A PHASE 1, NON-RANDOMIZED, OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-06651600 IN SUBJECTS WITH HEPATIC IMPAIRMENT AND IN HEALTHY SUBJECTS WITH NORMAL HEPATIC FUNCTION

Investigational Product Number:	PF-06651600
Investigational Product Name:	Not Applicable (NA)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable (NA)
Protocol Number:	B7981016
Phase:	1

Short Title: HEPATIC IMPAIRMENT STUDY OF PF-06651600

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 1	23 October 2019	• Revision of additional enrollment text in Section 4.1 for Part 1: If there are participants who withdraw or discontinue treatment from the normal and moderate impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor such that the number of completed evaluable participants in each group equals approximately 8. Rationale: To ensure an adequate number of participants (approximately 8) with evaluable PK data. • Revision of additional enrollment text in Section 4.1 for Part 2: As in Part 1, if there are participants who withdraw or discontinue treatment from the mild impairment group and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor such that the number of completed evaluable participants in the group equals approximately 8. Rationale: To ensure an adequate number of participants (approximately 8) with evaluable PK data. • Addition of rescreening criteria in Section 5.4 Screen Failure: Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Rescreening may only occur with Sponsor approval.

		Rationale: To allow rescreening of participants who have potentially become eligible due to resolution of conditions resulting in the initial screen failure. • Addition of additional enrollment and rescreening text in Section 9.2: Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Additional participants can be enrolled at the discretion of the sponsor to ensure an adequate number of participants in each group (approximately 8) with evaluable PK data. Refer to Section 4.1 and Section 5.4 for details. • Addition of signing new ICD for rescreening in Section 10.1.3: Participants who are rescreened are required to sign a new ICD. • All other changes are minor and updated to align with current Protocol Template.
Original protocol	16 April 2019	Not applicable (N/A)

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable.

1.2. Schema

Not Applicable.

1.3. Schedule of Activities (SoA)

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

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

Visit Identifier[a]	Screening Day -28 to Day -2[b]	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	EOS (Follow-up Phone Visit) 28+3 days[c]	Early Termination/ Discontinuation (DC)
Informed consent	X														
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X													
Medical History	X	X													
Prior/Concomitant Medications	X	X	→	→	→	→	→	→	→	→	→	→	X	X	
Full/Limited physical examination[d]	X	X					X						X		X
Height and weight	X														
Safety laboratory[e]	X	X					X						X		X
Demography	X														
Serum FSH in post-menopausal females only[f]	X														
Urine drug testing	X	X													
Alcohol/tobacco use & Breath alcohol test	X	X													
12-Lead ECG[g]	X	X													
Vital signs (supine blood pressure, pulse rate and temperature)	X		X				X						X		X
HIV, HBsAg, HBcAb, HCVAb[h]	X														
QFT-G Test or PPD skin test[i]	X														
Study treatment administration			X	X	X	X	X	X	X	X	X	X[j]			

Visit Identifier[a]	Screening Day -28 to Day -2[b]	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	EOS (Follow-up Phone Visit)[c]	Early Termination/ Discontinuation (DC)
Pharmacokinetic blood sampling									X	X	X	X	X		X
Pfizer Prep D1 banked sample(s)[k]			X												
CRU discharge													X		
Adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	X	X	X

Abbreviations: → = ongoing/continuous event; AE = adverse event; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRU = clinical research unit; DC = discontinuation; ECG = electrocardiogram; EOS = End of Study; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; PPD = purified protein derivative; QFT-G = QuantiFERON®-TB Gold In Tube; RNA = ribonucleic acid; TB = tuberculosis.

a. Day relative to start of study treatment (Day 1).
b. In participants with hepatic impairment, stable disease status is required defined as no clinically significant change in disease status within the last 30 days prior to the Screening visit, documented by the participant's recent medical history (for example: no worsening of clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time by more than 50%). If participants do not have such records, 2 screening visits (at least 14 days apart) must be performed within the 28-day screening period (Day-28 to Day -1) to demonstrate stability of the disease.
c. Contact will occur onsite or via telephone contact and must occur 28+3 days from administration of the final dose of investigational product.
d. Full physical exam at screening and Day 11. Limited physical exam at Day -1, Day 5, Early Termination and any time point as deemed necessary by the investigator.
e. Safety laboratory testing must be collected within 28 days prior to first dose of investigational product (see Section 8.2.4). Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed following at least 4 hours fasting. If re-testing is needed for confirmation and monitoring of abnormal post-dose laboratory findings, this should be collected within 24-48 hours while the subject is confined in the research unit and may be repeated as deemed clinically warranted (refer to Appendix 8, Section 10.8: Guidelines for Participant Safety Monitoring and Discontinuation). Additional laboratory assessments may be required to evaluate potential cases of Hy's Law or adverse events as deemed necessary by the investigator. Samples will also be collected if reason for discontinuation is related to an AE.
f. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
g. Additional ECG monitoring may be performed in the event of AE.
h. All participants will undergo Screening for hepatitis B and hepatitis C for eligibility. All participants will undergo testing for HBsAg and HBcAb. Participants who are HBsAg positive will not be eligible for this study. Participants who are HBsAg negative but HBcAb positive will be reflex-tested for hepatitis B surface antibody. Please refer to Section 10.2.1 for testing algorithm, reflex testing, and full eligibility criteria. For all participants in the study, hepatitis C testing will be performed using hepatitis C antibody. Participants who are HCVAb positive will be reflex-tested for HCV RNA. Participants who are positive for HCVAb and HCV RNA will not be eligible for this study (refer to Section 10.2.1).
i. 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 Criterion 6. Perform TB test procedure using the QFT-G test. If QFT-G test is not available or is indeterminate, a PPD test can be substituted for the QFT-G test only under specific circumstances described in Section 10.2.2.
j. Last day dosing is after an 8-hour fast.
k. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

Visit Identifier														
Study Day	**7**	**8**	**9**	**10**										**11**
Hours Before/After Day 10 Dose	**0**	**0**	**0**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**14**	**24**
Study treatment administration	X	X	X	X										
PK blood sampling	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X
Abbreviation: PK = pharmacokinetic.														

a. Predose sample collection.

2. INTRODUCTION

PF-06651600 is a selective covalent inhibitor of Janus kinase (JAK) 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases and is currently under development for the treatment of alopecia areata (AA), rheumatoid arthritis (RA), vitiligo, ulcerative colitis (UC), and Crohn's Disease (CD).

2.1. Study Rationale

Preliminary metabolite screening conducted in B7981001 study identified the parent as the principle circulating drug related material. CCI [redacted] The objective of this non-randomized, open label, multiple dose study is to characterize the effect of hepatic impairment on the pharmacokinetic(s) (PK) of PF-06651600 following administration of multiple 30 mg once daily (QD) doses of PF-06651600.

CCI [redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1	
Primary:	**Primary:**
• To estimate the effect of moderate hepatic impairment on the PK of PF-06651600 following multiple dose administration.	Plasma PF-06651600 PK Parameters. • AUC_{0-24}, $C_{max.}$
Secondary	**Secondary**
• To evaluate safety and tolerability of multiple doses of PF-06651600.	Assessment of TEAEs, clinical laboratory tests, vital signs, and physical exam.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate the effect of moderate hepatic impairment on additional PK parameters of PF-06651600.	• T_{max}, AUC_{last} and CL/F; • C_{trough} on Days 7, 8, 9,10, and 11.
Part 2 (if applicable)	
Primary:	**Primary:**
• To estimate the effect of mild hepatic impairment on the PK of PF-06651600 following multiple dose administration.	Plasma PF-06651600 PK Parameters. • AUC_{0-24}, $C_{max.}$
Secondary:	**Secondary:**
• To evaluate safety and tolerability of multiple doses of PF-06651600.	• Assessment of TEAEs, clinical laboratory tests, vital signs, and physical exam.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate the effect of mild hepatic impairment on additional PK parameters of PF-06651600.	• T_{max}, AUC_{last} and CL/F; • C_{trough} on Days 7, 8, 9, 10 and 11.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 non-randomized, open-label, multiple-dose, parallel-cohort study to investigate the effect of hepatic impairment on the plasma PK, safety and tolerability of PF-06651600 after multiple oral doses of 30 mg QD. At Screening, the Child-Pugh classification score will be utilized to assess entry criteria and to assign participants into the appropriate hepatic-impairment group (Table 1, Table 2, and Table 3). The participants' hepatic function will be ranked based on clinical signs and liver function test (LFT) results.

Table 1. Study Cohorts Based on Hepatic Function Categories

Cohort	Description	Child-Pugh Score	Number of Participants
1	Moderate hepatic impairment	Class B (7 to 9 points)	8
2	Normal hepatic function	Not Applicable	8
3	Mild hepatic impairment	Class A (5 to 6 points)	8

Table 2. Assessment of Hepatic Impairment: Child-Pugh Scale

Assessment Parameters	Assigned Score for Observed Findings		
	1 point	2 point	3 point
Encephalopathy grade (refer to Table 3 below)	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3

Table 3. Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, behavior, personality, neurological examination, electroencephalogram.
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles persecond (cps) waves on EEG.
2	Lethargic, time-disoriented, hyperactive reflexes, rigidity, slow waves on EEG.
3a	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slow waves on EEG.
4a	Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG.

a. Participants with clinically active Grade 3 or 4 encephalopathy are excluded.

Part 1: A total of approximately 16 participants will be enrolled in Part 1: 8 participants with moderate hepatic impairment and 8 healthy participants with normal hepatic function. Healthy participants with normal hepatic function will be enrolled after completion of moderate hepatic impairment participants and will be matched for age, weight, race, and gender to the mean demographics of participants in the moderate hepatic impairment group. Healthy normal participants will be enrolled to enable comparison of PK parameters between healthy participants and participants with moderate hepatic impairment.

Age/Weight/Race/Gender Matching Criteria:

Participants with Child-Pugh Class B (moderate) hepatic impairment will be enrolled first and their demographics will be pooled. Enrollment of age-, weight-, race- and gender-matched healthy participants with normal hepatic function will begin after all of the moderate hepatic impairment participants completed the in-patient portion of the study. Demographics of the healthy participants will be matched to the pooled demographics of the moderate impairment group such that the body weight of each healthy participant will be within ±15 kg of the mean body weight of the participants with hepatic impairment, age will be within ±10 years of the mean age of the participants with hepatic impairment, and the gender ratio for the group will be similar (±2 participants per gender) to the participants with hepatic impairment. In general, care will be taken when recruiting the healthy participants such that the entire group will be closely matched as possible in age and body weight to the participants with hepatic impairment. Other demographics, such as race and ethnicity, will be considered for matching to the hepatically-impaired population when possible.

Reasonable efforts will be made to enroll an adequate number of participants (1 to 3 participants) with Child-Pugh scores of 8 and 9 to ensure that the entire range of moderate hepatic impairment is represented.

If there are participants who withdraw or discontinue treatment from the normal and moderate impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor such that the number of completed evaluable participants in each group equals approximately 8.

After evaluation of results from Part 1 (see Section 9 Statistical considerations), Part 2 may be conducted if PF-06651600 area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) geometric mean ratio (GMR) for moderate hepatic impairment group compared to normal group is ≥2.0.

If the above mentioned criterion is not met, the study will stop after Part 1.

Part 2: Based on whether the decision criterion to proceed to Part 2 is met, approximately 8 participants with mild hepatic impairment will be enrolled. As in Part 1, hepatic impairment classification will be based on the Child-Pugh score. Healthy participants will not be enrolled in Part 2. When recruiting the Part 2 participants attempts to match the entire group with respect to age, gender and body weight to the participants in Part 1will be made.

Other demographics, such as race and ethnicity, may be considered for matching to the Cohort 1 and Cohort 2 population when possible.

As in Part 1, if there are participants who withdraw or discontinue treatment from the mild impairment group and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor such that the number of completed evaluable participants in the group equals approximately 8.

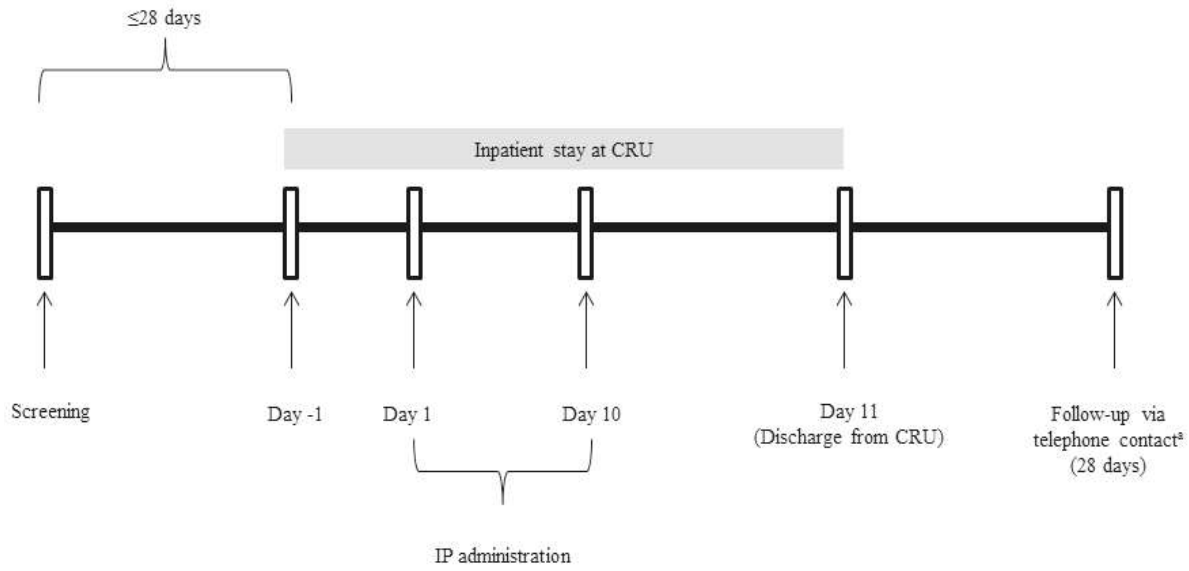
For both Parts 1 and 2: Screening will occur within 4 weeks of the first dose of study medication. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility.

Eligible participants will be admitted to the Clinical Research Unit (CRU) on Day -1 and will be confined in the CRU until Day 11. Starting on Day 1, participants will receive a 30 mg QD dose of PF-06651600 up to Day 9. On Day 10 the participants will receive a 30 mg QD dose of PF-06651600 after an 8-hour fast. Predose PK samples will be collected on Days 7, 8, 9 and 10 for assessment of minimum plasma concentration (C_{min}). Postdose serial blood samples at specified intervals (as per Schedule of Activities [SoA]) will be collected on Day 10 for 24 hours for PK assessments, prior to discharge from the CRU on Day 11.

Safety assessments (as specified in the SoA) will be performed during screening, prior to dosing on Day -1, Day 5 and Day 11. Day 1 vital signs will be collected prior to dosing. The total participation time (ie, CRU confinement time for study procedures) for each participant in this study is approximately 11 nights/12 days (excluding screening & Follow-Up contact). Participants will have a follow-up phone call 28+3 days after last dose administration to assess for AEs.

All procedures and their timelines follow the SoA. The overall study design is summarized below in Figure 1.

Figure 1. Study Design



Abbreviations: CRU = clinical research unit; IP = investigational product.

a. Follow-up telephone contact may occur as onsite visit for follow-up of clinically significant abnormal laboratory tests and/or ongoing AEs and must occur 28+3 days from administration of the final dose of investigational product.

4.2. Scientific Rationale for Study Design

The study is designed as a parallel cohort, open label study to investigate the effect of hepatic impairment on the PK of PF-06651600. The cohort of healthy participants will be served as a control group for the cohort/s with hepatic impairment. The study is designed as a 2-part study where participants with moderate hepatic impairment and normal hepatic function will be evaluated first in Part 1. Participants with mild hepatic impairment will be evaluated in Part 2 only if the results from Part 1 indicate that a dose adjustment may be required for participants with moderate hepatic impairment (ie, GMR ≥2.0).

The study will evaluate the multiple dose PK of PF-06651600 in healthy and hepatically impaired participants. CCI [redacted]

4.3. Justification for Dose

The study will use the PF-06651600 dose of 30 mg (3 × 10 mg tablets) QD, given orally for up to 10 days. The 30 mg dose of PF-06651600 is a clinically relevant dose of PF-06651600 used in efficacy and safety trials. The 30 mg dose of PF-06651600 is also appropriate considering that hepatic impairment is expected to increase the systemic exposures of PF-06651600.

Doses of PF-06651600 higher than of 30 mg QD have demonstrated their safety and tolerability for up to 14 days (dose of 400 mg QD) in healthy participants (B7981001), and up to 20 weeks (dose of 50 mg QD) in participants with AA (B7931005). The dose of 200 mg QD has demonstrated safety and tolerability for up to 8 weeks in RA participants (B7981006) (Section 2.2.4.3.2). CCI [redacted]

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 (Follow-up Phone Contact) and the investigator has reviewed the final safety data and determined that no additional evaluation is required.

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 in all 3 cohorts must meet ***all*** of the following inclusion criteria to be eligible for enrollment in the study:

Age and Sex:

1. Male or female participants who are between the ages of 18 and 70 years, inclusive, at the Screening visit.

2. Female participants are eligible to participate if they are not women of childbearing potential (WOCBP). 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:

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

Weight:

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

Informed Consent:

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

   Note: In the presence of hepatic encephalopathy, the investigator must assess if the participant is capable of giving a signed informed consent.

5.1.1. *Additional* Inclusion Criteria for Participants with Normal Hepatic Function (Cohort 2, *only*)

6. Healthy male or female participants. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead ECG, and clinical laboratory tests.

7. No known or suspected hepatic disease (see Section 5.2.1 for laboratory exclusion criteria related to hepatic function).

8. Breath alcohol test at Screening and Day -1 must be negative.

9. Participants must fit the demographic matching criteria, including:

   - A body weight that is ±15 kg of the mean of the moderate hepatic impairment group, as provided by the sponsor;
   - An age that is ±10 years of the mean of the moderate hepatic impairment group, as provided by the sponsor;
   - ***Attempts should be made*** to ensure that the male-to-female distribution in Cohort 2 is comparable to that in the moderate hepatic impairment group;
   - ***Attempts should be made*** to ensure that the race/ethnic distribution in Cohort 2 is comparable to that in the moderate hepatic impairment group.

5.1.2. *Additional* Inclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 1 and 3, *only*)

10. No other ongoing clinically significant abnormalities based on medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests except for the abnormal findings that are related to the participant's hepatic impairment.

11. Satisfy the criteria for Class A ***or*** Class B of the Child-Pugh classification (mild: Child-Pugh Scores 5-6 points, and moderate: Child Pugh Scores 7-9 points), within 28 days of investigational product administration.

12. Stable hepatic impairment, defined as no clinically significant change in disease status within the last 30 days prior to the Screening visit, documented by the participant's recent medical history (for example: no worsening of clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time [PT] by more than 50%). **If participants do not have such records, 2 screening visits (at least 14 days apart) must be performed within the 28-day screening period (Day-28 to Day -1) to demonstrate stability of the disease.**

    NOTE: Participants with encephalopathy grade 1 or 2 should be capable of providing a signed informed consent. Participants undergoing pharmacological treatment, with stable hepatic impairment, can be included in the study.

13. A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computed tomography scan, ***or*** magnetic resonance imaging (MRI). Information about the etiology of the hepatic dysfunction should be collected and maintained in the database.

14. Stable concomitant medications (as defined in Concomitant Therapy section) for the management of an individual participant's medical condition for at least 28 days prior to the first dose of investigational product. ***On a case-by-case basis***, with approval from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

15. ***Previous*** history of alcohol abuse is permissible provided that the participant is willing and able to abide by the lifestyle guidelines described in Caffeine, Alcohol, and Tobacco section of this protocol ***and*** breath alcohol tests, at Screening and on Day -1, are negative.

5.2. Exclusion Criteria

Participants in all 3 Cohorts with ***any*** of the following characteristics/conditions will ***not*** be included in the study:

Medical Conditions:

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

2. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1 (for criteria regarding tuberculosis [TB] infection, see Exclusion Criterion #6).

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

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

5. Participants who have been vaccinated with live or attenuated vaccines within 6 weeks of dosing (refer to Vaccine and Exposure to Infections Guidelines section).

6. Have evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection as evidenced by the following:

    - A positive QuantiFERON®-TB Gold In-Tube (QFT-G) test performed within the 12 weeks prior to Day 1. If the laboratory reports the test as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a purified protein derivative (PPD) test may be substituted for the QFT-G test only with approval from the Pfizer Medical Monitor on a case-by-case basis.

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

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

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

9. History of surgery that would be expected to alter absorption, distribution, metabolism and excretion properties of PF-06651600 (***for example***: status post porta-caval shunt surgery, prior bariatric surgery, gastrectomy, ileal resection).

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

10. Infection with hepatitis B or hepatitis C viruses according to protocol specific testing algorithm (refer to Section 10.2.1 Hepatitis B and C Testing Algorithm and Full Eligibility Criteria).

11. Significant trauma or major surgery within 1 month of the first dose of study drug.

12. Considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

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

Prior/Concomitant Therapy:

14. 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 investigational product on Day 1. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

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

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

15. History of significant adverse reaction to PF-06651600 or to drugs relevant to PF-06651600 (structural similarity or similar mechanism for adverse effects).

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving an investigational drug(s) within 28 days or 5 half-lives (whichever is longer) prior to Day 1.

Diagnostic Assessments:

17. A positive urine drug test for illicit drugs, at Screening or Day -1;

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

    - Hepatic impairment participants may be eligible to participate after approval from the sponsor if their drug screen is positive with a prescribed substance that is not expected to interfere with the PK of PF-06651600.

18. Screening 12-lead ECG that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy or brady arrhythmias) or indicating serious underlying heart disease (eg, cardiomyopathy, Wolff Parkinson-White syndrome).

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

20. Use of concomitant medications that prolong the QT interval.

Other Exclusions:

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

22. History of sensitivity to heparin or heparin-induced thrombocytopenia, ***only if*** heparin is used to flush intravenous (IV) catheters used during blood collections.

23. Unwilling or unable to comply with the Lifestyle Requirements outlined in Lifestyle Considerations section.

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

5.2.1. *Additional* Exclusion Criteria for Participants with Normal Hepatic Function (Cohort 2, *only*)

In addition, participants in the normal hepatic function cohort presenting with ***any*** of the following will ***not*** be included in the study:

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

26. An estimated glomerular filtration rate (eGFR) of <80 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (refer to Section 8.2.5) and serum creatinine measured with a standardized assay, with a single repeat permitted to assess eligibility, if needed.

27. ANY of the following abnormalities in clinical laboratory tests at screening:

    - Platelet count <150×109/L (150,000 cells/mm3);
    - White blood cell (WBC) count of <3.0 × 109/L (3000 cells/mm3);
    - Absolute neutrophil count (ANC) <1500 cells/mm3;
    - Absolute lymphocyte count (ALC) <800 cells/mm3;
    - Hemoglobin level <120 g/L (12.0 g/dL);
    - 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;
    - Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results. If results return to normal protocol acceptable limits within the screening period, the participant may enter the study.

28. Known or suspected hepatic impairment, including meeting ***any*** of the following criteria at Screening (with a single repeat permitted to assess eligibility, if needed):

    - Alanine aminotransferase (ALT) > upper limit of normal (ULN);
    - Aspartate aminotransferase (AST) > ULN;

- Total bilirubin > ULN;

  ***NOTE*:** Participants with Gilbert syndrome are eligible provided direct bilirubin level is ≤ ULN.

- Albumin < lower limit of normal (LLN);
- Alkaline phosphatase > ULN;
- Prothrombin time (PT) > ULN.

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

30. 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.

31. Screening supine 12-lead ECG demonstrating a corrected QT (Fridericia method, QTcF) interval >450 msec. If QTcF exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the participant's eligibility.

5.2.2. *Additional* Exclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 1 and 3, *only*)

In addition, participants in the hepatic impairment cohorts presenting with ***any*** of the following will ***not*** be included in the study:

32. Hepatorenal syndrome.

33. Life expectancy less than 1 year.

34. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than **4 weeks** prior to Screening.

35. Clinically active Grade 3 or 4 hepatic encephalopathy (refer to Table 3).

36. Ascites requiring regular large volume paracentesis.

37. Severe ascites and/or pleural effusion based on the investigator's clinical evaluation, which can be confirmed by appropriate imaging procedure (eg, ultrasound, chest X-ray, computed tomography scan/MRI).

38. Child-Pugh scores >9 points.

39. Participants who have previously had an organ transplant.

40. An eGFR of <60 mL/min/1.73 m^2 based on the CKD-EPI equation (refer to Section 8.2.5) and serum creatinine measured with a standardized assay, with a single repeat permitted to assess eligibility, if needed.

41. ANY of the following abnormalities in clinical laboratory tests at screening:

    - Platelet count <100 $\times 10^9$/L (100,000 cells/mm^3);
    - WBC count of <2.5 $\times$ 10^9/L (2500 cells/mm^3);
    - ANC <1500 cells/mm^3;
    - ALC <800 cells/mm^3;
    - Hemoglobin level <100 g/L (10 g/dL);
    - In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality (except for those parameters influenced by hepatic impairment) that could affect interpretation of study data or the participant's participation in the study;
    - Screening laboratory tests with abnormal results (except for those parameters influenced by hepatic impairment) may be repeated once to confirm abnormal results. If results return to normal protocol acceptable limits within the screening period, the participant may enter the study.

42. Screening supine BP >160 mm Hg (systolic) or >100 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is >160 mm Hg (systolic) or >100 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.

43. Screening ***supine*** 12-lead ECG demonstrating a QTcF interval >470 msec. If QTcF exceeds 470 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the participant's eligibility.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Vaccine and Exposure to Infections Guidelines

5.3.1.1. Subject Specific Recommendations

It is recommended that all participants should be up-to-date with respect to standard of care vaccinations. Vaccination of participants with live attenuated vaccines, eg, FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella)

vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live), is prohibited within the 6 weeks prior to first dose of investigational product, for the duration of the study, and for 6 weeks following completion of the study.

5.3.1.2. Guidance Regarding Household Contact Vaccine-Related Exposure

Current routine household contact with children and others who have been vaccinated with live attenuated vaccines may pose a risk during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines for immunosuppressed participants suggest that exposure (through routine contact) should be avoided following vaccination (of others) with these vaccines for the stated time period:

a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;

b. Oral polio vaccination for 6 weeks following vaccination;

c. Attenuated rotavirus vaccine for 10 days following vaccination;

d. FluMist® (intranasal flu vaccine) for 1 week following vaccination.

Participants should avoid exposure to recently vaccinated or infected persons and contact the investigator promptly should they develop signs or symptoms of infections.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations, and 8 hours prior to the collection of the predose PK sample and dose administration on Day 10. Water is permitted until 1 hour prior to dosing;

- On Days 1 through Day 9, PF-06651600 can be administered and collection of any PK samples will be under non-fasting conditions. Breakfast or snack or a light meal may be offered 1 hour after dosing.

- Water may be consumed without restriction beginning 1 hour after dosing. Drinks (except grapefruit or grapefruit-related citrus fruit juices-see below) may be consumed with meals and the evening snack;

- All participants (within each clinical site) will receive standardized meals for breakfast, lunch and dinner throughout the study. While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal;

- Breakfast will be provided on all days except on Day 10 (dosing day);

- Lunch will be provided approximately 4 hours after dosing;
- Dinner will be provided approximately 9 to 10 hours after dosing;
- An evening snack may be permitted;
- Participants will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of investigational product until collection of the final PK blood sample.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for ≥24 hours prior to the dose of investigational product on Day 1 (*plus* have a negative breath alcohol test on Screening and Day -1) and continue abstaining from alcohol through their confinement at the CRU.
- Participants will undergo a breath alcohol test at time points indicated in the SoA and may undergo additional testing at the discretion of the investigator.
- Consumption of caffeinated drinks and nicotine-containing products (≤5 cigarettes per day or equivalent) is permitted during participation in the study; however, participants will abstain from nicotine- or caffeine-containing products for at least 2 hours prior to any scheduled electrocardiogram or blood pressure determinations.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Rescreening may only occur with Sponsor approval.

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

For this study, the investigational product is PF-06651600.

PF-06651600 will be supplied by Pfizer as 10 mg round white to off-white tablets in bulk along with individual dosing containers and desiccants for unit dosing.

6.1.1. Administration

PF-06651600 will be administered at approximately 08:00 (±2 hours) from Day 1 until Day 10. PF-06651600 will be administered under non-fasting conditions on Days 1 to 9 and under fasting conditions on Day 10. Participants will swallow PF-06651600 whole, and will not chew PF-06651600 prior to swallowing.

Investigator site personnel will administer PF-06651600 during each period with ambient temperature water to a total volume of approximately 240 mL. In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating and drinking beverages other than water during the first 4 hours after dosing.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

4. 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. 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 in documentation to the site by the sponsor or designee.

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

6.2.1. Preparation and Dispensing

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

PF-06651600 tablets will be prepared at the CRU in the individual dosing containers by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers with desiccant and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

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

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

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 as defined in the SoA.

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

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

Participants with Normal Hepatic Function (Cohort 2, Only)

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

- Acetaminophen/paracetamol may be used at doses of <1 g/day.
- Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis after approval by the sponsor.

Participants with Impaired Hepatic Function (Cohorts 1 and 3)

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

6.5.1. Rescue Medicine

(Not Applicable).

6.6. Dose Modification

Dose modification for PF-06651600 is not allowed.

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 investigational product. If investigational product is permanently discontinued, the participant will remain in the study to be evaluated for safety.

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

See Appendix 8 (Section 10.8) for guidelines for participant safety monitoring and discontinuation

7.2. Participant Discontinuation/Withdrawal From the Study

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the 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 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, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

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

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

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

Withdrawal of Consent:

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

7.3. Lost to Follow up

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

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

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

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

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

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1 (Section 10.1).

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), this should be discussed with the Study Team.

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

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

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

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

If an intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate 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 105 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 concerns.

8.2.1. Physical Examinations

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

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

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

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

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Twelve (12)-Lead single 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 QTcF 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.

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 QTcF value is prolonged, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7 (Section 10.7).

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical safety laboratory tests to be performed and the SOA for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 calendar 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.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

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

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

8.2.5. Estimated Glomerular Filtration Rate

eGFR will be calculated using the following equation developed by the CKD-EPI, which utilize serum creatinine (SCr):

CKD-EPI

- If female and SCr is ≤0.7 mg/dL:

  Glomerular filtration rate (GFR) (mL/min/1.73 m^2) = 144 × $(SCr/0.7)^{-0.329}$ × 0.993^{age} (× 1.159, if black).

- If female and SCr is >0.7 mg/dL:

  GFR (mL/min/1.73 m^2) = 144 × $(SCr/0.7)^{-1.209}$ × 0.993^{age} (× 1.159, if black).

- If male and SCr is ≤0.9 mg/dL:

  GFR (mL/min/1.73 m^2) = 141 × $(SCr/0.9)^{-0.411}$ × 0.993^{age} (× 1.159, if black).

- If male and SCr is >0.9 mg/dL:

  GFR (mL/min/1.73 m^2) = 141 × $(SCr/0.9)^{-1.209}$ × 0.993^{age} (× 1.159, if black).

8.2.6. Pregnancy Testing

Pregnancy Testing will not be performed in this study since no WOCBP will be enrolled.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3 (Section 10.3).

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28+3 calendar days after the last administration of the investigational product.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

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

If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06651600 greater than 800 mg within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-06651600 can no longer be detected systemically (at least 4 days).
3. Obtain a blood sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately 0.5 mL plasma, will be collected for measurement of plasma concentrations of PF-06651600 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 (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT). Collection of samples more than 10 hours after 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).

Samples will be used to evaluate the PK of PF-06651600. Samples collected for analyses of PF-06651600 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, or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of PF-06651600 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

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

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for deoxyribonucleic acid (DNA) isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response. Genes and other analytes (eg, proteins, ribonucleic acid [RNA], nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in lab manual and other supporting documentation.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

In Part 1 approximately 16 participants will be enrolled (8 with moderate hepatic impairment and 8 with normal hepatic function). If it is decided to conduct Part 2, in Part 2 approximately 8 participants with mild hepatic impairment will be enrolled. The sample size is based on recommendation from the "Food and Drug Administration (FDA) Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".

Additional participants can be enrolled at the discretion of the sponsor to ensure an adequate number of participants in each group (approximately 8) with evaluable PK data. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Refer to Section 4.1 and Section 5.4 for details.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

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

9.4. Statistical Analyses

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

Analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06651600 AUC_{0-24} and maximum plasma concentration (C_{max}) between normal hepatic function group (Reference) and the moderate impaired hepatic function group (Test). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the geometric means (Test/Reference) and 90% CIs for the ratios.

Part 2 may be conducted if PF-06651600 AUC_{0-24} geometric mean ratio for moderate hepatic impairment group compared to normal group is ≥2.

Part 2

ANOVA will be used to compare the natural log transformed PF-06651600 AUC_{0-24} and C_{max} between normal hepatic function group (Reference) and the moderate and mild impaired hepatic function groups (Tests). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the geometric means (Test/Reference) and 90% CIs for the ratios.

Box and whisker plots for individual participant parameters (AUC_{0-24} and C_{max}) will be constructed by hepatic function group and overlaid with geometric means.

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

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, 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, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

9.4.3. Other Analyses

Pharmacogenomic (PGx) and biomarker data will be collected and retained for future analyses, but will not be analyzed, specifically, for this study.

9.4.3.1. Pharmacokinetic Analyses

9.4.3.1.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

PK parameters of PF-06651600 following single dose administration will be derived from the concentration time profiles as shown below in Table 4.

Table 4. Derivation of PK Parameters

Parameter	Definition	Method of Determination
AUC_{0-24}	Area under the plasma concentration-time profile from time 0 to 24 hours.	Linear/Log trapezoidal method.
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
C_{max}	Maximum plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.
CL/F	Apparent Clearance.	Calculated as AUC_{0-24}/Dose.
C_{trough}	Pre-dose concentration.	Observed from data as plasma concentration at 24 hours post-dose.

Abbreviation: PK = pharmacokinetic(s).

9.5. Interim Analyses

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

Additionally, PK data will be analyzed upon completion of Part 1 and based on the results decision will be made whether to progress to Part 2 (See Statistical Analyses section for details).

9.5.1. Data Monitoring Committee

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

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

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD) system.

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

advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 5) 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 concerns.

Table 5. 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)
PT/INR
	BUN/urea 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]
			At screening only:
			• FSH[b]
			• Urine drug testing[c]
			• Hepatitis Screening
			  • HBsAg ,HBcAb
			  • HCVAb[d]
			• Human immunodeficiency virus
			• QuantiFERON-TB Gold Test or PPD
			• eGFR-CKD-EPI
			• Breath alcohol[e]
			
			Testing as indicated:
			• FACS-TBNK

	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		

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CO_2 = carbon dioxide; eGFR = estimated glomerular filtration rate; FACS-TBNK = fluorescence-activated cell sorting- T-,B- and natural killer cells; FSH = follicle-stimulating hormone; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = Hepatitis C antibody; GGT = gamma-glutamyl transferase; INR = international normalized ration; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PPD = purified protein derivative; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell.

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. At Screening and Admission (Day -1). The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. HCV RNA reflex testing required if HCVAb is positive.
e. Complete at screening and Day -1.

Investigators must document their review of each laboratory safety report.

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

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

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

At screening, hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) will be tested:

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

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

c. If HBsAg is negative and HBcAb is positive, hepatitis B surface antibody (HBsAb) reflex testing is required:

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

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

At screening, hepatitis C antibody (HCVAb) will be tested:

a. Participants who are HCVAb positive will be reflex-tested for hepatitis C (HCV) RNA.

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

10.2.2. Tuberculosis Testing

During the Screening period, it must be determined and documented that a participant does not have evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) per the Inclusion Criteria. Participants with a negative TB screening conducted in the 12 weeks prior to Day 1 visit or during the Screening period must be documented in study records prior to Day 1.

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

10.2.2.1. Purified Protein Derivative Test

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

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the

participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the

sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

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

10.4.1. Male Participants Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study based on the following considerations:

- PF-06651600 is not likely to transfer to a partner through semen at pharmacologically relevant levels.

10.4.2. Female Participant Reproductive Inclusion Criteria

Only females who are not a WOCBP (see definitions below in Section 10.4.3) are eligible to participate. Therefore, no contraception methods are required for female participants.

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

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

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

3. Postmenopausal female.

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

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

Collection of Pregnancy Information

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

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

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

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06651600 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Samples for specified genetic analysis (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same 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.

Participants with significant laboratory abnormalities may require immediate re-testing (within 24-48 hours) and further monitoring. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

Special Considerations for Participants with Hepatic Impairment:

In this study, participants with mild and moderate hepatic impairment will be enrolled. A thorough review of participant's eligibility is required to ensure that only those with the aforementioned hepatic impairment categories based on Child-Pugh classification (Table 1, Table 2, and Table 3) are enrolled in the study. Participants with a history of severe ascites who are receiving treatment to control or prevent recurrence of severe ascites shall be assessed with a point score for the current degree of ascites; such participants should only be on pharmacological treatment. Participants requiring regular large volume paracentesis should be excluded from the study (refer to Section 5.1.2).

Participants with a history of stage 3 or stage 4 encephalopathy who are receiving medical treatment (eg, lactulose, neomycin, or xifaxan) to prevent recurrent encephalopathy should receive the point score for the current degree of encephalopathy. Participant with a clinically active stage 3 or 4 encephalopathy should be excluded from the study; participants with some degree of encephalopathy (ie, encephalopathy grade 1 and 2) should be capable of giving a signed informed consent. Only participants with documented stable hepatic impairment, including those with allowed treatment for hepatic impairment, can be enrolled in the study (refer to Inclusion Criteria 12). At any time point during a participant's study participation, any perceived clinical indication of potential worsening of hepatic impairment must be thoroughly evaluated and discussed with Pfizer clinician/designee for possible discontinuation from the study.

Participants with hepatic impairment may have preexisting ALT, AST, TBili values at baseline that may be above the ULN. Since such laboratory parameters are used in evaluating cases of potential DILI, a thorough investigation of any clinically significant changes or abnormalities in ALT, AST, TBili is required based on the participant's baseline values and overall clinical status. Any additional diagnostic procedures deemed clinically appropriate in order to fully evaluate the possibility of DILI on the background of hepatic impairment may be performed upon discussion with the Pfizer clinician or designee. Note that for any indication of potential worsening of hepatic impairment based on the investigator's clinical judgment, the Pfizer clinician or designee should be immediately notified for potential withdrawal of the study participant.

Refer to Appendix 8, Section 10.8: Guidelines for Participant Safety Monitoring and Discontinuation.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

- Marked sinus bradycardia (rate <40 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) atrioventricular (AV) block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

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

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

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes). • Type II second-degree (Mobitz II) AV block. • Complete (third-degree) heart block.
ECG Findings That Qualify as Serious Adverse Events
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30 seconds' duration). • Second- or third-degree AV block requiring pacemaker placement. • Asystolic pauses requiring pacemaker placement. • Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion. • Ventricular fibrillation/flutter. • At the discretion of the investigator, any arrhythmia classified as an adverse experience.
The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to ALL participants in Study B7981016. **Additional individual participant monitoring is at the discretion of the investigator and dependent on any safety concerns**. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a participant may be withdrawn for safety reasons at any time at the discretion of the investigator.

10.8.1. Participant Safety Monitoring

All potential treatment-related events of rash will be followed up until resolution or agreement with Pfizer.

The following laboratory abnormalities require immediate re-testing (within 24-48 hours) until resolution or agreement with Pfizer:

Laboratory Variable	Laboratory Value
Absolute Neutrophil Count	<1000/mm^3 (<1.0 × 10^9/L)
Hemoglobin	<10 g/dL (<6.21 mmol/L or <100 g/L) OR Decrease of ≥2.0 g/dL from baseline
Platelet count	<100,000/mm^3 (<100.0 × 10^9/L)[a]
Absolute Lymphocyte Count[b]	<600/mm^3 (<0.6 × 10^9/L)
Creatine kinase[c]	>3 × ULN
Aspartate aminotransferase	See Section 10.6, Appendix 6 for potential cases of drug-induced liver injury.
Alanine aminotransferase	See Section 10.6, Appendix 6 for potential cases of drug-induced liver injury.
Total bilirubin	See Section 10.6, Appendix 6 for potential cases of drug-induced liver injury.

Abbreviation: ULN = upper limit of normal; FACS-TBNK = fluorescence-activated cell sorting- T-,B- and natural killer cells.

a. <75,000/mm^3 (<75.0 × 10^9/L) for participants with hepatic impairment.
b. Participants with absolute lymphocyte count <500/mm^3 (0.5 × 10^9/L) will be reflex-tested for FACS-TBNK until the absolute lymphocyte count resolves or stabilizes at a level acceptable to the investigator and sponsor.
c. In addition to re-testing creatinine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN.

10.8.2. Participant Discontinuation Criteria

Treatment will be discontinued and the participant withdrawn from this study for:

Adverse Events:

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment or meeting other criteria that require the infection to be classified as serious adverse event;

- Treatment-related SAEs;
- Other serious or severe AEs, at the discretion of the investigator or sponsor.

ECG Findings:

- Confirmed QTcF >500 msec;
- Confirmed change from baseline in QTcF of >60 msec.

Laboratory Abnormalities:

All the following laboratory abnormalities require discontinuation if they are confirmed:

- Absolute Neutrophil Count <750/mm^3 (<0.75 × 10^9/L);
- Hemoglobin <9.0 g/dL (<5.59 mmol/L or <90 g/L) or a decrease of >30% from baseline (either criterion or both);
- Platelet count <75,000/mm^3 (<75.0 × 10^9/L);

  NOTE: Platelet count <50,000/mm3 (<50.0 × 109/L) for participants with hepatic impairment.

- Absolute Lymphocyte Count <500/mm^3 (<0.5 × 10^9/L).

  NOTE: Participants with absolute lymphocyte count <500/mm3 (0.5 × 109/L) will be reflex tested for fluorescence-activated cell sorting- T-,B- and natural killer cells (FACS-TBNK) until the absolute lymphocyte count resolves or stabilizes at a level acceptable to the investigator and sponsor.

- Creatine kinase >10 × ULN.

  NOTE: In addition to re-testing creatinine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN.

NOTE: In each case, if there is a need for additional investigations or diagnostic procedures, it should be promptly discussed with the Pfizer clinician or designee.

Additional Discontinuation Criteria For Participants with Normal Hepatic Function (Cohort 2):

- AST or ALT that meet ANY of the following:
  - >3 × ULN with at least one total bilirubin value >2 × ULN;

- >3 × ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

- Two sequential AST or ALT elevations >5 × ULN, regardless of total bilirubin or accompanying signs or symptoms.

Additional Discontinuation Criteria For Participants with Impaired Hepatic Function (Cohorts 1 and 3):

- AST or ALT >5 × Baseline values OR >20 × ULN, whichever is smaller, regardless of total bilirubin or accompanying signs or symptoms;

- AST or ALT >3 × Baseline value with at least one total bilirubin value >2 × Baseline value;

- AST or ALT >3 × Baseline values accompanied by signs or symptoms consistent with worsening hepatic injury (eg, increase from Baseline in PT/INR by >50%);

- Worsening in the category of hepatic impairment (ie, change from mild to moderate or severe, or change from moderate to severe per Child Pugh Classification);

- Any signs of bleeding that is considered clinically significant and secondary to hepatic impairment (eg, bleeding esophageal varices);

- New or clinically significant worsening of ascites;

- New or clinically significant worsening of encephalopathy;

- New or clinically significant worsening of pleural effusion;

- Any other clinically significant conditions consistent with clinically significant worsening of hepatic function that, as per assessment by the investigator or by the Pfizer Clinician/designee, may require urgent medical, surgical or other therapeutic intervention.

Prohibited Medications:

Participants who are treated with any prohibited medication during the course of the study may require discontinuation. Participants who are administered a prohibited medication should be discussed with the sponsor for possible withdrawal from the study.

Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers or sensitive or moderate sensitive CYP3A4 substrates.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Abs	absolute
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from zero to time of last measurable concentration
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BID	twice a day
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CD	Crohn's Disease
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CYP450	cytochrome P450
DC	discontinuation

Abbreviation	Term
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein Barr Virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS-TBNK	fluorescence-activated cell sorting- T-,B- and natural killer cells
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
JAK	Janus kinase

Abbreviation	Term
LFT	liver function test
LLN	lower limit of normal
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable
NOAEL	no observed adverse effect level
PCD	primary completion date
PD	pharmacodynamic(s)
PGx	pharmacogenomic
PK	pharmacokinetic(s)
PPD	purified protein derivative
PT	prothrombin time
PVC	premature ventricular complexes
QD	once daily
QFT-G	QuantiFERON®-TB Gold In-Tube
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
TB	tuberculosis
TEAEs	treatment emergent adverse events
TEC	hepatocellular carcinoma
TBili	total bilirubin
THC	tetrahydrocannabinol
TYK2	tyrosine kinase 2
UC	ulcerative colitis
ULN	upper limit of normal

Abbreviation	Term
US	United States
Vz/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

(None).