported TEAEs (in ≥5% of participant in total) included fatigue and headache (10.6% each), COVID-19, SARS-CoV-2 test positive, and diarrhoea (8.5% each), and vomiting and acute kidney injury (6.4% each).
- There were no clinically important trends in lab values. There were no notable changes from baseline in ECG parameters, or vital signs.

PK

- Following multiple IV infusions of PF-06730512 at doses of 300 mg Q2W and 1000 mg Q2W in adult participants with FSGS, peak serum concentrations were reached shortly past the end of 1-hour infusion. Serum PF-06730512 Day 71 C_{max} and AUC_{τ} increased approximately proportionally from 300 mg Q2W to 1000 mg Q2W.
- At steady state (Days 71 and 155), geometric mean CL ranged from 0.029 to 0.043 L/h, geometric mean V_{ss} ranged from 5.4 to 6.5 L, mean t½ ranged from 224 to 252 hours.

Immunogenicity

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The overall incidence of immunogenicity was low, with only 1 participant in Cohort 1 being confirmed positive for ADA, and none for NAb. As the overall immunogenicity incidence was low, there was insufficient data to fully evaluate the effect of ADA/NAb on PK and safety. No AEs, clinically significant findings nor differences in PK were observed in relation to ADA/NAb.