A PHASE 1, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY FOLLOWING SINGLE SUBCUTANEOUS DOSE OF PF-06480605 IN CHINESE HEALTHY PARTICIPANTS

Study Intervention Number:	PF-06480605
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Short Title: Evaluation of the pharmacokinetics, safety and tolerability of single dose of PF-06480605 in Chinese healthy participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	29 Dec 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Evaluation of the pharmacokinetics, safety and tolerability of single dose of PF-06480605 in Chinese healthy participants

Rationale

The purpose of this study is to evaluate the PK, safety, tolerability, immunogenicity, and PD of PF-06480605 in Chinese healthy adult participants. The information of the PK, safety, tolerability, immunogenicity, and PD in Chinese healthy participants is being collected to support further clinical development as well as drug registration in China. Characterizing PK in Chinese participants is set as one of the primary objectives in order to meet the requirement of CDE.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of PF-06480605 following administration of single SC dose of PF-06480605 450 mg and 150 mg (if needed) in Chinese healthy adult participants. • To evaluate the safety and tolerability following administration of single SC dose of PF-06480605 450 mg and 150 mg (if needed) in Chinese healthy adult participants	• Serum PF-06480605 primary PK parameters, as permitted by data: C_{max}, T_{max}, $AUC_{14\ days}$, AUC_{inf}, and $t_{½}$. • Assessment of AEs, vital signs, 12 lead electrocardiograms, physical examination findings, and clinical safety laboratory measurements
Secondary:	**Secondary:**
• To further evaluate the PK of PF-06480605 • To evaluate the immunogenicity of PF-06480605. • To evaluate the PD biomarker (if feasible) which may be informative in demonstrating the pharmacologic effect of PF-06480605.	• Serum PF-06480605 PK parameters, as permitted by data: AUC_{last}, C_{max}(dn), AUC_{inf}(dn), AUC_{last}(dn), V_z/F, and CL/F. • Incidence of the development of ADA and NAb. • Total sTL1A protein concentration in serum.

Overall Design

This is a Phase 1, single-center, randomized, double-blind, third-party open (ie, participant blind, investigator blind and sponsor open), placebo-controlled study to investigate PK, safety, tolerability, immunogenicity, and PD of PF-06480605 following a single subcutaneous dose of PF-06480605 450 mg and 150 mg (if needed) in Chinese healthy adult participants. Optional 150 mg cohort will be conducted only if data from the 450 mg cohort do not confirm expected PK based on previous studies in healthy Western and Japanese participants as well as UC patients.

Number of Participants

A maximum of approximately 24 participants (18 with active treatment and 6 with placebo) will be randomized and receive the study intervention such that approximately 12 participants are assigned to each cohort (450 mg and 150 mg) to ensure that 11 evaluable participants per cohort will complete the study. Participants, who drop out from the study if the number of participants completing at least the follow-up visit at Day 57 per cohort decreases to 10 or lower, will be replaced.

Intervention Cohorts and Duration

Within 28 days of successful completion of the screening process, eligible participants will be enrolled and randomized to receive a single dose of PF-06480605 450 mg or 150 mg (if needed) or placebo. Participants will be admitted into the clinical research unit (CRU) approximately 1 day prior to dosing and required to stay overnight in the CRU at least through completion of the Day 5 evaluations. Participants will return for outpatient follow-up visits through Day 114.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

The maximum sample size of approximately 24 participants is not based on any statistical considerations. Those participants will be enrolled and receive the study intervention such that approximately 12 participants are assigned to each cohort (450 mg and 150 mg) to ensure that 11 evaluable participants per cohort will complete the study. In each cohort, 12 participants will be randomly assigned at an allocation ratio of 3:1 to the active treatment and placebo arms.

Participants will be enrolled to both cohorts sequentially, starting with the 450 mg cohort first. When the 150 mg cohort is determined to be needed, the 150 mg cohort with entirely new participants will be opened. The 150 mg cohort will be started only if it indicates the ethnic PK difference (eg, more than two-fold higher exposure) based on all available serum concentrations data of PF-06480605 obtained until the timing the PK sample is collected at Day 14 after administration, by comparing the dose-normalized mean exposures (or dose-normalized mean concentrations profiles) in this study versus dose-normalized mean exposures in Western study B7541001 and Japanese study B7541006. If the 150 mg is not

needed, then only approximately 12 participants will be administered the study intervention or placebo.

Cohort	Treatment	Number of participants
1	PF-06480605 450 mg	9
	Placebo	3
2 (optional)	PF-06480605 150 mg	9
	Placebo	3

Participants, who dropout from the study if the number of participants completing at least the follow-up visit at Day 57 per cohort decreases to 10 or lower, will be replaced.

If a participant discontinues before completing the part of the study to which they have been randomized, or withdraws for reasons unrelated to the safety of the study intervention, the participant may be replaced at the discretion of the investigator upon consultation with the sponsor.

Serum concentrations and serum PK parameters will be summarized descriptively.

Safety and tolerability data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations.

Overall incidence of development of ADA and NAb will be reported by incidence with respect to time. Both titer and positive/negative will be reported for the ADA and NAb assays by time points samples were collected.

The total sTL1A protein concentration in serum will be summarized by time and presented in a tabular or graphical form.

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data of 450 mg SC cohort through Day 14 during the course of the study for the purpose of determining whether or not to conduct 150 mg SC cohort, and preliminarily assess any ethnic differences between Chinese and non-Chinese, thus to support China joining further global Phase 2 and/or Phase 3 studies.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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] Abbreviations used in this table may be found in Appendix 7.	**Screen**	**CRU confinement**									**Follow-up visits**[b]						
Days Relative to Day 1	**-28 to -2**	**-1**	**1**				**2**	**3**	**4**	**5**	**10**	**15**	**29**	**43**	**57**	**85**	**114 /ET**
Hours After Dose	**-**	**-**	**0**	**1**[c]	**2**[c]	**6**[c]	**24**[c]	**48**[c]	**72**[c]	**96**[c]	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent & demography	X																
CRU confinement		X	→	→	→	→	→	→	→	X							
Visit to the CRU	X	X									X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X															
Medical/medication history	X	X															
Review alcohol/tobacco	X	X															
Report prior or concomitant treatments	X	X	→	→	→	→	→	→	→	→	X	X	X	X	X	X	X
Contraception check	X	X									X	X	X	X	X	X	X
Physical exam (including height & body weight at Screen, only)[d]	X	X															
12-Lead ECG (single)	X		X							X	X						X
Supine blood pressure, pulse rate and temperature	X		X							X	X						X
Chest radiographs[e]	X																
Adverse event monitoring	X	→	→	→	→	→	→	→	→	X	X	X	X	X	X	X	X
Study treatment administration			X[f]														
Injection Site Reaction			X[f]	X[f]	X[f]												
Blood sample for																	
Safety laboratory (after ≥4 h fast) (refer to Section 10.2)	X	X[g]					X			X	X	X			X	X	X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 7.	**Screen**	**CRU confinement**								**Follow-up visits**[b]						
Days Relative to Day 1	**-28 to -2**	**-1**	**1**				**2**	**3**	**4**	**5**	**10**	**15**	**29**	**43**	**57**	**85**	**114 /ET**
Hours After Dose	**-**	**-**	**0**	**1**[c]	**2**[c]	**6**[c]	**24**[c]	**48**[c]	**72**[c]	**96**[c]	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Serum FSH in females amenorrheic ≥12 months, only[h]	X																
Serum Pregnancy test (WOCBP only)[i]	X	X[g]															
HIV, HBcAb, HBsAb, HBsAg, HCVAb and syphilis	X																
HBVDNA (refer to Section 5.2)[j]	X														X		X
Interferon Gamma Release Assay (IGRA)[k]	X																X
COVID-19 test[l]	X[l]									X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Pharmacokinetic blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Soluble TL1A			X				X			X		X	X		X	X	X
Immunogenicity (ADA, NAb)			X									X	X		X	X	X
Urine Samples for																	
Urine drug testing	X	X[g]															
Urine pregnancy test (WOCBP only)[i]													X		X	X	X
Urinalysis	X	X[g]					X			X	X	X			X	X	X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 7.	**Screen**	**CRU confinement**									**Follow-up visits**[b]						
Days Relative to Day 1	**-28 to -2**	**-1**	**1**				**2**	**3**	**4**	**5**	**10**	**15**	**29**	**43**	**57**	**85**	**114 /ET**
Hours After Dose	**-**	**-**	**0**	**1**[c]	**2**[c]	**6**[c]	**24**[c]	**48**[c]	**72**[c]	**96**[c]	**-**	**-**	**-**	**-**	**-**	**-**	**-**

a. Day relative to start of study treatment (Day 1).

b. Procedure are completed within ±3 days.

c. Procedures are completed within ±10% of the collection time (ie, 2 hours ±12 minutes; 6 hours ±36 minutes, etc).

d. A full physical examination may be done at screening or Day -1. Brief physical examination to follow up open AEs after Day -1 may be done.

e. Chest X-ray or other appropriate diagnostic imaging (ie, CT or MRI) should be performed at screening (unless taken within 3 months prior to the screening). Chest X-rays are required and should be performed as per local guidelines and standard of care (eg, posterior anterior and lateral views). Official reading must be located in the source documentation.

f. Participants should be monitored for a minimum of 2 hours after administration of PF-06480605 to assess the injection site.

g. Test results must be reviewed by a physician and deemed acceptable in order to proceed with participation in study.

h. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.

i. Serum or Urine Pregnancy tests must have a sensitivity of at least 25 mIU/mL. See Section 8.2.6.

j. If HBsAg is negative, HBcAb is negative, HBsAb is positive, and no unequivocal documentation of prior HBV vaccination is available or HBsAg is negative, HBcAb is positive, and HBsAb is positive, the participant is required to undergo HBVDNA reflex testing at screening. If HBVDNA is undetectable in the HBVDNA reflex testing in screening and the participant is enrolled the study, HBVDNA testing must be performed on Day 57 and 114/ET.

k. Acceptable IGRA assays are QuantiFERON®-TB Gold In Tube (QFT-G) test and T-SPOT®.TB (T-Spot) test. A documented TB test performed within 12 weeks prior to Day 1 is acceptable. Participants with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in Section 5.2 Exclusion Criteria 6. A negative PPD test can be substituted for the QFT-G test or T-Spot test only under specific circumstances described in Section 5.2, Exclusion Criteria 6. For subject with negative TB test at screen, TB test can be repeated at Day 114.

l. Testing for active COVID-19 infection, including testing methodology and frequency will follow CRU's practice. These tests may not be needed if the pandemic is over.

2. INTRODUCTION

PF-06480605 is a fully human IgG1 monoclonal antibody against TL1A, a member of the TNF family of cytokines, that is currently in development for the treatment of CD and UC. The mechanism of action of PF-06480605 is to neutralize the binding and subsequent signaling of TL1A to its functional receptor DR3 on immune cells of the innate and adaptive immune system.

2.1. Study Rationale

The purpose of the study is to evaluate the PK, safety, tolerability, immunogenicity, and PD of PF-06480605 in Chinese healthy adult participants. The information of the PK, safety, tolerability, immunogenicity, and PD in Chinese healthy participants is being collected to support further clinical development as well as drug registration in China.

2.2. Background

TL1A is a member of the TNF family of cytokines also known as TNF sub-family 15. TL1A is a ligand for its functional receptor DR3, also known as TNF receptor sub-family 25.[1] TL1A expression on antigen presenting cells (monocytes, macrophages, dendritic cells) and DR3 expression on effector cells (T cells, NK and NKT cells) is highly dependent on pro-inflammatory conditions.[2,3,4] In vivo and in vitro evidence support a co-stimulatory role for the TL1A/DR3 pathway on T cells and in enhancing effector cell functions, inflammatory cell expansion and cytokine secretion. In agreement, this pathway has been implicated in the regulation of pathogenic Th1, Th2, Th9, and Th17 T-helper responses, and of ILC2, NK and NK-T cell responses, in immune-mediated diseases.[5,6,7,8,9,10,11,12,13] Studies of DR3 or TL1A gene-deficient mice or mice treated with anti-TL1A antibodies demonstrate a role for this pathway in a number of autoimmune disease models.[8,14] Moreover, significant literature data from nonclinical species and humans implicate TL1A most prominently in the pathophysiology of IBD. Numerous genome wide association studies have linked several polymorphisms of the TL1A gene to UC and CD in patient populations of Japanese, European, and Asian origin.[1,15,16,17,18,19] Additionally, human inflamed IBD tissues show high levels of TL1A and DR3 expression and several independent laboratories have demonstrated that antibody blockade of TL1A prevents or attenuates established gut inflammation in a number of murine IBD models).[4,6,9,20,21,22,23,24,25]

2.2.1. Nonclinical Overview

The nonclinical safety profile of PF-06480605 has been adequately characterized in vitro and in mice, New Zealand White rabbits, and cynomolgus monkeys in vivo to support chronic administration in clinical trials.

Further details are provided in the current IB.

2.2.2. Clinical Overview

To date (24 Dec 2020), the clinical development programs for PF-06480605 comprise FIH study in healthy adult participants (B7541001; SAD and MAD study; completed), phase 1

study in Japanese healthy adult participants (B7541006; single subcutaneous dose at two dose levels; clinically completed), and a phase 2a study in participants with UC (B7541002; open label study; completed). Refer to the IB for more details on the clincial information with PF-06480605.

2.2.2.1. Safety

2.2.2.1.1. B7541001

The B7541001 study was a Phase 1, randomized, double-blind, third-party open, placebo-controlled, single and multiple dose escalation study to evaluate the safety and tolerability of the single and multiple dose of PF-06480605 in healthy adult participants. PF-06480605 doses evaluated in the SAD period were: 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 800 mg IV doses. The MAD dose cohorts evaluated were: 30 mg, 100 mg and 300 mg SC (Q2W) × 3 doses, and 500 mg IV (Q2W) × 3 doses.

A total of 92 healthy participants, 60 and 32 participants in the SAD and MAD periods, respectively, were assigned to and received study treatment (PF-06480605 or placebo). Single doses up to 800 mg IV and multiple doses up to 300 mg SC (Q2W) and 500 mg IV (Q2W) were administered. Six (6) participants discontinued from the study: 3 participants each from the SAD period and the MAD period, which included 1 placebo participant from each period. There were no study discontinuations attributed to treatment-related AEs). There were 2 participants who were lost to follow-up; one participant in the SAD PF-06480605 100 mg cohort and 1 participant in the SAD PF-06480605 600 mg cohort. Additionally, there were 2 participants who were no longer willing to participate in the study; one participant in the MAD PF-06480605 30 mg cohort and 1 participant in the SAD placebo cohort. One participant in the MAD placebo cohort discontinued due to other reasons (withdrawn at investigator request, non-AE).

There were no deaths, SAEs, severe AEs, AEs resulting from ADA/NAbs, or participants with dose reduced or temporary discontinuations due to AEs during the FIH study with PF-06480605. Additionally, there were no clinically significant laboratory abnormalities, vital signs, or ECGs.

In the single dose period, there were 45 all-causality TEAEs reported by 21 participants out of the 44 participants treated with PF-06480605. Of these, 15 events were determined to be treatment-related and were reported by 13 participants. There were 20 all-causality TEAEs reported by 7 participants out of the 16 participants treated with placebo, of which 9 events were determined to be treatment-related and were reported by 5 participants.

In the multiple dose period, there were 44 all-causality TEAEs reported by 17 participants out of the 24 participants treated with PF-06480605. Of these, 21 events were determined to be treatment-related and were reported by 11 participants. There were 17 all-causality TEAEs reported by all of the 8 participants treated with placebo, of which 6 events were determined to be treatment-related and were reported by 5 participants.

Overall, headache was the most commonly reported all-causality (7 PF-06480605 participants and 3 placebo participants) and treatment-related (5 PF-06480605 participants)

TEAE. The second most commonly reported treatment-related TEAE was abdominal pain which was reported by 3 PF-06480605 participants and 1 placebo participant.

The incidence of TEAEs between cohorts in the SAD period and between cohorts in the MAD period was similar. Overall, there was a higher incidence of treatment-related TEAEs in the MAD cohorts compared with the SAD cohorts, although the incidence of TEAEs did not increase with higher doses of PF-06480605.

The majority of TEAEs were mild in severity. There was a higher incidence of moderate severity TEAEs reported by participants in MAD cohorts compared with SAD cohorts. The study's only treatment-related moderated severity TEAE, abdominal pain, was reported by a participant from a MAD cohort. There were no severe TEAEs reported.

There were no participants from the SAD period who discontinued from the study due to an AE. In the MAD period, there was 1 participant who discontinued from the study due to a treatment- unrelated AE, pyuria, on study Day 14. The event was determined to be mild and the participant recovered in one day.

2.2.2.1.2. B7541002

The B7541002 study was a Phase 2a, multicenter, single arm, open-label, 2-stage study to evaluate the efficacy, safety, tolerability and PK of PF-06480605 in participants with moderate to severe UC.

A total of 50 participants were enrolled and treated with PF-06480605 500 mg IV Q2W for a total of 7 doses in the study. Among the 50 participants treated, 33 (66.0%) participants reported at least 1 all-causality TEAEs. The most frequently (≥3) reported all-causality TEAEs were Arthralgia and Colitis ulcerative in 6 (12.0%) participants each, Abdominal pain, Alopecia, Back pain, Nasopharyngitis, Nausea, and Pharyngitis in 3 (6.0%) participants each.

Eight (8, 16.0%) participants among the 33 participants reported treatment-related TEAEs. TEAEs reported were Abdominal pain, Acrochordon, Alanine aminotransferase increased, Alopecia, Arthralgia, Aspartate aminotransferase increased, Back pain, Diastolic hypertension, Haematoma, Headache, Hypertension, Infusion site bruising, Muscle spasms, Nausea, Oedema peripheral, Oropharyngeal pain, Pruritus, and Vertigo in 1 (2.0%) participant each.

Eight (8) participants had Grade ≥3 laboratory abnormalities. Three (3) participants had hematology laboratory abnormalities (lymphocyte count decreased) and 5 participants had chemistry laboratory abnormalities (creatine phosphokinase increased, hypokalemia and hyponatremia). There were no deaths reported in the study.

There were two participants who discontinued study drug treatment. One participant discontinued treatment after 6 doses of study drug due to worsening UC. This participant also discontinued the study. One participant discontinued treatment-related to a SAE, alopecia.

Within the study, there were 4 SAEs reported. Three of these SAEs resulted from worsening of underlying disease activity. The fourth SAE was a case of alopecia /baldness, which was reported as related to the study drug by the investigator as an SUSAR but unrelated by the sponsor.

2.2.2.1.3. B7541006

B7541006 is an Phase 1, randomized, double-blind, third-party open (ie, participant-blind, investigator-blind and sponsor-open), placebo-controlled, dose escalating clinical study to evaluate the safety, tolerability, immunogenicity, PK and PD of PF-06480605 in Japanese healthy adult participants. The study consists of 2 cohorts, and 6 participants were randomized to PF-06480605 and 2 participants were randomized to placebo in each cohort. Each participant received PF-06480605 (150 mg or 450 mg) or placebo subcutaneously.

The preliminary data from study B7541006 showed that PF-06480605 was safe and well tolerated in Japanese healthy participants receiving either150 mg or 450 mg. Till date (24 Dec 2020), no deaths, serious AEs, or discontinuations due to AEs was reported in this study. All TEAEs were observed in 150 mg cohort and were mild to moderate in severity and considered recovered. No vital sign or ECG abnormality was clinical remark judged by the investigators in both cohorts.

2.2.2.2. Immunogenicity

2.2.2.2.1. B7541001

The incidence of ADA ranged from 50% to 100% for SAD and MAD cohorts. In participants receiving PF-06480605, 56 participants out of 68 participants were considered to be positive for ADA. The overall confirmed treatment induced incidence rate was 82.4%; however, there were 11 participants for whom PF-06480605 concentrations remained above the assay tolerance level throughout the study. For drug tolerance, the assay has the potential to report a false negative at drug concentrations higher than the stated amount, which may result in the inconclusive ADA results. Positive ADA samples were detected as early as 336 hours (14 days) post-dose in the SAD cohorts and on Day 29 in the MAD cohorts.

The incidence of NAb ranged from 0% for 2 SAD and 2 MAD cohorts to 100% for the 3 mg IV cohort. In participants receiving PF-06480605, 24 participants out of 68 participants were considered positive for NAb. The overall confirmed NAb incidence rate was 35.3%; however, there were 43 participants for whom PF-06480605 concentrations remained above the assay tolerance level throughout the study. Positive NAb samples were detected as early as 672 hours (28 days) post-dose in the SAD cohorts and 1680 hours (70 days) post-dose in the MAD cohorts. Where data were available, mean serum PF-06480605 concentrations were lower in participants identified as ADA positive, compared to participants identified as ADA not-positive, and were even lower in participants with NAb log titer ≥0.70. Differences in mean serum PK parameters, namely exposure, between participants identified as ADA positive and ADA not-positive as well as between participants with NAb log titer <0.70 and ≥0.70 were more apparent for participants in MAD cohorts but no direct conclusions were able to be drawn from the data.

2.2.2.2.2. B7541002

The incidence of ADA as analyzed by the ADA assay with acid pretreatment (being different from the assay used in study B7541001, positive controls and negative controls were pre-treated with acetic acid before co-incubation with biotin-labeled PF-06480605 and ruthenium-labeled PF-06480605 prepared in neutralization buffer. While a true limit of drug tolerance was not demonstrated, the assay tolerated up to 2000 ng/mL at both PC levels based strictly on a comparison of these levels to the cutpoint was 82% with titer values ranging from 1.31 to 4.42 and 1 value above the assay range (>4.64). Five (5) participants (10%) tested NAb positive with the cell-based NAb assay and had relatively low titer values ranging from 0.809 to 1.38. Following PF-06480605 administration, the median time to first detection of ADA and NAb were 140 and 114 days, respectively.

The immunogenic impact on PK appeared to be minimal based on the similarity of the PK profiles in ADA positive and negative subjects and NAb positive and negative subjects while trends of lower sTL1A target engagement starting from Week 8 were observed for ADA and NAb positive participants compared to the ADA and NAb negative participants. There were no statistically significant effects of ADA and NAb status on the endoscopic improvement, remission (secondary endpoint), endoscopic remission, or remission (exploratory endpoint) at Week 14. However, the small sample size, large variability and the high incidence of ADA did not provide sufficient information to make a definitive conclusion on the impact of ADA/NAb on the PK, PD and efficacy.

2.2.2.2.3. B7541006

To date (24 Dec 2020), there is no immunogenicity data from study B7541006.

2.2.2.3. Pharmacokinetics

2.2.2.3.1. B7541001

Following single IV infusion dosing of PF-06480605 under fasted conditions at doses ranging between 1 mg to 800 mg, the C_{max} was observed around 1.5 to 2 hours after the end of a 1-hour infusion followed by a multiphasic decline of serum concentrations over time, with mean $t_{½}$ values ranging between 6 to 23 days. Mean $t_{½}$ values at the lower doses appeared to be shorter than those observed at the higher doses which may be due in part to sensitivity of the assay (more quantifiable serum concentrations above the limit of quantification at later time points for the higher doses) and in part of CL values which were appeared to decrease with increasing doses.

Overall, PF-06480605 AUC increased in a greater than dose proportional manner across the 1 mg to 800 mg dose range, while C_{max} appeared to increase in an approximately dose proportional manner across the dose range studied.

Geometric mean PF-06480605 CL values appeared to decrease with increasing doses, with a mean estimate of 0.0180 L/hr at the 1 mg dose and 0.00688 L/hr at the 800 mg dose. V_{ss} was low, indicating that drug is localized mainly to the vascular compartment with mean values ranging between 3.4 to 5.5 L across all doses.

Following multiple SC dose administration of PF-06480605 at 30-mg, 100-mg, and 300-mg doses Q2W for a total of 3 doses, absorption from the site of injection was variable, with peak serum concentrations achieved within a median time at which T_{max} of 96 to 216 hours post-dose on Day 1, 192 to 335 hours post-dose on Day 15, and 48 hours post-dose on Day 29.

Dose normalized PK exposure (as measured by geometric mean AUC from time 0 to time τ, the dosing interval [AUC_τ] and C_{max}) on Day 1 indicated that following SC administration, exposure increased in a dose proportional manner with an increase in dose, while exposure on Days 15 and 29 trended toward greater than dose proportional increases across the 30 mg to 300 mg SC doses.

CL/F and V_z/F for the 100 mg to 300 mg SC doses (individual values for 30-mg SC dose) on Day 29 were approximately similar across all 3 SC doses, with geometric mean CL/F and V_z/F values ranging between 0.0131 and 0.0167 L/hr and 8.1 and 8.5 L, respectively. Mean $t_{½}$ values for the SC doses (individual values for 30 mg SC dose) on Day 29 ranged between 8.7 and 21 days with the longer $t_{½}$ values observed at the 100 mg and 300 mg doses. Mean observed R_{ac} based on geometric mean AUC_τ on Day 29 ranged between 2.4 and 3.2, and $R_{ac, Cmax}$ based on geometric mean C_{max} on Day 29 ranged between 2.3 and 4.2, representing the magnitude of accumulation following SC Q2W administration for a total of 3 doses.

Apparent bioavailability/estimate of bioavailability for the SC doses relative to IV dosing (F) values based on geometric mean AUC_τ for the 30 mg, 100 mg, and 300 mg SC doses on Day 1 were 47%, 44%, and 42%, respectively, relative to the corresponding IV doses from the SAD portion of the study.

Following multiple dose administration of a 500 mg IV dose Q2W for a total of 3 doses, higher geometric mean AUC_τ, values were observed on Days 15 and 29 compared to Day 1 with similar C_{max} values observed across all dosing days. Mean R_{ac} based on geometric mean AUC_τ on Day 29 was 2.1, and $R_{ac, Cmax}$ based on geometric mean C_{max} on Day 29 was 1.4. CL and V_{ss} geometric mean values on Day 29 were 0.00776 L/hr and 5.6 L, respectively. Mean $t_{½}$ was 20 days.

2.2.2.3.2. B7541002

Following multiple dose administration of 500 mg PF-06480605 intravenously Q2W for a total of 7 doses in subjects with moderate to severe UC, C_{max} was observed around 1.03 hours after the end of a 1 hour infusion. After the achievement of C_{max}, PF-06480605 serum concentration exhibited a biphasic decline over time, with mean $t_{½}$ of 19.3 days. Geometric mean AUC_τ over a dosing interval of 14 days (336 hours) was 57610000 ng•hr/mL and geometric mean of C_{max} value was 263400 ng/mL. The geometric mean CL value was 0.00868 L/hr. V_{ss} was low (geometric mean value of 4.69 L), indicating that PF-06480605 was primarily distributed in the plasma volume. On average, the PK of PF-06480605 in UC patients was generally consistent with the PK concentration-time profiles in healthy volunteers.

2.2.2.3.3. B7541006

Up to 24 Dec 2020, study B7541006 is clinically completed, and only the preliminary PK results of Cohort 1 (150 mg SC) are available. The PK of PF-06480605 up to Day 5 in Japanese healthy participants was comparable to Western healthy participants.

2.3. Benefit/Risk Assessment

PF-06480605 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data in Chinese healthy participants for further clinical development. In healthy participants, the TL1A/DR3 signaling pathway is expected to be quiescent, therefore, limited PD modulating would be expected.

PF-06480605 was determined to be well tolerated and to have an acceptable safety profile in the clinical studies.

The overall confirmed treatment induced ADA incidence rate in healthy participants and UC patients was approximately 82%. The overall confirmed NAb incidence rate was 35.3% in healthy participants and 10% in UC patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06480605 may be found in the investigator's brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: PF-06480605		
Potential risk of infections.	PF-06480605 is an immunomodulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation.	Participants with infection history will be excluded (See Section 5.2) and the risk of infection will be monitored in the study.
Potential fetal risk.	Although no fetal toxicity was observed at NOAEL level for PF-06480605 in rabbits. The potential effect in human fertility PF-06480605 is still not clear.	WOCBP who are unwilling or unable to use contraception as defined in the study protocol will be excluded (See Section 5.3.4. and Appendix 4).
Potential risk of secreting into human milk.	It is not known whether PF-06480605 is secreted into human milk.	PF-06480605 should not be administered to breastfeeding women and exposure during breastfeeding should be reported to Pfizer Safety (See Section 8.3.5.2).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of PF-06480605 following administration of single SC dose of PF-06480605 450 mg and 150 mg (if needed) in Chinese healthy adult participants. • To evaluate the safety and tolerability following administration of single SC dose of PF-06480605 450 and 150 mg (if needed) in Chinese healthy adult participants	• Serum PF-06480605 primary PK parameters, as permitted by data: C_{max}, T_{max}, $AUC_{14\ days}$, AUC_{inf}, and $t_{½}$. • Assessment of AEs, vital signs, 12 lead electrocardiograms, physical examination findings and clinical safety laboratory measurements
Secondary:	**Secondary:**
• To further evaluate the PK of PF-06480605 • To evaluate the immunogenicity of PF-06480605. • To evaluate the PD biomarker (if feasible) which may be informative in demonstrating the pharmacologic effect of PF-06480605.	• Serum PF-06480605 PK parameters, as permitted by data: AUC_{last}, C_{max}(dn), AUC_{inf}(dn), and AUC_{last}(dn), V_z/F and CL/F. • Incidence of the development of ADA and NAb. • Total sTL1A protein concentration in serum.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, single-center, randomized, double-blind, third-party open (participant blind, investigator blind, sponsor open), placebo -controlled study to investigate PK, safety, tolerability, immunogenicity, and PD of PF-06480605 following a single subcutaneous dose of PF-06480605 450 mg and 150 mg (if needed) in Chinese healthy adult participants. Optional 150 mg cohort will be conducted only if data from 450 mg cohort does not confirm expected PK based on previous studies in healthy Western and Japanese participants as well as UC patients.

A maximum of approximately 24 participants (18 with active treatment and 6 with placebo) will be randomized and receive the study intervention such that approximately 12 participants are assigned to each cohort (450 mg and 150 mg) to ensure that 11 evaluable participants per cohort will complete the study. Participants will be enrolled to both cohorts sequentially, starting with the 450 mg cohort first. When the 150 mg cohort is determined to be needed, the 150 mg cohort with entirely new participants will be opened.

The 150 mg cohort will be started only if it indicates the ethnic PK difference (eg, more than two-fold higher exposure) based on all available serum concentrations data of PF-06480605 obtained until the timing the PK sample is collected at Day 14 after administration, by comparing the dose-normalized mean exposures (or dose-normalized mean concentrations profiles) in this study versus dose-normalized mean exposures in Western study B7541001 and Japanese study B7541006.

Table 1. Randomization Scheme

Cohort	Treatment	Number of participants
1	PF-06480605 450 mg	9
	Placebo	3
2 (optional)	PF-06480605 150 mg	9
	Placebo	3

Participants, who drop out from the study if the number of participants completing at least the follow-up visit at Day 57 per cohort decreases to 10 or lower, will be replaced.

If a participant discontinues before completing the part of the study to which they have been randomized, or withdraws for reasons unrelated to the safety of the study intervention, the participant may be replaced at the discretion of the investigator upon consultation with the sponsor.

Within 28 days of successful completion of the screening process, eligible participants will be enrolled and randomized to receive a single dose of PF-06480605 450 mg or 150 mg (if needed) or placebo. Participants will be admitted into the CRU approximately 1 day prior to dosing and required to stay overnight in the CRU at least through completion of the Day 5 evaluations. Participants will return for outpatient follow-up visits through Day 114.

4.2. Scientific Rationale for Study Design

This Phase 1 study is designed to characterize the PK, safety, tolerability, immunogenicity, and PD of PF-06480605 after single SC dose administration in Chinese healthy adult participants.

To date (24 Dec 2020), no PK or safety data of PF-06480605 in Chinese are available. Although there is no expected relevant PK difference between Chinese and non-Chinese (Japanese and Westerners) because monoclonal antibodies are generally known that the absence of ethnic differences in their distribution and elimination, similar to that of endogenous IgG[26] , characterizing PK in Chinese participants is set as one of the primary objectives in order to meet the requirement of CDE on the application for China joining in global Phase 2 study B7541007. Furthermore, the safety and tolerability of PF-06480605 in human was already confirmed and concluded as well-tolerated in non-Chinese participants, however, in order to confirm the safety and tolerability of PF-06480605 in Chinese healthy participants prior to administer PF-06480605 to Chinese patients, establishing safety and tolerability of PF-06480605 in Chinese healthy participants is set as co-primary objective. Corresponding endpoints are set as the same as the PK and safety assessments of Study B7541001 in Westerners and Study B7541006 in Japanese.

Regarding the secondary objectives and the secondary endpoints, the further PK evaluation and the immunogenicity evaluation are set in this study, which allows to compare the results of PK and immunogenicity of PF-06480605 in Western healthy participants in Study B7541001 and Japanese healthy participants in Study B7541006.

Total sTL1A protein concentration in serum will be evaluated to confirm the target engagement and the consistency with the results in Study B7541001 and Study B7541006.

The study duration and frequency of each assessment were decided based on information of previous studies. Day 114 was considered the necessary period to reduce blood levels sufficiently, and no treatment-related AEs were observed after Day 85 in previous studies. Sample collection points for PK, immunogenicity and PD were selected based on the results in Study B7541001 and/or Study B7541006. In addition, based on considering the clinical practice and minimal neccitiy for PK evaluation, participants, who drop out from the study if the number of participants completing at least the follow-up visit at Day 57 per cohort decreases to 10 or lower, will be replaced.

It is common to use a double-blind design (participant- and investigator-blinded) with placebo control to evaluate the safety and tolerability of the drug, while sponsor is open to allow more efficient decision-making, especially in early stage of the development.

In the definitive EFD study, PF-06480605 was intravenously administered by bolus injection to pregnant New Zealand White female rabbits once daily on GD 7 and 14 at 0, 60, 180, or 500 mg/kg/dose. The maternal and developmental NOAEL for PF-06480605 in rabbits was the highest dose tested, 500 mg/kg/dose, based on a lack of test article-related effects. Also, there were no findings in male or female reproductive organs in the 3- or 6-month toxicity studies in mice and cynomolgus monkeys, respectively. It is not known whether PF-06480605 can affect male fertility or whether PF-06480605 is secreted in human milk. Because of the investigational nature of this product, PF-06480605 should not be administered to pregnant women or women who are nursing an infant. Given the unlikely risk of human teratogenicity/fetal toxicity all acceptable effective methods of contraception will be required for approximately 5 half -lives (a minimum of 114 days [±3 days]), following the last dose of study intervention (see Appendix 4). The potential risk of exposure to PF-06480605 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin of 34,852 is >100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100fold is based on applying a 10fold safety factor for interspecies extrapolation and a 10fold safety factor for susceptible populations.[27]

4.3. Justification for Dose

In current study, a single SC dose level of 450 mg with an optional lower SC dose of 150 mg were selected based on the safety, tolerability, PK and modeling and simulation results in previous studies to compare safety and PK among Westerner, Japanese and Chinese. Based on results of simulation using a population PK-PD model developed from the combined data of Studies B7541001 and B7541002, percentage of patients maintaining ⩾ 90% sTL1A coverage throughout the dosing period with 150 mg or 450 mg SC doses every 4 weeks (Q4W) were > 80%. The dose levels of 450 mg and 150 mg were studied in Japanese healthy participant study B7541006, and are being evaluated for the safety and efficacy in Study B7541007 in UC patients, while 450 mg is the highest dose used in both studies. An optional

dose of 150 mg was selected in case the high dose does not confirm expected PK based on previous studies in healthy Western and Japanese participants as well as UC patients.

As described in Section 2.2.2.1, up to now, single IV doses of up to 800 mg, multiple SC doses of up to 300 mg × 3 with 2-week intervals and multiple IV doses of up to 500 mg × 3 with 2-week intervals were generally safety and well tolerated in Western healthy participants in Study B7541001. Apparent bioavailability/estimate of bioavailability for the SC doses relative to IV dosing (F) values based on geometric mean AUC_{τ} for the 30-mg, 100-mg, and 300-mg SC doses on Day 1 were 47%, 44%, and 42%, respectively, relative to the corresponding IV doses from the SAD portion of the study. Dose normalized PK exposure (as measured by geometric mean AUC_{τ} and C_{max}) on Day 1 indicated that following SC administration, exposure increased in a dose proportional manner with an increase in dose, while exposure on Days 15 and 29 trended toward greater than dose proportional increases across the 30-mg to 300-mg SC doses.

Considering these results from Study B7541001, exposure following a single 450 mg SC dose is much less likely to exceed the exposure of the single 800 mg IV dose observed in Study B7541001 and is expected to be safe and tolerable. As expected, the preliminary data in Japanese Study B7541006 demonstrated that single dose up to 450 mg SC was clinically safe and well tolerated in Japanese healthy participants, and no AE was observed in 450 mg cohort. Therefore, the concern of unacceptable safety and tolerability is not expected in Chinese healthy participants with administration of a single 450 mg SC dose.

The preliminarily partial PK data in Japanese Study B7541006 showed no ethic PK difference between Japanese and Westerners by comparing the individual concentration-time profiles till Day 5 (around C_{max}). The full PK profile in Japanese healthy participants will be available in Feb/Mar 2021, and the comparison with Western healthy participants will be performed afterwards.

Taken together, the likelihood of needing 150 mg cohort is low. 150 mg cohort will be conducted only if any of the following scenarios is observed in Chinese healthy participants following a single 450 mg SC dose:

- It indicates the ethnic PK difference (eg, more than two-fold higher exposure) based on all available serum concentrations data of PF-06480605 obtained until the timing the PK sample at day 14 after administration, by comparing the dose-normalized mean exposures (or dose-normalized mean concentrations profiles) in this study versus dose-normalized mean exposures in study B7541001 and B7541006, and/or,

- Sponsor need to initiate 150 mg cohort for other consideration.

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 visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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 nonmedical 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

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

Age and Sex:

1. Male and female participants must be 18 to 45 years of age, inclusive, at the time of signing the ICD.

    - 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. Male and female Chinese participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital sign and 12-lead ECG.

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

Weight:

4. BMI of 19 to 27 kg/m^2; and a total body weight >50 kg.

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

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. History of HIV infection, hepatitis B, hepatitis C or syphilis; positive testing for HIV, hepatitis B, HCVAb or serological reaction of syphilis.

    - For hepatitis B, all participants must undergo testing for HBsAg, HBcAb, and HBsAb.

        - Participants who are negative for all 3 serology tests may be eligible.

        - Participants who are HBsAg positive will be excluded.

        - HBsAg negative, HBcAb positive, and HBsAb negative particpants are to be excluded from the study.

        - Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study.

        - Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at screening.

            - If HBV DNA is detectable, participants will be excluded.

            - If HBV DNA is not detectable, participants may be eligible. If the participant is included in the study, for subsequent visits HBVDNA testing must be performed according to the Schedule of Activities.

3. History of allergic or anaphylactic reaction to a therapeutic drug.

4. History of recent active infections within 28 days prior to the screening visit.

5. Participants with a fever within 48 hours prior to dosing.

6. History of TB or active or latent or inadequately treated infection.

    Have evidence of untreated or inadequately treated active or latent Mycobacterium TB infection as evidenced by the following:

a. A positive QFT-G test or positive or borderline T-Spot test performed within the 12 weeks prior to Day 1. If the laboratory reports the test as indeterminate, the test should be repeated. A negative PPD test may be substituted for the QFT-G test or T-Spot test only with approval from the Pfizer Medical Monitor on a case by case basis. For participants with negative QFT-G or T-Spot test at screen, repeated TB test will be perfomed at Day114.

b. Chest radiograph with changes suggestive of active TB infection within 3 months prior to Screening. Chest radiograph should be performed according to local standards of care or country-specific guidelines.

c. History of either untreated or inadequately treated latent or active TB infection.

   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 test, a T-Spot test, nor a PPD test need be obtained. Details of the previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.

   A chest radiograph should be obtained if not done within the 3 months prior to Screening. To be considered eligible for the study, the chest radiograph must be negative for active TB infection.

   A participant who is currently being treated for active TB infection must be excluded from the study.

   A participant who is being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

9. Recent exposure to live vaccines within 28 days of the screening visit.

Prior/Concurrent Clinical Study Experience:

10. Known exposure to anti-TL1A (PF-06480605) or any type of anti-TL1A therapy.

11. Previous administration with an investigational drug within 114 days (±3 days) (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

12. A positive urine drug test.

13. A positive pregnancy test.

14. 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.

15. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate -age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected- using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

16. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study specific- laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST or ALT level >1.5 × ULN;
    - Total bilirubin level >1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - Hemoglobin level ≤120 g/L (12.0 g/dL);
    - Platelet count ≤150 × 10^9/L (150,000 cells/mm^3);
    - WBC count of ≤3.0 × 10^9/L (3000 cells/mm^3);
    - ANC <1500 cells/mm^3;

- ALC <800 cells/mm^3;
- eGFR <90 mL/min/1.73 m^2 based on the CKD-EPI 2009 equation[28];
- In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that could affect interpretation of study data or the participant's participation in the study.

Dianwo dadianhOther Exclusions:

17. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
18. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 90 days prior to dosing.
19. History of sensitivity to heparin or heparin -induced thrombocytopenia
20. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

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.
- While participants are confined, their 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 the start of dosing and during confinement in the CRU.
- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during confinement in the CRU. 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.

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 and his or her partner(s) 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 SoA, 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 randomly assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-06480605 and its placebo.

6.1. Study Intervention(s) Administered

For this study, the study interventions are PF-06480605 and its placebo.

PF-06480605 is a sterile solution for subcutaneous injection. PF-06480605 will be provided in dosage strength of 100 mg/mL in single-use, sterile vials. Each vial contains 200 mg of PF-06480605 in 2 mL of solution. Placebo for PF-06480605 will also be provided by Pfizer as a sterile liquid solution in single-use, sterile vials.

PF-06480605 and placebo are supplied in a 6 mL glass vial and a 2 mL extractable volume with a stopper and aluminum overseal. All vials will be provided in cartons and both will be labeled according to local regulatory requirements. The site will take all necessary precautions to maintain the investigator and site personnel blind.

6.1.1. Administration

Participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Study medication does not require fasting, but it should be noted that the safety laboratory test at Day -1 prior to the study medication need a fast of at least 4 hours. Study medication will be administered subcutaneously. Injection should occur at a site on the abdomen. All participants will be administered one or more 1.5 mL SC injections. The number of SC injections depends on the doses such that one SC injection for 150 mg, and three SC injections for 450 mg. Thus, the number of SC injections will be maximal 3 times. Each injection is to occur at a different site on the abdomen, approximately 1 cm apart.

Administer study intervention according to the IP manual.

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.

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 temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. 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. 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.

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

5. Study interventions should be stored in their original containers and in accordance with the labels.

6. See the IP manual for storage conditions of the study intervention.

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.

9. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

10. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, 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.

PF06480605 and placebo will be prepared and dispensed by qualified unblinded site personnel according to the IP manual. The study intervention will be administered by unblinded administrator to the participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Participants will be randomly assigned to receive study intervention from a central randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all study intervention according to the randomization schedule and assigned treatment for the individual participant.

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

This is an investigator- and participant-blind (Sponsor open) placebo-controlled study. Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. The investigator site staff with the exception of the site pharmacist(s), pharmacy assistant(s) and study drug administrator(s) and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide

information necessary to potentially alter the dose escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

The study intervention will be administered by investigator site personnel. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

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 study intervention. Recent exposure to live vaccines within 28 days of the screening visit is prohibited. 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 ≤1 g/day.All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.6. Dose Modification

Dose modification is not allowed in the current study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at 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 study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following as outlined in Section 7.2.

If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for PF-06480605. See the SoA for data to be collected at the time of discontinuation of study intervention.

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

Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants are noted to have 2 consecutive SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA 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 enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1 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.

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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 study intervention 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.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study specific procedures.

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

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, 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.

A participant who qualified for this protocol but did not enroll from an earlier cohort may be used in a subsequent cohort without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical

assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

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 IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate 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 230 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 SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 brief 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.

Height and weight will also be measured and recorded as per the SoA. 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. Chest Radiography

Chest X-ray (posterior-anterior and lateral views are recommended, however local guidelines should be followed) or other appropriate diagnostic image (ie, CT or MRI) should be taken at Screening or within 3 months prior to Screening and read by a qualified radiologist or pulmonologist and must show no evidence of abnormalities including but not limited to current, active TB or previous inactive TB, general infections, heart failure or malignancy. Documentation of the official reading must be located and available in the source documentation.

8.2.3. 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.

8.2.3.1. Temperature

Temperature will be measured according to local practice at times specified in Section 1.3 of this protocol. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.4. Electrocardiograms

12-lead ECGs should be collected at times specified in the SoA section 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. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; 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 ≥60 msec from the baseline **and** is >450 msec; 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 c) 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).

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 values of potential clinical concern are listed in Appendix 6.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 114 days (±3 days) after the last dose of 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.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

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

If laboratory values from nonprotocol 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 study intervention.

8.2.6. 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 SoA. Serum pregnancy tests will be conducted at screening and pre-dose. Urine pregnancy tests will be conducted after dosing mothly over the duration of the study. 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 study intervention or placebo. 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 IRBs/ ECs or if required by local regulations.

8.2.7. Injection Site Reactions

Each participant will be monitored a minimum of 2 hours after the study intervention. After 2 hours the injection site will be monitored for redness, swelling, or any type of inflammation and this should be recorded as an injection site reaction, if applicable on the appropriate CRF. If the participant has a delayed reaction, (after they leave the investigative site) this should also be captured as an injection site reaction, on the adverse event CRF page.

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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 study intervention), through and including a minimum of 114 calendar days (±3 days) after the administration of the study intervention.

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 AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

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 upon awareness 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 study intervention must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study 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 study intervention 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

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 study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
    - 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 study intervention prior to or around the time of conception and/or is exposed during his partner's pregnancy.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 114 days (± 3 days).
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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).

Abnormal pregnancy outcomes are considered SAEs. 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), 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 including 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 study intervention.

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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. 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. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease -Related Events and/or Disease -Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

Exposures to the study intervention 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 study intervention;
- 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 within 24 hours.

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 the 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-06480605 greater than 500 mg within 2-weeks will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF06480605 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a casebycase basis).

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

Blood samples of approximately 3 mL, to provide approximately 1.2 mL serum, will be collected for measurement of serum concentrations of PF-06480605 as specified in the SoA. 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 dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) 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 dose 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). In follow-up visits (after Day 5), collection of samples that are obtained within 3 days of planned visit will not be captured as a protocol deviations, 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 serum PF-06480605 concentration. Samples collected for analyses of serum PF-06480605 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.[redacted]

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

Samples collected for measurement of serum concentrations of PF-06480605 will be analyzed using a validated analytical method in compliance with applicable 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.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Blood samples of approximately 8 mL, to provide approximately 3 mL serum, will be collected into appropriately labeled collection tubes (no additives). Serum samples will be collected and aliquoted for the analysis of serum sTL1A at times specified in the SoA.

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 dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) 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 dose 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). In follow-up visits (after Day 5), collection of samples that are obtained within 3 days of planned visit will not be captured as a protocol deviations, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT).

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, [redacted]

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD 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.

8.7. Genetics

8.7.1. Specified Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Blood samples of approximately 3 mL, to provide approximately 1.2 mL serum, will be collected for determination of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) as specified in the SoA. 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.

Samples collected for determination of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, CCI [redacted]

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

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

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

Immunogenicity information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.10. 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 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 formal statistical hypothesis testing will be conducted for PK/PD and safety analyses.

9.2. Sample Size Determination

The maximum sample size of approximately 24 participants is not based on any statistical considerations. Those participants will be enrolled and receive the study intervention such that approximately 12 participants are assigned to each cohort (450 mg and 150 mg) to ensure that 11 evaluable participants per cohort will complete the study. In each cohort, 12 participants will be randomly assigned at an allocation ratio of 3:1 to the active treatment and placebo arms.

Participants will be enrolled to both cohorts sequentially, starting with the 450 mg cohort first. When the 150 mg cohort is determined to be needed, the 150 mg cohort with entirely new participants will be opened. The 150 mg cohort will be started only if it indicates the ethnic PK difference (eg, more than two-fold higher exposure) based on all available serum concentrations data of PF-06480605 obtained until the timing the PK sample is collected at Day 14 after administration, by comparing the dose-normalized mean exposures (or dose-normalized mean concentrations profiles) in this study versus dose-normalized mean exposures in Western study B7541001 and Japanese study B7541006. If the 150 mg is not needed, then only approximately 12 participants will be administered the study intervention or placebo.

Cohort	Treatment	Number of participants
1	PF-06480605 450 mg	9
	Placebo	3
2 (optional)	PF-06480605 150 mg	9
	Placebo	3

Participants, who drop out from the study if the number of participants completing at least the follow-up visit at Day 57 per cohort decreases to 10 or lower, will be replaced.

If a participant discontinues before completing the part of the study to which they have been randomized, or withdraws for reasons unrelated to the safety of the study intervention, the participant may be replaced at the discretion of the investigator upon consultation with the sponsor.

9.3. Analysis Sets

For purposes of PK and safety analyses, the following analysis sets are defined:

Safety Analysis Set	All randomized participants who applied at least 1 dose of study intervention.
PK Concentration Set	All randomized participants who applied at least 1 dose of study intervention and for whom at least 1 concentration value is reported.
PK Parameter Set	All randomized participants who applied at least 1 dose of study intervention and for whom at least 1 of the PK parameters of interest (eg, AUC_{inf} and C_{max}) is calculated.
Immunogenicity Analysis Set	All randomized participants who applied at least 1 dose of study intervention with at least 1 post-treatment anti-drug (PF-06480605) antibody determination.
PD Analysis Set	All randomized participants who have at least 1 PD assessment.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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.

9.4.1. General Considerations

No formal statistical tests will be performed. Descriptive analyses or summaries will be provided for all endpoints by treatment for each cohort.

Additionally, a population PK model will be developed to characterize the PK and assess the effect of ethnicity on PK using all available data. The detailed analysis plans will be described in a separate pharmacometric analysis plan.

9.4.2. Primary Endpoint(s)

The primary endpoints consist of PK and safety endpoints. For the PK endpoints, all PK analyses will be based on PK concentration (or parameter) set. The following PK parameters of PF-06480605 will be calculated for each participant, as applicable, using noncompartmental analysis of concentration-time data. PK parameters are described in Table 2.

Table 2. Serum PF-06480605 Pharmacokinetic Parameters (Primary endpoints)

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
$AUC_{14\ days}$	Area under the curve from time 0 to Day 14 (336 hours)	Linear/log trapezoidal method
AUC_{inf}[a]	Area under the curve from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ was the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time profile

a. If data permitted.
Pharmacokinetic parameters were calculated using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4).

Actual PK sampling times will be used in the derivation of PK parameters.

All safety analyses will be performed on the safety analysis set. The safety endpoints include Treatment-emergent AEs and SAEs, withdrawals from treatment due to AEs, vital signs, 12 lead electrocardiograms parameters, and clinical safety laboratory measurements. 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 by treatment for each cohort 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 postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

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.

9.4.3. Secondary Endpoint(s)

The second endpoints are PK, immunogenicity and PD endpoints, and the PK endpoints are shown in Table 4.

All PK and immunogenicity analyses will be based on PK concentration (or parameter) and immunogenicity analysis sets, respectively.

Table 3. Serum PF-06480605 Pharmacokinetic Parameters (Secondary endpoints)

Parameter	Definition	Method of Determination
AUC_{last}	Area under the curve from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method
C_{max} (dn)	Dose normalized C_{max}	C_{max}/dose
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last}/dose
AUC_{inf} (dn)[a]	Dose normalized AUC_{inf}	AUC_{inf}/dose
V_z/F[a]	Apparent volume of distribution	Dose/(AUC_{inf}*k_{el})
CL/F[a]	Apparent clearance	Dose/AUC_{inf}

a. If data permitted.
Pharmacokinetic parameters were calculated using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4).

Serum concentrations and serum PK parameters will be summarized descriptively.

Safety and tolerability data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations.

Overall incidence of development of ADA and Nab will be reported by incidence with respect to time. Both titer and positive/negative will be reported for the ADA and NAb assays by time points samples were collected. Data permitting, the impact of ADA and NAb on PK, PD and safety profiles may be explored.

The total sTL1A protein concentration in serum will be summarized by time and presented in a tabular or graphical form. Further details will be documented in the SAP.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data of 450 mg SC cohort through Day 14 and during the course of the study for the purpose of determing whether or not to conduct 150 mg SC cohort, and preliminarily assess any ethnic differences between Chinese and non-Chinese, thus to support China joining further global Phase 2 or Phase 3 studies.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a 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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), 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 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 study intervention, 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 or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative 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 or his or her legally authorized representative 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 or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

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 and/or paper form and will be password protected or secured in a locked room 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 will 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 participants 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 and medical record identification. 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 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer -sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (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 corresponding study results are 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 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 contributes 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 and/or paper form and are password protected or secured in a locked room 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 eCRF that are 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 source document agreement*)*.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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 sponsor or designee/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.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 the 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 Investigator Site Master File..

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention 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 will be performed at times defined in the SoA 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 issues.

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• FSH[b] • Urine drug screening[c] • Pregnancy test[d] • HIV, HBsAg, HBcAb, HBsAb, HCVAb[e] • Serology reaction of syphilis test[e] • HBV-DNA[f] • Interferon Gamma Release Assay (IGRA)[g] • Covid-19 test[h]
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

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

b. At Screening only, for confirmation of postmenopausal status.

c. At Screening, the minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

d. Serum or urine pregnancy tests for female participants of childbearing potential. Serum pregnancy tests will be conducted at screen and pre-dose. Urine pregnancy tests will be conducted after dosing monthly over the duration of the study.

e. At Screening only.

f. If HBsAg is negative, HBcAb is negative, HBsAb is positive, and no unequivocal documentation of prior HBV vaccination is available or HBsAg is negative, HBcAb is positive, and HBsAb is positive, the participant is required to undergo HBVDNA reflex testing at screening. If HBVDNA is undetectable in the HBVDNA reflex testing in screening and the participant is enrolled the study, HBVDNA testing will be performed according to the Schedule of Activities.

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

g. Complete at screening. For subject with negative TB test (IGRA assay) at screen, TB test can be repeated at Day 114.

h. Testing for active COVID-19 infection, including testing methodology and frequency will follow CRU's practice. These tests may not be needed if the pandemic is over.

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study.

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. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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 study intervention 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 study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- 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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 providers.

- 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

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

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 an acceptable contraceptive method as described below during the intervention period (for a minimum of 114 days [±3 days] after the last dose of study intervention). 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

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:

6. 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.

7. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if 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

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 woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

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

   - Oral;

   - Intravaginal;

   - Transdermal;

- Injectable.

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

   - Oral;

   - Injectable.

8. Sexual abstinence.

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

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

10. Male or female condom with or without spermicide.

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

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

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow -up

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 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 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, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (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 samples for acetaminophen/paracetamol 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 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.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 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) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as 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 (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >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 SAEs

- 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.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
→	ongoing/continuous event
τ	tau
Abs	Absolute
ADA	anti-drug antibodies
AE	adverse event
ALC	Absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{τ}	AUC from time 0 to time τ, the dosing interval
$AUC_{14\ days}$	AUC from time 0 to Day 14 (336 hours)
AUC_{inf}	AUC from time 0 extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	AUC from time 0 to T_{last}
AUC_{last}(dn)	dose normalized AUC_{last}
AV	atrioventricular
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CD	Crohn's disease
CDE	Center of Drug Evaluation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKDEPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
C_{last}	last quantifiable concentration
C_{last*}	predicted serum concentration at the last quantifiable time point
C_{max}	maximum observed concentration
C_{max}(dn)	dose normalized Cmax
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
DCT	data collection tool

Abbreviation	Term
DILI	drug-induced liver injury
DMC	data monitoring committee
dn	dose normalized to 1 mg
DNA	deoxyribonucleic acid
DR3	Death Receptor 3
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eNCA	electronic non-compartmental analysis
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	apparent bioavailability/estimate of bioavailability for the SC doses relative to IV dosing
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GD	Gestation Days
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
HBVDNA	hepatitis B DNA
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
IBD	inflammatory bowel disease
ICD	informed consent document
ICH	International Council for Harmonisation
IFN	interferon
IgG	immunoglobulin G
IGRA	Interferon Gamma Release Assay
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

Abbreviation	Term
IRB	institutional review board
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
LBBB	left bundle branch block
LFT	liver function test
MAD	multiple ascending doses
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable
NAb	neutralizing antibodies
NOAEL	no-observed-adverse-effect level
PC	positive control
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QFT-G	QuantiFERON-TB GoldIn-Tube
Q2W	every 2 weeks
Q4W	every 4 weeks
QRS	part of electrocardiographic wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	observed accumulation ratio
$R_{ac, Cmax}$	observed accumulation ratio for Cmax
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
sTL1A	soluble TL1A
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th1	T helper type 1
Th2	T helper type 2
Th9	T helper type 9

Abbreviation	Term
Th17	T helper type 17
TL1A	tumor necrosis factor like ligand 1A
T_{max}	time at which Cmax occurred
TNF	tumor necrosis factor
$t_{½}$	terminal elimination half life
TBili	total bilirubin
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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