A PHASE 1, NON-RANDOMIZED, OPEN LABEL, SINGLE DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-06700841 IN PARTICIPANTS WITH RENAL IMPAIRMENT AND IN HEALTHY PARTICIPANTS WITH NORMAL RENAL FUNCTION

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Short Title: Renal Impairment Study of PF-06700841

Protocol Amendment Summary of Changes Table

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1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable.

1.2. Schema

Not Applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier[a]	Screening[b]		Day -1[b]	Day 1	Day 2	Day 3	Day 4	Follow-up Contact	Early Termination/ Discontinuation (DC)
	Day -28 to Day -2								
Days Relative to Day 1	S1	S2						28-35 Days[c]	
Informed consent	X								
Admission to CRU			X						
Confinement to CRU			X	→	→	→	X		
Inclusion/exclusion criteria	X		X						
Medical history	X		X						
Demography[d]	X								
Physical examination[e]			X				X		X
Height and weight assessment[f]	X	X	X					X[g]	
Safety laboratory tests (blood and urine)[h]	X	X[i]	X				X	X[g]	X
eGFR assessment[j]	X	X	X					X[g]	
QuantiFERON®-TB Gold Test or PPD skin test[k]	X								
Illegal drug/tobacco/alcohol use	X		X						
Urine alcohol test or alcohol breath test	X		X						
Urine or serum pregnancy test (WOCBP only)	X		X				X		X
Contraception check[l]	X	X	X					X	X
Serum FSH in post-menopausal females amenorrheic ≥12 months and under 60 years of age	X								
Urine drug screen	X		X						
Single supine 12-Lead ECG	X			X[m]			X		X

Visit Identifier[a]	Screening[b]		Day -1[b]	Day 1	Day 2	Day 3	Day 4	Follow-up Contact	Early Termination/ Discontinuation (DC)
	Day -28 to Day -2								
Days Relative to Day 1	S1	S2						28-35 Days[c]	
Vital signs (supine BP, pulse rate) and temperature	X			X			X		X
HIV, HBsAg, HBcAb, HCVAb testing[n]	X								
Investigational product administration				X					
Plasma PK for PF-06700841 and M1				X	X	X	X		X
Urine PK for PF-06700841 and M1				X	X	X	X		
CCI [redacted]			[redacted]						
Prior/concomitant treatments	X	X	X	→	→	→	X	X	X
CRU discharge							X		
Serious and nonserious adverse event monitoring	X	X	X	→	→	→	X	X	X

Abbreviations: → = ongoing/continuous event; BP = blood pressure; DC = discontinuation; eGFR = estimated glomerular filtration rate; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; PK = pharmacokinetic; PPD = purified protein derivative; QFT-G = QuantiFERON®-TB Gold; S1= Screening Visit 1; S2= Screening Visit 2; WOCBP = women of childbearing potential; M1 = a major metabolite of PF-06700841.

Visit Identifier[a]	Screening[b]		Day -1[b]	Day 1	Day 2	Day 3	Day 4	Follow-up Contact	Early Termination/ Discontinuation (DC)
	Day -28 to Day -2								
Days Relative to Day 1	S1	S2						28-35 Days[c]	

a. Day relative to start of study treatment (Day 1).
b. Screening will consist of 2 CRU outpatient visits (Screening Visits 1 and 2) between 3 to 14 days apart, with the 1st screening visit occurring within 28 days prior to investigational product administration (Day 1). The 2nd screening visit is only to demonstrate stable renal function with difference between eGFRs at Screening visit 1 (S1) and Screening visit 2 (S2) required to be ≤25% of the value obtained at S1. If participant meets all screening criteria at S2 visit, and Day -1 visit can be performed immediately, the participant may be admitted to the unit at conclusion of S2 visit. Other screening procedures completed during the first visit (S1) do not need to be repeated. See Section 4.1 for outpatient visit screening schedule.
c. Contact may occur via telephone contact and must occur 28 to 35 days from administration of the investigational product or from the time of early termination/discontinuation. If participant demonstrates an increase of >25% in serum creatinine from Day -1 to Day of discharge, he or she will be asked for a follow-up visit to collect eGFR.
d. Demographics will include race, age and gender.
e. Complete physical examination at Day -1, Day 4, and early termination. Limited physical examination at any time point as deemed necessary by the investigator.
f. Height to be obtained at S1 only, weight to be obtained at S1, S2 and Days -1.
g. Only when the participant demonstrates an increase of >25% in serum creatinine from Day -1 to Day of discharge. Only serum creatinine and weight information will be collected for eGFR assessment.
h. Safety laboratory assessments include chemistry, hematology and urinalysis (and microscopy, if needed) and will be performed at S1, on Day -1, Day 4 and early termination day. All the assessments must be collected following at least a 4 hour fast.
i. Serum creatinine only will be assessed on S2 for eGFR assessment.
j. To confirm eligibility, participants must have stable renal function defined as ≤25% difference for eGFR values at S2 compared to the value at S1. The average of the 2 screening eGFR values will be used for participant stratification and group assignment (provided stable renal function is still demonstrated). If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of the S1 and S2 eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment. The Day -1 eGFR value will be used for PK analysis. The eGFR determination will utilize the 4-variable MDRD equation. A follow-up eGFR will be collected at Day 28 (with window of +3 days to allow for holidays) for any participant who demonstrates an increase of >25% in serum creatinine from Day -1 to Day of discharge.
k. If QFT-G test cannot be performed, or if results are indeterminate, participants may be screened using PPD Tuberculin Test (Mantoux method), with approval of medical monitor.
l. Confirmation of appropriate use only.
m. Triplicate 12-lead ECG will be performed at 0 hr pre-dose on Day 1. Single 12-lead ECG will be collected at 1, 3, and 6 hr post-dose on Day 1.
n. HBsAb will be performed as reflex testing for any participant who is HBsAg negative and HBcAb positive (Section 10.2.1). HCV RNA will be performed as reflex testing for any participant who is HCV Ab positive (Section 10.2.1).

[redacted] CCI [redacted]

Pharmacokinetic Sampling Schema

Visit Identifier														
Study Day	**1**										**2**		**3**	**4**
Hours Before/After Dose	**0**[a]	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**24**	**36**	**48**	**72**
Investigational product administration	X													
PK blood sampling[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK urine collection[c]	X	→	→	→	→	→	→	→	→	→	X	→	X	X
Abbreviation: →= ongoing/continuous event, PK = pharmacokinetic.														

a. Predose sample collection.
b. Blood samples are to be collected for plasma PK assessment of both PF-06700841 and M1.
c. Urine collections during intervals of ≤24, >24 and ≤48, and >48 and ≤72 hours after dosing on Day 1. During the subsequent designated urine collection intervals ([0-24], [24-48], and [48-72] hours post dose), participants will void ALL urine produced during the designated collection interval, including a forced void at the end of the collection interval, directly into pre-weighed urine collection container. Urine samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs, **only** if it is determined by the study team that there is a need to do so, based on review of PF-06700841 and M1 plasma PK results.

2. INTRODUCTION

PF-06700841 is a potent tyrosine kinase 2 (TYK2)/Janus kinase (JAK) 1 inhibitior that is currently being developed for the treatment of patients with inflammatory diseases, including systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), psoriasis (PsO), alopecia areata (AA), vitiligo, inflammatory bowel disease (IBD), hidradenitis suppurativa (HS) and atopic dermatitis (AD).

2.1. Study Rationale

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanism for PF-06700841 was cytochrome P450 (CYP450) mediated oxidation. The contribution of individual CYP450 involved in the metabolism of PF-06700841 (1 μM) was assessed in a preliminary reaction phenotyping study using a human hepatocyte relay method. Greater than 88% of the PF-06700841 metabolism observed was attributed to CYP450 with CYP3A4 identified as the major contributor (fraction metabolized [fm] = 0.62). In the first in human study, B7981001, urinary recovery of PF-06700841 was low, with <16% of the dose recovered unchanged in urine across all doses (geometric mean Ae_{τ}% of 8.9% to 15.5%), indicating that the renal pathway plays a minimal role in PF-06700841 excretion.

Evidence suggests that the pharmacokinetics (PK) of drugs that are not only excreted by the kidney can be affected by renal impairment through inhibition of pathways of hepatic and gut drug metabolism and transport.[1] Consequently, recent European Medicines Agency (EMA) guidelines suggest that renal impairment studies be conducted in patients with decreased renal function for nearly all small molecules, even if the drug or its active metabolite is not primarily eliminated by the kidneys.[2] The revised Food and Drug Administration (FDA) Draft Guidance on renal impairment studies also recommends that a PK study be conducted in participants with renal impairment when the drug is likely to be used in patients with impaired renal function.[1]

PF-06700841 is intended for chronic use in patients, some of whom may have some degree of impaired renal function. Therefore, the purpose of this study is to characterize the effect of renal impairment on the plasma PK of PF-06700841. Findings from this study will be used to develop dosing recommendations so that the dose and/or dosing interval may be adjusted appropriately in the presence of renal disease.

2.2. Background

PF-06700841 is a dual TYK2/JAK1 inhibitor with a high selectivity profile over other human kinases. The clinical efficacy of JAK1 inhibition with tofacitinib has been established in PsA, PsO and in IBD.[3,4,5] PF-06700841 targets the JAK1-dependent pathways, and in addition, inhibiting TYK2 is expected to lower interleukin (IL)-12, IL-23 and Type I interferon (IFN) signaling to a greater degree than JAK1 inhibition alone. Accumulating evidence indicates that the IL-23/T help 17 (Th17) pathway plays an important role in the pathology of PsO, PsA, AA and IBD. Inhibition of both JAK1 and TYK2 is expected to provide greater therapeutic benefit in the treatment of plaque PsO, PsA, AA, AD, SLE, HS, vitiligo and IBD. In Study B7931001, PsO participants receiving active treatment with PF-06700841 (30 mg or 100 mg once daily [QD] for 28 days) had clinically meaningful decreases in disease activity

as measured by Psoriasis Area and Severity Index (PASI; a validated PsO clinical disease activity metric accepted by regulatory agencies). Preliminary safety, efficacy, and pharmacodynamics results from Study B7931001 support further development of PF-06700841 in plaque PsO, PsA (based on the PsO data) and possibly IBD. A Phase 2 study B7931004 to assess the safety and efficacy of several dose levels of PF-06700841 in participants with moderate-to-severe chronic plaque PsO was completed. PF-06700841 is currently under assessment in 4 ongoing Phase 2 studies in AA (B7931005), ulcerative colitis (UC) (B7981005), Crohn's Disease (CD) (B7981007) and SLE (B7931028). Ongoing and future studies with PF-06700841 explore doses up to 60 mg given QD.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-06700841 can be found in the current Investigator Brochure (IB).

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP450 enzymes were implicated in the clearance of PF-06700841 in initial parent drug conversion studies in rat, monkey, and/or human liver microsomes and hepatocytes. There was no evidence of aldehyde oxidase-mediated PF-06700841 metabolism in a human cytosol screen. The contribution of individual CYP450 involved in the metabolism of PF-06700841 (1 μM) was assessed in a preliminary reaction phenotyping study using a human hepatocyte relay method. Greater than 88% of the PF-06700841 metabolism observed was attributed to CYP450 with CYP3A4 identified as the major contributor (fm = 0.62). Human Absorption, Distribution, Metabolism and Elimination (ADME) study (B7931014) is ongoing to definitively assess elimination pathways and metabolic profiles.

Additional information of the nonclinical PK and metabolism of PF-06700841 is available in the current IB.

2.2.3. Nonclinical Safety

No adverse findings were observed in oral repeat-dose toxicity studies with PF-06700841 in rats and monkeys up to 6 and 9 months in duration, respectively. PF-06700841-related, non-adverse, target organs identified include the immune and hematolymphopoietic systems (thymus, spleen, lymph nodes, and bone marrow), cardiovascular system (blood pressure, heart rate, corrected QT wave interval [QTc]), gastrointestinal tract (body weight and weight gain effects), and adrenal gland (vacuolation). The findings in the thymus, spleen, lymph nodes, and bone marrow are consistent with the pharmacological activity of PF-06700841. The no-observed-adverse-effect level (NOAELs) in the 6-and 9-month toxicity studies were 45 mg/kg/day in rats (unbound C_{max} of 8280 ng/mL and area under the curve from time 0 to 24 hours [AUC_{24}] of 69,700 ng•h/mL) and 20 mg/kg/day in monkeys (unbound maximum plasma concentration [C_{max}] of 2260 ng/mL and AUC_{24} of 10,700 ng•h/mL). Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high systemic exposures in pregnant, but not in non-pregnant rabbits.

In oral embryo-fetal development studies in rats and rabbits, adverse PF-06700841-related developmental effects occurred (lower embryo-fetal viability and mean fetal body weights, fetal skeletal malformations, external malformations). The developmental NOAEL in rabbits was 1 mg/kg/day (unbound C_{max} of 174 ng/mL and AUC_{24} of 608 ng•h/mL).

The developmental NOAEL in rats was not established and is <2 mg/kg/day (unbound C_{max} of 482 ng/mL and AUC_{24} of 2240 ng•h/mL), the lowest dose tested. No effects on female reproductive organs, as assessed by histopathologic examination, were noted in either the rat or monkey repeat-dose toxicity studies. PF-06700841 is not mutagenic in bacterial reverse mutation assays. Although PF-06700841 was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei in vivo in rats at 55 mg/kg/day (unbound C_{max} = 7730 ng/mL and AUC_{24} = 88,300 ng•h/mL), the highest dose tested in the 1-month oral toxicity study.

Further details of the nonclinical safety program are provided in the current IB.

2.2.4. Clinical Overview

The sponsor's clinical development program for PF-06700841 consists of 3 completed Phase 1 studies in healthy participants and PsO participants (B7931001, B7931009 and B7931010), 1 complete Phase 2 study in PsO (B7931004), and is currently under assessment in 6 ongoing Phase 2 studies in AA (B7931005), UC (B7981005), CD (B7981007) and SLE (B7931028), vitiligo (B7981019), PsA (B7931030), and 1 planned Phase 2 study in HS (C2501007). In addition, 2 Phase 1 studies in healthy participants are clinically complete and preparation of the clinical reports including a study to assess effect of PF-06700841 on QTc interval (B7931019) and a human ADME study using 14C microtracer (B7931014). A drug interaction study with a potent CYP3A4 inhibitor, itraconazole (B7931033) is ongoing. The studies described above have all used oral administration of PF-06700841. The topical development program consists of 1 completed Phase 1 study (B7931029), and 2 ongoing Phase 2 studies in AD (B7931022) and PsO (B7931023).

Included in this Clinical Overview are summaries of the results from only the clinically completed Phase 1 studies, B7931001, B7931009, B7931010, B7931014 and B7931019, Phase 2 study in PsO, B7931004 and ongoing Phase 2 study in AA with an interim analysis study result (B7931005).

2.2.4.1. Safety Overview

Overall, PF-06700841 was generally well-tolerated in healthy volunteers (B7931001, B7931009, B7931010, B7931014, and B7931019); PsO (B7931001 and B7931004) and AA participants (B7931005). There were no clinical meaningful findings in vital signs, suicidal behavior or ideation, or potential Hy's Law cases reported during these studies.

Refer to the IB for more details on the clinical safety information with PF-06700841.

2.2.4.1.1. Phase 1 Studies

In first-in-human (FIH) study B7931001, the most commonly reported all causality treatment-emergent adverse events (TEAEs) across active participants in both healthy volunteers and PsO participants were blood creatinine increased, leading to 5 withdrawals in the study. Participants in the multiple ascending dose [MAD] and PsO periods that had increased serum creatinine (SCr) ≥0.3 mg/dL did not demonstrate significant changes in S Cystatin-C based estimated glomerular filtration rate (eGFR), suggesting that the change in creatinine - based eGFR might be caused by changes in renal handling of creatinine, rather than by alteration of renal function. The most frequently reported laboratory abnormalities were increases in low-density lipoprotein (LDL), serum creatinine, and decreases in neutrophil counts in participants receiving PF-06700841 during single ascending dose [SAD]/MAD and psoriatic period. Neutrophil count decreased (reported in 4 participants during the MAD period), leading to 3 withdrawals in the study.

In B7931009, B7931010 and B7931014 studies, oral administration of PF-06700841 was well-tolerated in healthy participants investigated in the study. There were no deaths, serious adverse events (SAEs), severe adverse events (AEs), discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. There were no clinically significant findings observed in laboratory parameters, vital signs, electrocardiogram (ECG) parameters.

A formal through QT study (B7931019) suggested PF-06700841 has a small effect on QT prolongation. Following a single dose of 200 mg PF-06700841, the maximum placebo-corrected QT interval corrected using Fridericia's correction factor (QTcF) change from baseline was observed at 3 hours post-dose with mean of 14.6 ms and 90% confidence interval (CI) of (12.4, 16.8 ms). As expected, the maximum mean change in QTcF observed following administration of 400 mg moxifloxacin was 13.8 ms (90% CI:11.6, 16.0 ms). Despite QTc effect observed after single doses of PF-06700841 200 mg and moxifloxacin 400 mg, there were no clinically significant findings in ECG categorical analyses in that QTc change from baseline >60 msec or QTc absolute value >500 msec was not observed. Based on the concentration-QTcF analysis, the primary analysis defined in this study, the estimated QTcF increase at predicted C_{max} of PF-06700841 60 mg QD, the highest clinical dose used in ongoing Phase 2 studies, is approximately 8.8 ms with the upper bound of 90% CI (10.2 ms) slightly exceeding 10 ms threshold.

2.2.4.1.2. Phase 2 Studies

A total of 189 PsO participants out of 212 enrolled in B7931004 were exposed to at least 1 dose of PF-06700841 during the study. The proportion of participants with all-causality TEAEs was comparable across all treatment arms but numerically higher in the active treatment arms (64.0% to 76.7%) than the placebo group (56.5%). The majority of participants in all treatment arms experienced mild or moderate all-causality TEAEs, and only 5.2% experienced severe all-causality TEAEs.

Overall, there were no dose-dependent increases in the all-causality TEAEs. Most TEAEs in the Infection and Infestation class were mild to moderate except 1 participant who had 2 serious infections after taking a single dose of 60 mg PF-06700841 on Day 1. One (1) participant in the 30 mg QD to 100 mg once a week (QW) group had squamous cell carcinoma of skin reported on Day 2 of treatment. One (1) participant in the 30 to 10 mg group was confirmed to be pregnant after being in the study for 42 days and was discontinued from the study with obstetrical ultrasound demonstrating fetal cleft lip.

Decreased reticulocytes, hemoglobin, and neutrophils were observed in the participants on active treatment during 4-week induction phase and returned toward baseline level during 8-week maintenance phase. Increases in serum creatinine from baseline were observed in all active treatment arms with no association of change in cystatin C based renal function measurement. Other commonly reported laboratory abnormalities were elevation of LDL with no clinical meaningful changes in LDL/high density lipoprotein (HDL) ratio. Creatine kinase (CK) levels >10 × upper limit of normal (ULN) were observed in two participants without adverse event (AE). One moderate AE of CK-myoglobin increase was reported by one participant in the 30 to 10 mg QD group during the induction period, which was considered to be related to the investigational product by the investigator. No participant was discontinued from the study due to CK elevation.

In Study B7931005, 47 AA participants were exposed to at least 1 dose of PF-06700841. The most commonly reported TEAEs in the active treatment arm was in the Infections and Infestations system organ class (SOC) (51.1% in the investigational product vs 40.4% in the placebo). Other TEAEs were Gastrointestinal Disorders (23.4% in the investigational product vs 25.5% in the placebo). Most of those TEAEs were mild. There were 2 participants receiving PF-06700841 that experienced rhabdomyolysis after strenuously exercising during the study, which were not considered to be related to the investigational product by investigator assessment. Three participants experienced mild decreases in neutrophils, one participant had a mild reduction in platelets, and one participant a mild reduction in lymphocytes.

2.2.4.2. Summary of PF-06700841 Pharmacokinetics in Human

In Study B7931001, following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 was absorbed rapidly with median time to maximum concentration (T_{max}) of 1 hour or less. Mean terminal half-life ($t_{½}$) ranged from 3.8 to 7.5 hours. In general, both the area under the concentration-time curve from time 0 to infinity (AUC_{inf}) and C_{max} appeared to increase proportionally with dose from 1 mg to 100 mg. Increases from 100 mg to 200 mg appear more than dose proportional, especially for AUC_{inf}.

On Day 10 of multiple dose administration, PF-06700841 was absorbed rapidly with median T_{max} of 1 to 1.5 hours or less across the entire range of doses, from a total daily dose of 10 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 was similar with that observed following single dose administration. Mean $t_{½}$ ranged from 4.9 to 10.7 hours. Both area under the concentration-time curve from time 0 to time τ ($AUC_{τ}$) and C_{max} generally appeared to increase proportionally with dose from 10 mg to 100 mg QD, with a trend towards greater than proportional increase from 100 mg to 175 mg QD.

Accumulations, following once daily dosing, ranged from 1.1 to 1.4 for AUC_t and 0.8 to 1.1 for C_{max}. The urinary recovery of unchanged (Ae_τ%) PF-06700841 on Day 10 across all doses ranged from 8.9% to 15.5%. Following multiple dose administration of PF-06700841 to participants with PsO for 28-days, the overall exposure observed was comparable to that in healthy participants at same dose level.

The relative bioavailability of a solid dose formulation of PF-06700841 relative to a solution and the food effect on the solid dosage formulation was also evaluated. Following single oral 100 mg doses under fasting conditions, median T_{max} was 0.5 hours for the tablet formulation and 1.0 hours for the solution. The ratios of adjusted geometric means between tablet versus solution formulation were 96.2% for AUC_{inf} and 94.3% for C_{max}. When the tablet was administered following a high fat meal, T_{max} was delayed with median of 4.0 hours and the AUC_{inf} and C_{max} were 82.3% and 64.3%, respectively of those observed when tablets were given fasted.

In Study B7931009, higher exposure in Japanese participants (n=6) observed compared to that in non-Japanese participants from B7931001 study: the mean steady state C_{max} were 1114 (14%) vs 734.1 (29%) ng/mL and steady state mean AUC_{24} were 9888 (33%) vs 6089 (38%) ng•h/mL for Japanese participants and non-Japanese participants respectively after multiple doses of 100 mg QD.

In the recently clinically completed ADME study B7931014, the preliminary metabolite profiling analysis identified a single major metabolite M1 (PF-06802530). PF-06802530 is primarily formed via CYP3A-mediated hydroxylation of PF-06700841 and mainly eliminated via renal excretion.

B7931004 study was recently completed. In this study, PK samples were collected at pre-dose and/or 0.5 hours post-dose at each visit over 12-week treatment. Post-dose samples were also collected up to 4 hours at Weeks 4 and 12. Plasma concentrations of PF-06700841 observed were as expected based on PK in PsO participants.

2.3. Benefit/Risk Assessment

PF-06700841 is not expected to provide any clinical benefit to healthy participants or participants with renal impairment in this study. This study is designed primarily to characterize the effect of renal impairment on the plasma PK of a single dose of PF-06700841. The data from this study are expected to provide the basis for development of dosing recommendations for target patient populations who may have renal impairment.

Based on the data in Phase 1 program, the clinical safety profile of PF-06700841 appears to be acceptable at dosages up to 200 mg single dose and 175 mg repeated daily doses administered orally. Based on the clinical experience with PF-06700841 and/or other JAK inhibitors (eg, Xeljanz® [tofacitinib], Jakafi® [ruxolitinib], baricitinib, filgotinib and upadacitinib), anticipated risks with PF-06700841 include: (1) an increase in susceptibility to infection, (2) viral reactivation, (3) malignancy and lymphoproliferative disorders, (4) alterations in laboratory parameters, including: decreased neutrophil counts, decreased lymphocyte counts, decreased hemoglobin level, decreased platelet counts, alterations in the

hepatic transaminases and serum creatinine. There was one AE of herpes zoster infection in a PsO participant treated with 100 mg PF-06700841 for 4 weeks. Laboratory changes can be managed by monitoring criteria as well as adjustment of the inclusion/exclusion criteria.

Based on in vitro data, moderate and strong CYP3A inhibitors or inducers, strong P-glycoprotein (P-gp) inhibitors, P-gp substrates and substrates of organic cation transport 2 (OCT2)/multidrug toxin extrusion protein (MATE) with a narrow therapeutic index, will be prohibited during PF-06700841 treatment periods in ongoing Phase 2 studies to minimize any potential significant drug interaction. Detailed information about in vitro assessments on drug metabolism, enzyme phenotype and drug-drug interaction can be found in the IB.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06700841 may be found in the IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• Part 1: To evaluate the effect of severe renal impairment on the PK of PF-06700841 and M1, a major metabolite of PF-06700841, following single oral dose administration. • Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the PK of PF-06700841 and M1 following single oral dose administration.	• Plasma PF-06700841 and M1 PK parameters: C_{max} and $AUC_{inf.}$
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of single oral dose of PF-06700841 in participants with renal impairment and in healthy participants with normal renal function.	• Safety: treatment-emergent adverse events, clinical laboratory tests, vital signs, physical examination and ECGs.
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[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, non-randomized, open-label, single-dose, parallel-cohort study to investigate the effect of renal impairment on the plasma PK, safety and tolerability of PF-06700841 after single oral dose of 30 mg in approximately 2 clinical research units (CRU). A staged approach, as outlined in detail below, will be followed in the study.

Participants will be selected and categorized into normal renal function or renal impairment groups based on their estimated glomerular filtration rate (eGFR) as shown in Table 1.

Table 1. Renal Function Categories by eGFR Ranges

Cohort	Renal Impairment[a]	Estimated eGFR[b] (mL/min)	Number of Participants
1	Severe Renal Impairment	<30 and not requiring dialysis	8
2	None (Normal)	≥90	8
3	Moderate Renal Impairment	≥30 to <60	8
4	Mild Renal Impairment	60 – 89	8

a. Stages of renal impairment are based on Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD).[1]

b. Estimate of eGFR based on Modification of Diet in Renal Disease (MDRD) formula. The average of the 2 screening eGFR value will be used for group assignment.
- Step 1: eGFR (mL/min/1.73m^2) = 175 × $(S_{cr, std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay.
- Step 2: Convert the MDRD-derived, body surface area (BSA)-adjusted eGFR obtained above to absolute eGFR (mL/min) for eligibility assessment using the following equation: eGFR (mL/min) = eGFR (mL/min/1.73m^2) × participant's BSA where BSA is calculated as $BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$.

Part 1: A total of approximately 16 participants will be enrolled in Part 1; approximately 8 participants with severe renal impairment (Cohort 1) and approximately 8 with normal renal function (Cohort 2) to ensure at least 6 evaluable participants in each group. Participants from the severe renal impairment group will be recruited first. The demographics will be pooled across study sites to determine an average value for age and weight in the severe impairment group. Subsequently, the healthy participants will be recruited later such that each participant's age is within ±10 years and weight is within ±15 kg of the mean of severe renal impairment group. An attempt will be made to maintain a similar male/female ratio composition between groups. Care will be taken when recruiting the healthy participants such that the entire group is not of substantially different age or of substantially different body weight than the severely renally impaired participants. Approval from the sponsor must be obtained ***before*** proceeding with dosing healthy participants with normal renal function.

If there are participants who withdraw or discontinue treatment from the normal or severe renal impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor.

Criteria to proceed to Part 2: After statistical evaluation of results from Part 1 (see Section 9.4), Part 2 will be conducted if the point estimate of PF-06700841 or M1 area under the concentration-time curve from time 0 to infinity (AUC_{inf}) geometric mean ratio (GMR) for the severe renal impairment group (compared to the normal group as control) is ≥1.5. If this criterion is not met, the study will stop after Part 1.

Part 2: Based on whether the decision criterion to proceed to Part 2 is met, approximately 8 participants each with moderate (Cohort 3) and mild (Cohort 4) renal impairment will be enrolled to ensure at least 6 evaluable participants in each group. As in Part 1, renal impairment classification will be based on eGFR. Healthy participants will not be enrolled in

Part 2. Healthy participants from Part 1 will be used as the control group for the moderate and mild impairment participants.

When recruiting the Part 2 participants, attempts to match the entire group to the participants in Part 1 with respect to age, gender and body weight will be made. Other demographics, such as race and ethnicity, may be considered for matching the Part 1 and Part 2 populations when possible. Statistical considerations to account for any differences in demographics are detailed in Section 9.4.

As in Part 1, if there are participants who withdraw or discontinue treatment from the moderate or mild impairment group and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor.

For both Parts 1 and 2: All participants in both normal and renal impairment groups will provide informed consent and undergo Screening evaluations to determine their eligibility. Participant screening for participation in this study will consist of 2 CRU outpatient visits not more than 14 days apart (but at least 3 days apart), with the 1st screening visit occurring within 28 days prior to administration of investigational product. Each participant will be admitted to the research unit on Day -1 (at least 12 hours prior to the dosing of PF-06700841 on Day 1). An eGFR value for group placement (provided stable renal function is still demonstrated) will be obtained by the average of the 2 screening values (using the Modification of Diet in Renal Disease [MDRD] equation). If the renal function stability criterion is met but the renal function classification category changes between Screening Visit 1(S1) eGFR and the average of the S1 and Screening Visit 2 (S2) eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment.

Eligible participants will be admitted to the CRU on Day -1 and will be confined in the CRU until Day 4. If participant meets all screening criteria at S2 visit, and Day -1 visit can be performed immediately, the participant may be admitted to the unit at conclusion of S2 visit.

On the morning of Day 1, the participants will receive a 30 mg single dose of PF-06700841 after a fast of at least 10 hours. No food will be allowed for at least 4 hours post-dose. Serial blood and urine samples at specified intervals (as per Schedule of Activities) will be collected for 72 hours post-dose for plasma and urine PK assessments, prior to discharge from the CRU on Day 4. The eGFR value will be determined on Day -1 and will be used in PK analysis.

Safety assessments (as specified in the Schedule of Activities) will be performed during S1, on Day -1 and prior to dosing on Day 4. Only serum creatinine will be additionally assessed on S2 for eGFR estimation. Physical examinations, vital sign measurements, and clinical laboratory tests will be conducted and AEs will be monitored as per Schedule of Activities to assess safety. The total participation time (ie, CRU confinement time for study procedures) for each participant in this study is approximately 4 nights/5 days (excluding screening &

Follow-Up contact). Participants will have a follow-up phone contact 28-35 days after last IP administration to assess for AEs. If participant demonstrates an increase of >25% in SCr from Day -1 to Day of discharge, he or she will be asked for a follow-up visit to collect eGFR.

All procedures and their timelines follow the Schedule of Activities.

Calculation of eGFR:

The following MDRD equation will be used to calculate eGFR ($S_{cr, std}$ denotes serum creatinine measured with a standardized assay for serum creatinine):

$eGFR\ (mL/min/1.73m^2) = 175 \times (S_{cr, std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$

Note that the value of eGFR, which is directly obtained from the laboratory or calculated using the equation above, is generally normalized to an average body size of 1.73 m^2 for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtered drugs (including secreted drugs), renal elimination capacity is related to absolute glomerular filtration rate (GFR) in mL/min. To use the MDRD-derived, body surface area (BSA)-adjusted value of eGFR to obtain absolute glomerular filtration rate (GFR) (mL/min) for renal disease classification or participant assignment into different renal disease groups, this value should be multiplied by the individual participant's BSA (ie, measured BSA/1.73 m^2). The BSA of an individual can be calculated by the following formula as described below:

$$BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$$

In summary, GFR in mL/min calculated as below will be used for renal impairment group placement:

Step 1: Obtain the MDRD-derived eGFR:

- $eGFR\ (mL/min/1.73m^2) = 175 \times (S_{cr, std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$ where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay.

Step 2: Convert the MDRD-derived, BSA-adjusted eGFR obtained above to absolute GFR (mL/min) for eligibility assessment using the following equation:

- **eGFR (mL/min)** = eGFR ($mL/min/1.73m^2$) × participant's BSA where BSA is calculated as $BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$.

Creatinine clearance (CL_{CR}) will also be estimated from a spot serum creatinine measurement using the following Cockcroft-Gault (C-G) equation:

$$CL_{CR}\ (mL/min) = \frac{(140 - age\ [years]) \times total\ body\ weight\ (kg) \times (0.85\ for\ females)}{72 \times serum\ creatinine\ (mg/dL)}$$

Note that eGFR calculated by the MDRD equation will be used for categorization of degrees of renal impairment. Nevertheless, renal function will be estimated using both C-G and MDRD equations in this study and dose recommendations will be made using both C-G and MDRD equations.

To be enrolled into the study, participant must demonstrate stable renal function, with ≤25% change based upon screening S1 eGFR and screening S2 eGFR (calculated by the MDRD equation). The S2 eGFR assessment should be performed between 3 to 14 days after the S1 eGFR assessment. The average of these 2 eGFR values will be used for group placement based on the renal function classification category.

- If the renal function stability criterion is met and the renal function classification category remains the same between S1 eGFR and the average of the S1 and S2 eGFRs, participant will be eligible for enrollment.

- If the renal function stability criterion is not met, participant will be screen failed.

- If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of the S1 and S2 eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment.

In case of screen failure related to eGFR stability and/or change in the renal function classification category, participant may be re-screened once after a 30-day period, provided that the initial screen failure is not due to an Inclusion/Exclusion criterion that results in permanent disqualification from enrollment (eg, medical history). This can be done only with sponsor's approval.

Please see Table 2 below regarding demonstration of stable renal function:

Table 2. Criteria to Establish Stable Renal Function

Renal function Measurement	eGFR (mL/min)	Criterion for stability
S1	G1	
S2 (Within 3 to 14 days after S1)	G2	$\Delta = \lvert G2-G1 \rvert \times 100/G1$[a] If $\Delta \leq 25\%$; stable If $\Delta > 25\%$; not stable

Abbreviations: S1= Screening Visit 1; S2= Screening Visit 2.

a. Parenthesis of | | represents absolute values.

4.2. Scientific Rationale for Study Design

This study is a phase 1, non-randomized, open-label, single-dose, parallel-group study of PF-06700841 in participants with severe renal impairment and participants with normal renal impairment (Part 1) and in participants with mild and moderate renal impairment (Part 2), matched for age, body weight and, to the extent possible, for gender composition. Details on age and body weight matching criteria are specified in Section 4.1.

Since PF-06700841 is primarily eliminated through a CYP450 mediated oxidation with CYP3A4 as the major contributor (fm = 0.62) and renal excretion as unchanged is minor (<16%), a reduced study design is proposed as suggested in the current draft guidance by FDA and EMA.[2,6] In the reduced study, only participants with severe renal impairment and participants with normal renal function will be studied first. Therefore, the effect of renal impairment on PF-06700841 PK will be initially evaluated in the renally impaired population most likely to be of impact. The impact of renal impairment on expression of CYP enzymes, if any, is expected to be minimal and hence can also be evaluated in the severely renally impaired population to estimate the degree of impact. If the study results confirm that severe renal impairment does not alter PK to an extent that warrants dosage adjustment, no further study is warranted. If the results do not support such a conclusion, Part 2 will be conducted in participants with moderate and mild renal impairment, based on the decision criterion outlined in Section 4.1.

Single dose PF-06700841 PK appeared to be linear in the dose ranges of 1 - 100 mg, with more than dose-proportional increase especially in area under the concentration time curve from time 0 extrapolated to infinity (AUC_{inf}) from 100 mg to 200 mg in the FIH study. In multiple dose period of the same study, both area under the concentration-time curve from time 0 to time τ (AUC_{τ}) and C_{max} appeared to increase proportionally with dose from 10 mg to 100 mg QD, with a trend towards greater than proportional increase from 100 mg to 175 mg QD. No direct enzyme inhibition/induction or time-dependent enzyme inhibition has been identified in in vitro studies. Considering a linear PK at the therapeutic dose range being tested in Phase 2 studies (10 – 60 mg QD), in which single dose PK behavior can predict multiple dose PK, a single dose study will be conducted to evaluate the PF-06700841 PK under conditions of renal impairment.

In the preliminary data of ADME study B7931014, PF-06802530 (M1) was identified as a major circulating metabolite, which was predominantly eliminated in the urine. The potential effects on the cardiovascular system for both PF-06700841 and PF-06802530 (M1) were evaluated in in vitro human ether-à-go-go-related gene (hERG) potassium channel assay. The hERG 50% inhibitory concentration (IC_{50}) for PF-06700841 was 33.4 µM (13,000 ng/mL) and the 10% inhibitory concentration (IC_{10}) is approximately 4 µM (1560 ng/mL), which are 49× and 5.9×, respectively, the predicted human unbound C_{max} of 264 ng/mL at a human dose of 60 mg QD. The IC_{50} for PF-06802530 (M1) was >50 µM (>20,300 ng/mL) and the IC_{10} was approximately 6.5 µM (2640 ng/mL), which are >77× and approximately 10× the predicted human unbound C_{max}. Due to the QT prolongation concern of M1, combined with its primary elimination pathway of renal excretion, understanding of M1 exposure change in renal impairment is also important in addition to understanding

parent (PF-06700841) exposure change. Therefore, M1 plasma PK with or without renal impairment will be collected and characterized in this study.

PF-06700841 is not highly bound to human plasma proteins, with unbound fraction (f_u) of 0.61 observed in the in vitro protein binding study. Thus, no additional blood samples will be collected in this study for ex vivo protein binding analysis.

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4.3. Justification for Dose

The study will use the PF-06700841 single dose of 30 mg, administered orally. Doses up to 60 mg of PF-06700841 have been used in longer term efficacy and safety clinical trials. PF-06700841 30 mg is appropriate considering that systemic exposures of PF-06700841 and M1 may be increased in the presence of renal impairment.

Doses of PF-06700841 up to 200 mg single dose and 175 mg QD was generally safe and well-tolerated in the Phase 1 clinical study B7931001. There were no deaths, SAE, and serious infection reported in the study. Doses of PF-06700841 up to 60 mg QD was also generally safe and well-tolerated in PsO (B7931001 and B7931004) and AA participants (B7931005). There were no clinical meaningful findings in vital signs, ECG, suicidal behavior or ideation, or potential Hy's Law cases reported during these studies.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

5.1.1. All Participants

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants who are between the ages of 18 and 75 years, inclusive, at the Screening visit.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

Weight:

3. Body mass index (BMI) of ≥17.5 to ≤40 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.1.2. ***Additional*** Inclusion Criteria for Healthy Participants with Normal Renal Function (Cohort 2 ***only***)

1. No clinically relevant abnormalities identified by a detailed medical history, full physical examination, including temperature, blood pressure (BP) and pulse rate measurement, 12-lead ECG and clinical laboratory tests.

2. Normal renal function (eGFR ≥90 mL/min) at 2 Screening visits based on the MDRD equation.

3. Demographically comparable to the group of participants with impaired renal function.

    - The each participant's body weight within ±15 kg of the mean body weight of the severe renal impairment cohort (Cohort 1).

    - The each participant's age within ±10 years of the mean age of the severe renal impairment cohort (Cohort 1).

- ***Attempts will be made*** to ensure that the male-to-female composition of Cohort 2 is comparable to that in the severe renal impairment cohort (Cohort 1); cohorts cannot be comprised entirely of any one gender.

- Other demographic characteristics, such as race and ethnicity, matched as closely as possible to the renal impairment cohort (Cohort 1).

5.1.3. ***Additional*** Inclusion Criteria for Participants with Impaired Renal Function (Cohort 1 and Cohorts 3 & 4 [if applicable] ***only***)

1. Good general health commensurate with the population with chronic kidney disease (renal impairment). "Health" is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, measurement of pulse rate and 12-lead ECG as well as clinical laboratory tests (except serum creatinine and eGFR). Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease and other common co-morbidities in this population are possible exemptions, as long as, in the opinion of the investigator, the participant is medically stable, is on a stable drug regimen, and can abide by the meals and dietary restrictions outlined in protocol Section 5.3.

2. Meet the following eGFR criteria during the screening period based on the MDRD equation:

   - Severe renal impairment: eGFR <30 mL/min, but not requiring hemodialysis.

   - Moderate renal impairment (Part 2 only): eGFR ≥30 mL/min and <60 mL/min.

   - Mild renal impairment (Part 2 only): eGFR between 60 – 89 mL/min.

   The eGFR values obtained at the 2 screening visits should not be more than 25% different (see Section 4.1).

3. Any form of renal impairment except acute nephritic syndrome (participants with history of previous nephritic syndrome but in remission can be included).

4. Stable concomitant drug regimen (as defined in Section 6.5) for the management of individual participant's medical conditions; ***on a case-by-case basis***, with input from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

5.2. Exclusion Criteria

5.2.1. All Participants

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Renal transplant recipients.

2. Urinary incontinenence without catheterization.

3. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1.

4. Known history of pulmonary embolism or recurrent deep vein thrombosis (DVT).

5. Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or superficial skin infection within 1 week prior to Day 1. NOTE: participants may be rescreened after the infection resolves.

6. Have evidence of untreated or inadequately treated active or latent infection with Mycobacterium tuberculosis (TB) infections as following (see details in Appendix 2).

   - A positive QuantiFERON-TB Gold (QFT-G) In-Tube test performed within the 3 months prior to screening. If the laboratory reports the test result as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a purified protein derivative (PPD) test may be substituted for the QFT-G In-Tube test only with approval from the Pfizer Medical Monitor on a case by case basis;

     Note: If a participant has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi drug regimen) TB infection, neither a QFT-G In-Tube test nor a PPD test need be obtained.

     A participant who is being treated for latent or active TB infection is not eligible for this study.

7. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

8. Known immunodeficiency disorder, including positive serology for human immunodeficiency virus (HIV) at screening, or a first-degree relative with a hereditary immunodeficiency.

9. Any present malignancies or history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

10. History of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.

11. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection).

    NOTE: participants who have undergone cholecystectomy and/or appendectomy are eligible for this study so long as the surgery occurred more than 6 months prior to Screening.

12. 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 IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

13. Participants who have been vaccinated with live or attenuated vaccines within the 6 weeks of dosing, or are to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of dosing.

14. Use of concomitant medications that prolong the QT interval within 10 days prior to first dose of IP or 5 half-lives (if known), whichever is longer. A list of these medications can be found at: http://www.crediblemeds.org.[7]

15. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half lives (whichever is longer) prior to Day 1. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case by case basis following approval by the sponsor.

    Herbal supplements and hormone replacement therapy must be discontinued at least 28 days prior to the first dose of investigational product; Depo-Provera® must be discontinued at least 6 months prior to dosing of investigational product.

    For participants with ***renal impairment***, stable concomitant medications (including herbal supplements) may be given following **approval by the sponsor** if they are considered necessary for the welfare of the study participants (eg, standard therapy for underlying diseases), are not contraindicated with the IP, and are unlikely to interfere with the PK of the IP.

Prior/Concurrent Clinical Study Experience:

16. Treatment with an investigational drug(s) within **30 days** or 5 half-lives (whichever is longer) preceding the first dose of IP.

Diagnostic Assessments:

17. Infection with hepatitis B or hepatitis C viruses according to protocol-specific testing algorithm as described in Appendix 2 (Section 10.2.1).

18. ANY of the following abnormalities in clinical laboratory tests at screening, and confirmed by a single repeat, if deemed necessary:

    a. Absolute neutrophil count $<1.5 \times 10^9$/L ($<1500/mm^3$);

    b. Platelet count $<150 \times 10^9$/L or $<150,000/mm^3$;

    c. Absolute lymphocyte count of $<0.8 \times 10^9$ /L ($<800/mm^3$);

    d. Enzymes aspartate amino transaminase (AST) or alanine amino transaminase (ALT) values
    >2 × ULN;

    e. Total bilirubin >1.5 × ULN; participants with Gilbert's syndrome would be eligible for this study provided the direct bilirubin is ≤ ULN;

19. In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that that could affect interpretation of study data or the participant's participation in the study.

20. Screening laboratory tests with abnormal results may be repeated **once** to confirm abnormal results (with the same screening number); the last value will be used to determine eligibility.

21. Sites may be permitted to re-screen participants (with a new screening number) who initially do not meet eligibility criteria **once** following agreement with the sponsor.

22. A positive urine drug test, for illicit drugs, at Screening:

    NOTE: repeat urine drug testing is ***not*** permitted in this study.

    - Renal impairment participants may be eligible to participate after approval from sponsor if their drug screen is positive for a prescribed substance that is not expected to interfere with the PK of PF-06700841.

23. ANY of the following conditions at screening:

    a. Screening 12-lead ECG that demonstrates:

- Clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, cardiomyopathy, Wolff-Parkinson–White syndrome);

- Confirmed QT interval corrected using Fridericia's correction factor (QTcF) >450 msec for participants with normal renal function and >470 msec for participants with impaired renal function.

b. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes.

Other Exclusions:

24. 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 Pfizer employees, including their family members, directly involved in the conduct of the study.

25. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months of Screening.

26. Female participants of childbearing potential who are unwilling or unable to use highly effective methods of contraception as outlined in Section 5.3.4 for the duration of the study and for at least 28 days after the administration of investigational product, pregnant female participants, female participants planning to become pregnant during the duration of the study until 28 days after the administration of investigational product, breastfeeding female participants.

27. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within **60 days** prior to the dose of investigational product.

28. History of sensitivity to heparin or heparin-induced thrombocytopenia, ***only if*** heparin is used to flush intravenous catheters used during serial blood collections.

29. Unwilling or unable to comply with the Lifestyle Considerations outlined in Section 5.3.

5.2.2. *Additional* Exclusion Criteria for Healthy Participants with Normal Renal Function (Cohort 2, *only)*

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Evidence or history of clinically significant dermatological condition (eg, contact dermatitis, AD, PsO) or visible rash present during physical examination.

3. Screening supine BP >140 mm Hg (systolic) or >90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is >140 mm Hg (systolic) or >90 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 participant's eligibility.

4. Hemoglobin <11.0 g/dL (or 110 g/L).

5.2.3. ***Additional*** Exclusion Criteria for Participants with Impaired Renal Function (Cohort 1 and Cohorts 3 & 4 [if applicable] ***only***)

1. Participants requiring hemodialysis and/or peritoneal dialysis.

2. Participants with other clinically significant disease that may affect the safety of the participant or that may affect the PK of PF-06700841 (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing). Participants with any significant hepatic, cardiac, or pulmonary disease or participants who are clinically nephrotic. Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease, etc. are not cause for exclusion as long as, in the opinion of the investigator, the participant is medically stable and any drugs that are administered for these conditions are not expected to interfere with the PK of PF-06700841.

3. Screening BP ≥180 mm Hg (systolic) or ≥110 mm Hg (diastolic), following at least 5 minutes of supine rest. If initial BP is ≥180 mm Hg (systolic) or ≥110 mm Hg (diastolic), the BP should be repeated two more times and the average of the 3 BP values should be used to determine the participant's eligibility.

4. Hemoglobin <10 g/dL (or 100 g/L) for participants not receiving erythropoietin, or <9.0 g/dL (or 90 g/L) for participants receiving erythropoietin.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample and investigational product administration on Day 1. There will be no restriction to breakfast on the other days provided other restrictions are followed.

- Water is permitted until 1 hour prior to IP administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit related citrus fruit juices see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- Participants will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the investigational product administration until collection of the final PK blood sample.
- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to dosing until collection of the final PK sample of each study period. Participants will additionally abstain from caffeine-containing products at least 2 hours prior to any scheduled vital sign and ECG measurements.
- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly

and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Rescreening may only occur with sponsor approval. In the event that the participation of a participant in the study is delayed, outdated screening procedures can be repeated. Rescreened participants should be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Interventions Administered

For this study, the investigational product is PF-06700841 (provided as 5 and 25 mg tablets).

PF-06700841 5 and 25 mg tablets will be supplied by Pfizer to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Investigational products will be administered orally and according to the conditions described in the Schedule of Activities section and Meals and Dietary Restrictions section of this protocol.

Following an overnight fast of at least 10 hours, participants will receive 30 mg PF-06700841 tablets (as 1 × 5 mg and 1 × 25 mg) at approximately 08:00 hours (plus or minus 2 hours) on Day 1 with approximately 240 mL ambient temperature water. Participants will swallow the 2 tablets of PF-06700841 whole, and will not manipulate or chew the investigational product prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after PF-06700841 dosing.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the label.

7. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

8. The sponsor or designee will provide guidance on the destruction of unused study intervention (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.

6.2.1. 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 participant 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, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-06700841 tablets will be prepared at the CRU in the individual dosing containers by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. All participants enrolled will receive treatment according to the dose/schedule.

6.4. Study Intervention Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the investigational product was taken.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Acetaminophen/paracetamol may be used at doses of ≤3 g/day.

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment. Note that another approved method of contraception must then be used (Section 10.4.4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Concomitant drug and non-drug treatment will be collected. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6.5.1. Participants with Healthy Renal Function (Cohort 2 Only)

In general, participants will abstain from all concomitant treatments (prescription or over the counter) as described in the Exclusion Criteria section of the protocol, except for the treatment of AEs. Of note, the following ***restrictions*** apply:

- Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis ***after*** approval by the sponsor.

6.5.2. Participants with Impaired Renal Function (Cohort 1 and Cohorts 3 & 4 [if applicable])

Participants are permitted to be on stable doses of background medications if they are considered necessary for the welfare of the study participants (eg, standard therapy for the underlying disease), are not contraindicated with the investigational product, and are unlikely to interfere with the PK of the investigational product. ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the end of study on Day 4.

- Approved concomitant medications should be administered to renally impaired participants at least 2 hours prior to dosing or withheld until 4 hours after PF-06700841 dosing.

6.6. Dose Modification

Dose modifications for PF-06700841 are not allowed.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue investigational product. If investigational product is permanently discontinued, the participant will remain in the study to be evaluated for safety.

See the Schedule of Activities for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the Schedule of Activities for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the case report form (CRF) and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants 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 participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this

information. Participants 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 posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant 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.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier group may be used in the study without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. CCI [redacted]

Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

If an intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate, temperature and BP) should be collected prior to the insertion of the catheter.

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.

The total blood sampling volume for individual participants in this study is approximately 88 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A limited physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the Schedule of Activities. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants 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.

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate 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 pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

In some cases, it may be appropriate to repeat abnormal vital signs to rule out measurement errors due to eg, improperly placed BP measurement cuff.

8.2.2.1. Temperature

Temperature will be measured orally (other body locations, eg tympanic, are acceptable provided the same method is used and documented throughout the study). No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Twelve (12)-lead ECGs should be collected at times specified in the Schedule of Activities of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements (predose on Day 1). Additional ECG monitoring will occur if a) a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec for participants with normal renal function (Cohort 2) and >470 msec for participants with impaired renal function (Cohort 1, 3, and 4); or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec for partipants with normal renal function (Cohort 2) and >470 msec for participants with impaired renal function (Cohort 1, 3, and 4); or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted.

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 be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG should be performed before laboratory blood collection.

A paper or digital copy of the ECG should be filed in the participant's chart and must be available to the sponsor upon request. Any clinically significant changes will be recorded and evaluated further, as clinically warranted. Participants will be discontinued from study with a confirmed QTc >500 milliseconds or a confirmed QTc change from baseline of >60 milliseconds.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the Schedule of Activities for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 calendar day after the study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive investigational product.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the Schedule of Activities. WOCBP must be using be using a permitted contraceptive method to be eligible for study participation (see Appendix 4 Section 10.4.3). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product(s).

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure 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.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. 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.

8.3.5.3. 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 participant 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.

8.3.6. Medication Errors

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

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

Medication errors include:

- Medication errors involving participant exposure to the investigational products;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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 nonserious, 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**.

8.4. Treatment of Overdose

For this study, any dose of PF-06700841 greater than 200 mg within a 24-hour time period will be considered an overdose.

There is no specific antidote for PF-06700841, therefore Pfizer dose not recommend specific treatment for an overdose of PF-06700841.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-06700841 can no longer be detected systemically (at least 4 days).

3. Obtain a blood sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-06700841 and M1

Two (2) blood samples of approximately 3 mL to provide a minimum of 1.2 mL, will be collected into appropriately labeled tubes containing potassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of PF-06700841 and M1, respectively, at times specified in the Schedule of Activities. The appropriate additive will be added to the sample collected for M1 PK. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after IP administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT). Collection of samples more than 10 hours after IP administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT).

Samples will be used to evaluate the PK of PF-06700841 and M1. Samples collected for analyses of PF-06700841 and/or M1 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, CCI [redacted].

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-06700841 and M1 will be analyzed using a validated analytical method in compliance with applicable 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.

8.5.2. Urine for Analysis of PF-06700841 and M1

Urine will be collected at the intervals outlined in Schedule of Activities. Each participant will empty his/her bladder just prior to dosing. During the subsequent designated urine collection intervals ([0-24], [24-48], and [48-72] hours post dose), participants will void ALL urine produced during the designated collection interval, including a forced void at the end of the collection interval, directly into pre-weighed urine collection container. Each collection interval should have it's own collection container(s). During the entire collection interval, the container(s) should be stored at 4°C. At the end of each urine collection interval, all urine collected will be thoroughly mixed, total weight of urine will be determined first (weigh the empty container first and then weigh the container at the end of the collection) and then the volume of urine will be calculated by assuming specific gravity of urine = 1 and recorded on the CRF. An urine aliquot will be withdrawn for measurement of drug concentrations.

Additional details for collection, processing and storage of urine for analysis of PF-06700841 and M1 will be added to the laboratory manual and provided to the investigator site prior to the start of the study.

Urine samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs, **only** if it is determined by the study team that there is a need to do so, based on review of plasma PK results for PF-06700841 and M1.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

CCI [redacted]

CCI

[redacted]

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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.

9.1. Statistical Hypotheses

No statistical hypothesis will be tested in this study.

9.2. Sample Size Determination

In Part 1, approximately 8 participants will be enrolled into the normal renal function group and the severe renal impairment group to ensure approximately 6 evaluable completers in each group. If Part 2 is conducted, approximately 8 participants will be enrolled to the mild and moderate renal groups to ensure approximately 6 evaluable completers per group. The sample size is based on recommendations from the "FDA Guidance for Industry - Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling".[8]

Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
PK Concentration	The PK concentration population is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.
PK Parameter	The PK parameter analysis population is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of primary interest measured.
Safety	All assigned to investigational product and who take at least 1 dose of investigational product.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Part 1

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} and C_{max} for PF-06700841 and M1 between normal renal function group (Reference) and the severe impaired renal function group (Test). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Part 2 may be conducted if either PF-06700841 or M1 AUC_{inf} GMR for severe renal impairment group compared to normal group is ≥1.5.

Part 2

ANOVA will be used to compare the natural log transformed AUC_{inf} and C_{max} for PF-06700841 and M1 between normal renal function group (Reference) and the moderate and mild impaired renal function groups (Test). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the adjusted geometric means (Test/Reference) and 90% CIs for the ratios. If

substantial differences in demographic characteristics between healthy and impaired participants are observed, weight and age may be explored as covariates.

Box and whisker plots for individual participant parameters (AUC_{inf} and C_{max}) will be constructed by renal function group and overlaid with geometric means.

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

If Part 2 is executed and data for normal, mild, moderate and severe impairment groups are available, additional analysis will be performed to assess relationship between appropriate PK parameters (CCI renal clearance [CL_r], CCI) and renal function (eGFR). Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

Plots of PK parameters (CCI CL_r, CCI) versus renal function (eGFR) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify participants from different renal function groups.

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination 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/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are 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.

9.4.2.1. Electrocardiogram Analyses

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

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

Table 3. Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline	-	30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

CCI

[redacted]

9.4.3.1. Pharmacokinetic Analyses

9.4.3.1.1. Analysis Population

The PK concentration population will be defined as all participants treated in whom at least 1 plasma concentration value is reported.

The PK parameter analysis population is defined as all participants dosed who have at least 1 of the PK parameters of primary interest.

9.4.3.1.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-06700841 and M1 following single dose administration will be derived from the concentration time profiles as detailed in Table 4. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 4. Plasma PK Parameters

Parameter	Analyte	Definition	Method of Determination
CCI	[redacted]	[redacted]	[redacted]
AUC_{inf}*	PF-06700841, M1	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, Where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
AUC_{72}	PF-06700841, M1	Area under the plasma concentration-time profile from time 0 to 72 hours post dose	Linear/Log trapezoidal method.
C_{max}	PF-06700841, M1	Maximum plasma concentration	Observed directly from data.
CCI	[redacted]	[redacted]	[redacted]
C C I	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]
CCI			

* As data permit.

If urine samples need to be analyzed (See Section 8.5.2), the following urine PK parameters (Table 5) will be calculated for PF-06700841 and M1 (as data permit):

Table 5. Urine PK Parameters

Parameter	Analyte	Definition	Method of Determination
Ae_{72}	PF-06700841, M1	Total amount of unchanged drug excreted in the urine over 72 hours	Sum of amount excreted for each collection period.
Ae_{72}%	PF-06700841, M1	Total amount of unchanged drug excreted in the urine over 72 hours, expressed as percent of dose	$100\times(Ae_{72}/Dose)$
CL_r	PF-06700841, M1	Renal clearance	Ae_{72}/AUC_{72}

Urine PK parameters will be analyzed and summarized using descriptive statistics.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study 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 addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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 product, regardless of the geographical location in which the study is conducted. US Basic Results are generally 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 participant 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 [CSR] synopses in which any data that could be used to identify individual participants have 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.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Data Handling Plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant 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 participant'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. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 6) will be 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.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Monocytes (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %)	BUN/urea and creatinine[a] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein Uric acid Creatine kinase **Additional Assessments for Hy's Law:** AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Creatine kinase (repeat) Direct bilirubin Indirect bilirubin GGT PT/INR Total bile acids	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[b]	• FSH[c] • Pregnancy test (β-hCG)[d] • eGFR • HBsAg[e] • HBcAb[e] • HbsAb[e] • HCVAb[e] • HIV[e] • QuantiFERON®-TB Gold Test or PPD[e] • Breath or urine alcohol test[f] • Urine drug screening[g] • Urine myoglobin[h]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; INR = international normalized ration; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; qual = qualitative; RBC = red blood cell; S1= Screening Visit 1; S2= Screening Visit 2; THC = tetrahydrocannabinol; ULN = upper limit of normal; WBC = white blood cell.

a. Only serum creatinine on Screening Day 2 (S2) for eGFR assessment.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
c. At Screening (S1) for confirmation of postmenopausal status only.
d. Urine or Serum β-hCG for female participants of childbearing potential according to Schedule of Activities.
e. Complete at screening (S1). Previous testing for QuantiFERON®-TB Gold Test will be accepted if completed within 3 months prior to screening. Otherwise should be completed at screening and results available prior to Day -1. If QFT-G test cannot be performed, or if results cannot be determined positive or negative, participants may be screened using PPD Tuberculin Test (Mantoux method) with approval of medical monitor. HBsAb will be performed as reflex testing for any participant who is HBsAg negative but HBcAb positive. HCV RNA will be performed as reflex testing for any participant who is HCV Ab positive.
f. Complete at screening (S1) and Day -1.
g. At Screening (S1) and Day -1. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
h. Reflex testing for creatine kinase >10 × ULN.

Investigators must document their review of each laboratory safety report.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing prior to dosing must be negative for participants to receive investigational product.

10.2.1. Hepatitis B and C Testing Algorithm and Full Eligibility Criteria

All participants will undergo screening for hepatitis B and C for eligibility.

At screening, HBsAg and HBcAb will be tested:

a. If both tests are negative, the participant is eligible for study inclusion.

b. If HBsAg is positive, the participant must be excluded from participation in the study.

c. If HBsAg is negative and HBcAb is positive, HBsAb reflex testing is required:

   i If HBsAb is negative, the participant must be excluded from participation in the study;

   ii If HBsAb is positive, the participant is eligible for study inclusion.

At screening, HCVAb will be tested:

a. Participants who are HCVAb positive will be reflex-tested for HCV RNA.

b. Participants who are positive for HCVAb and HCV RNA will not be eligible for this study.

10.2.2. Tuberculosis Testing

During the Screening period, it must be determined and documented that a participant does not have evidence of untreated or inadequately treated active or latent infection with Mycobacterium tuberculosis (TB) per exclusion criterion #6 (Section 5.2.1). The results of TB screening conducted within 3 months prior to screening or during the Screening period must be documented in study records prior to Baseline.

QFT-G In-Tube test is the preferred testing method. If the laboratory reports that the QFT-G test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, then participants may be screened using the PPD Tuberculin Skin Test (Mantoux method) with approval of the Pfizer Medical Monitor.

10.2.2.1. Purified Protein Derivative Test

If the QFT-G In-Tube test cannot be performed or if the QFT-G results are indeterminate, then participants may be screened using the PPD Tuberculin Test (Mantoux method) if approved by the Pfizer medical monitor.

Participants must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study. The test should be performed according to local standards (eg, induration of <5 mm being a negative result).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death.
b. Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

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

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.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- 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. 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.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or

courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below (Section 10.4.4) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s).

- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. 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. Premenarchal.

2. 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.

3. Postmenopausal female.

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

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

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - 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.

Highly Effective Methods That Are User Dependent

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

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

3. 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.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an 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 participant or participant's partner becomes or is found to be pregnant during the participant'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 participant 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).

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 preprocedure 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

CCI [redacted]

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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or 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 laboratory 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 participant’s individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 participant 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 for suspected cases of Hy's law, additional 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, and alkaline phosphatase. 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 coformulated 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) and collection of serum sample for acetaminophen drug and/or protein adduct levels 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.**

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.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 beats per minute [bpm]) lasting minutes.
- New PR interval prolongation >280 millisecond (msec).
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) atrioventricular (AV) block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Abs	absolute
AD	atopic dermatitis
ADME	Absorption, Distribution, Metabolism and Elimination
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC_{τ}	area under the concentration-time curve from time 0 to time τ
AV	atrioventricular
CCI	[redacted]
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CD	Crohn's disease
CFR	Code of Federal Regulations
C-G	Cockcroft Gault
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	Chronic Kidney Disease
CL_{cr}	creatinine clearance
CL_r	renal clearance
CCI	[redacted]
C_{last}	last quantifiable concentration
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report

Abbreviation	Term
CT	clinical trial
CYP450	cytochrome P450
DC	discontinuation
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EBV	Epstein Barr Virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
fm	fraction metabolized
FSH	follicle-stimulating hormone
f_u	unbound fraction
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C
HCVAb	hepatitis C antibody
HDL	lipoprotein
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
IB	investigator's brochure
IBD	inflammatory bowel disease
IC_{10}	10% inhibitory concentration
IC_{50}	50% inhibitory concentration
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
JAK	Janus kinase
K_2EDTA	ethylenediaminetetraacetic acid
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	low density lipoprotein
LFT	liver function test
MAD	multiple ascending dose
MATE	multidrug toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
msec	millisecond
N/A	not applicable
NOAEL	no-observed-adverse-effect level
OCT2	organic cation transport 2
P-gp	p-glycoprotein
PASI	Psoriasis Area and Severity Index
PCD	primary completion date
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PsA	psoriatic arthritis
PsO	psoriasis
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT
QTcF	QT interval corrected using Fridericia's correction factor
QFT-G	QuantiFERON®-TB Gold
qual	qualitative
QW	once a week
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SLE	systemic lupus erythematosus
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TB	tuberculosis
TEAEs	treatment emergent adverse events
TBili	total bilirubin
Th17	T help 17
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
TYK2	tyrosine kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

1. National Kidney Foundation. (2002) K/DOQI Clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis. 39(2 Suppl 1):S1-266.

2. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function. EMA Committee for Medicinal Products or Human use. 20 Feb 2014.

3. Nalbandian A, Crispin JC, Tsokos GC. Interleukin-17 and systemic lupus erythematosus: current concepts. Clin Exp Immunol 2009; 157(2):209-15.

4. Ardoin ST and Pisetsky DS. Developments in the scientific understanding of lupus. Arthritis Res Ther 2008; 10(5):218.

5. Schwatzman-Morris J and Putterman C. Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. Clin Dev Immunol 2012; 2012:1-9.

6. FDA. Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling; March 2010. Accessed 07 December 2017. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf.

7. Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, (Accessed on 15 Apr 2019), AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.

8. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function Study Design, Data Analysis, and Impact on Dosing and Labeling. FDA Guidance, March 2010.