A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE STUDY TO COMPARE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-04965842 IN ADULT SUBJECTS WITH MILD AND MODERATE HEPATIC IMPAIRMENT RELATIVE TO SUBJECTS WITH NORMAL HEPATIC FUNCTION

Investigational Product Number:	PF-04965842
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	B7451020
Phase:	1

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	23 July 2018	Not applicable (N/A)

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SCHEDULE OF ACTIVITIES

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

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

Visit Identifier	Screening ≤-28[a]	Day -1	Day 1										Day 2		Day 3	Day 4	Follow-up Contact
																	Days 29-36
Hours Postdose			**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**14**	**24**	**36**	**48**	**72**	**--**
Informed consent	X																
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Eligibility assessment (inclusion/exclusion criteria)	X	X															
Child-Pugh Classification	X[b]																
Demography	X																
Medical history	X																
PE (height & body weight at Screening, only)[c]	X	X														X	
Alcohol/tobacco use & Breath alcohol test	X	X															
Contraception use	X	X															X
Single, supine 12-lead ECG	X	X				X										X	
Vital assessment (blood pressure & pulse rate)	X		X													X	
Safety laboratory tests (blood & urine)[d]	X	X				X							X			X	
HepBcAb, HepBsAb, HepBsAg, HCVAb[e], HIV tests	X																
QFT-G Test or PPD skin test[f]	X																
Serum or urine pregnancy test (WOCP only)[g]	X	X														X	
Serum FSH in post-menopausal females amenorrheic ≥12 months only	X																
[redacted]		[redacted]															
[redacted]		[redacted]															

Visit Identifier	Screening ≤-28[a]	Day -1	Day 1										Day 2		Day 3	Day 4	Follow-up Contact
																	Days 29-36
Hours Postdose			**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**14**	**24**	**36**	**48**	**72**	**--**
Investigational product administration			X														
PK blood sampling for PF-04965842 [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine drug test	X	X															
Prior/concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Serious and non-serious AE monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
CRU discharge																X	

Abbreviations: →= ongoing/continuous event; AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HepBcAb = hepatitis B core antibody; HepBsAb = hepatitis B surface antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HCV RNA = Hepatitis C virus ribonucleic acid; HIV = human immunodeficiency virus; PE = physical examination; PK = pharmacokinetics; PPD= purified protein derivative; QFT-G = QuantiFERON®-TB Gold; TB = tuberculosis; WOCP = women of childbearing potential.

a. Screening must occur within 28 days prior to investigational product administration.

b. A second Screening visit to be performed for hepatic impairment subjects if a subject is not able to provide documentation of stable hepatic impairment, defined as no clinically significant change in disease status within the 28 days prior to the Screening visit, as documented by the subject's recent medical history (for example: no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time by more than 50%). Refer to Screening section for details.

c. Full PE at Screening; limited PE at all other time points.

d. Includes chemistry, hematology and urinalysis (and microscopy, if needed).

e. HCV RNA reflex testing required if HCVAb is positive.

f. A chest x-ray is required if a positive QFT-G or PPD, unless previously performed and documented within 12 weeks prior to screening.

g. Serum pregnancy test must be used at the Screening visit. Urine or serum pregnancy test may be used on Day -1 and Day 4. Day -1 pregnancy test must be negative in order for the subject to be dosed on Day 1.

[redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-04965842 is a janus kinase (JAK) 1 inhibitor that is currently being developed for the treatment of atopic dermatitis (AD).

The JAK family, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function. Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK dimer or trimer combination to transduce their signal. JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL) -4, -5, -6, -13,-21, -31, interferon gamma (IFN-γ), and interferon alpha (IFN-α). JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones including erythropoietin, IL-3, granulocyte-macrophage colony-stimulating factor and prolactin. IL-12 and IL-23 are dependent on TYK2 and JAK2 for transmitting their signals.

Following cytokine activation, receptor-associated JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs.[1] Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription.[2]

Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-22, IL-31, and IFN-γ, require JAK1 for signal transduction, suggesting that selective JAK1 inhibitors, that modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[3]

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. PF-04965842 has a high degree of selectivity against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated subjects with moderated to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

1.2. Background

1.2.1. Overview of Disease State

AD also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[4,5] Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves until late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time.

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a topical treatment in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD. In addition, dupilumab, an injectable monoclonal antibody targeting IL-4 and IL-13 was recently approved for the treatment of AD. Additional treatments generally reserved for severe AD include phototherapy and systemic agents (eg, corticosteroids, ciclosporin, recombinant IFN-γ, mycophenolate mofetil, methotrexate, azathioprine, intravenous [IV] immunoglobulin).[6]

1.2.2. Rationale for Development of PF-04965842

PF-04965842 is being developed as an oral treatment for patients with moderate to severe AD based on its mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies. The clinical development program for PF-04965842 includes healthy subjects, subjects with psoriasis and subjects with AD.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure. A summary of the components relevant to this study are presented below.

1.2.3. Previous Human Experience with PF-04965842

PF-04965842 has been assessed in 5 completed clinical studies: 3 Phase 1 studies in healthy subjects (B7451001, B7451004, and B7451008), 1 Phase 2 study in subjects with psoriasis (B7451005) and 1 Phase 2 study in subjects with AD (B7451006). A total of 423 subjects received PF-04965842 or placebo in the 5 completed clinical studies with 335 subjects having received at least 1 dose of PF-04965842 (n=61 in Study B7451001; n=12 in Study B7451004; n=6 in study B7451008, n=45 in Study B7451005; n=211 in Study B7451006).

1.2.3.1. Summary of Safety Data from Completed Studies

Based on the clinical experience with PF-04965842 and its mechanism of action, the potential risks of treatment with JAK inhibitors include: (1) viral reactivation; (2) serious infection and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) decreased neutrophil counts; (6) decreased platelets; and (7) alterations in the lipid profile.

In the completed Phase 1 and 2 studies in healthy subjects, subjects with psoriasis and subjects with AD, PF-04965842 was generally safe and well tolerated.

In the completed Phase 1 studies in healthy subjects receiving single doses of PF-04965842 up to 800 mg and multiple doses up to 200 mg twice daily (BID) or 400 mg once daily (QD), the most commonly reported adverse events (AEs) were diarrhea, nausea, vomiting, headache, acne, and dizziness. Following single or multiple dose of PF-04965842, most reported treatment emergent AEs (TEAEs) were mild or moderate in severity. In Study B7451001, during the single-ascending dose phase, 1 subject in the placebo group had maximum QT interval corrected for heart rate using Fridericia's correction (QTcF) of 450 to <480 msec, and 1 subject in the PF-04965842 800 mg treatment group had maximum QTcF interval increase from baseline of 30 to <60 msec. In the multiple-ascending dose phase, 3 subjects (1 each in the placebo, PF-04965842 30 mg QD, and 100 mg QD treatment groups) had maximum QTcF interval of 450 to <480 msec, and 2 subjects in the PF-04965842 200 mg BID treatment group had maximum QTcF interval increase from baseline of 30 to <60 msec. There were no clinically significant changes in electrocardiogram (ECG) findings in Studies B7451004 and B7451008.

In the completed Phase 2 study in subjects with moderate to severe psoriasis (Study B7451005), the most frequently reported AEs across the PF-04965842 treatment groups (200 mg BID, 200 mg QD, and 400 mg QD) were nausea, followed by headache. Other commonly reported AEs included neutropenia and neutrophil counts decreased, thrombocytopenia and platelet count decreased. One of the subjects in the 200 mg QD group with an AE categorized as infections and infestations was reported as having VIIth nerve paralysis (Bell's palsy) and later developed herpes zoster (shingles). The incidences of normal and abnormal ECG recordings were similar across all treatment groups at each time point. None of the abnormal ECG recordings were determined to be clinically significant by the investigator.

In the completed 12-week Phase 2b study (Study B7451006) in subjects with AD, AEs and serious AEs (SAEs) were numerically higher in subjects receiving PF-04965842 (10, 30, 100, and 200 mg QD) compared to placebo, but did not appear to increase with dose. The most common AEs were in the infections and infestations, skin and subcutaneous tissue disorders and gastrointestinal disorders system organ class (SOC), and the majority of the AEs were mild. The most commonly reported TEAE across all the treatment groups was dermatitis atopic (38 events), and viral upper respiratory tract infection (33 events). The most frequently reported treatment-related TEAE was nausea. There were 2 cases of non-serious herpes zoster, 1 in the 10 mg group (not treatment-related), and 1 in the 30 mg group (treatment-related). There were 2 subjects (doses of ≥100 mg QD) with treatment related SAEs reported, the SAEs were eczema herpeticum and pneumonia. One (1) subject randomized to the PF-04965842 10 mg group reported an SAE of malignant melanoma. Dose-dependent mean platelet count decreases from baseline were observed with a nadir at Week 4. At Week 4 the mean platelet count and the 90% confidence interval (CI) were within the normal reference range for both the 100 mg dose and 200 mg dose. In these treatment groups, the mean platelet count increased towards baseline after Week 4. There were no clinically significant findings in vital signs or physical examinations. Most of the

ECG results were normal. The incidences of normal and abnormal ECG recordings were similar between PF-04965842 and placebo groups at each time point.

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1.3. Rationale for Study

CCI

The primary purpose of this non-randomized, single-dose, open-label study is to characterize the effect of mild and moderate hepatic impairment on the plasma PK of PF-04965842 following administration of a single 200 mg oral dose.

1.3.1. Rationale for Study Design

This is a Phase 1 non-randomized, open-label, single-dose, parallel-group study of PF-04965842 in subjects with mild and moderate hepatic impairment and subjects with normal hepatic function, matched for age, body weight and as much as practically possible gender. Details on age- and body weight- matching criteria are specified in Study Overview section.

The Child-Pugh classification system (refer to Table 1, Table 2 and Table 3) will be used to define the two cohorts of subjects with mild (Child-Pugh Class A) and moderate hepatic impairment (Child-Pugh Class B). All subjects will be required to offer their own consent to participate in this study; as such subjects with clinically active Grade 3 or Grade 4 encephalopathy (refer to Table 3) will be excluded.

CCI [redacted] ll subjects enrolled in this study will receive 1 single oral 200 mg dose of PF-04965842. To adequately characterize the elimination phase of the plasma PF-04965842 concentration-time profile in the cohorts with mild and moderate hepatic impairment, where the elimination half-life of PF-04965842 may be prolonged, the PK sampling will be collected serially up to 72 hours postdose.

CCI [redacted] subjects will be excluded if there is concomitant clinical evidence of renal impairment – defined as estimated glomerular filtration rate (eGFR) ≤60 mL/min. This is to enable a more clear assessment of the effect of hepatic impairment on PF-04965842 disposition.

Subjects with severe hepatic impairment (Child-Pugh Class C, score: >9) are not selected for this study because (1) the percent of subjects with severe hepatic disease is low for the indication under development, and (2) these subjects are already at risk of infection from their hepatic disease and further exposure to an immunosuppressant and trial-related procedures and restrictions would pose an undue risk.

CCI [redacted] In order to minimize the variability in the PK of PF-04965842 due to drug-drug interactions (DDIs), use of inhibitors and inducers of CCI [redacted] is not permitted during the study and within 14 days or 5 half-lives (whichever is longer) prior to administration of investigational product. Refer to Concomitant Treatment(s) section for complete details regarding permitted and excluded concomitant medications.

CCI [redacted] CCI [redacted]

PF-04965842 is not teratogenic based on nonclinical studies. Both male and female subjects of childbearing potential, as well as female subjects who are of non-childbearing potential, will be enrolled given the availability of embro-fetal development (EFD) toxicity studies with PF-04965842. In addition, the nonclinical data support no need for male contraception because PF-04965842 is not genotoxic, and the amount of PF-04965842 estimated to be available to a partner via drug in ejaculate is well below the developmental no-observed-adverse-effect level (NOAEL) in the definitive rat and rabbit EFD studies. PF-04965842 did not affect male fertility or spermatogenesis but did decrease female fertility. However measures will be taken to limit the risk of pregnancy in female subjects (refer to SCHEDULE OF ACTIVITIES, Contraception section and Pregnancy Testing section).

1.3.2. Rationale for Dose

A single oral dose of 200 mg PF-04965842 will be used in this study as it is the highest dose being evaluated in the Phase 3 AD program. This dose selection also takes into account safety considerations for subjects with mild and moderate hepatic impairment in whom an increase in plasma concentration of PF-04965842 may be observed. Oral doses of PF-04965842 as high as 800 mg (single dose), repeated doses as high as 400 mg QD and 200 mg BID (up to 10 days), and 200 mg QD (up to 12 weeks) have been found to be safe and well tolerated. Thus, based on the safety data of PF-04965842 and prior clinical experience, with the single oral dose of 200 mg, exposure (AUC_{inf}) increase up to ~ 8.2-fold CCI [redacted] if observed in subjects with mild and moderate hepatic impairment is not likely to pose any additional safety risks.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4. Summary of Benefit Risk Assessment

This is a single dose study to assess the PK of PF-04965842 in subjects with and without hepatic impairment. CCI [redacted]

There is no known benefit for subjects participating in this trial. The data from this study will be used to develop the dosing recommendations for the target patient population so that dose and/or dosing interval may be adjusted appropriately in the presence of hepatic disease. Based on the clinical safety profile of PF-04965842, the risk to subjects receiving a single 200 mg dose is deemed to be minimal. Appropriate risk evaluation and monitoring have been incorporated into this protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To estimate the effect of mild and moderate hepatic impairment on the PK of PF-04965842 following single oral administration in adult subjects with hepatic impairment relative to age- and body weight-matched subjects with normal hepatic function.	Plasma PF-04965842 PK parameters: • C_{max}, AUC_{inf}.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of a single oral dose of PF-04965842.	• Assessment of TEAEs, clinical laboratory tests, vital signs, physical exam, and 12-lead ECGs.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1 non-randomized, open-label, single-dose, parallel-cohort study to investigate the effect of mild and moderate hepatic impairment on the plasma PK, safety and tolerability of PF-04965842 after a single 200 mg oral dose.

At Screening, the Child-Pugh classification score will be utilized to assess entry criteria and to assign subjects into the appropriate hepatic-impairment group (Table 1, Table 2 and Table 3). The subjects' hepatic function will be ranked based on clinical signs and liver function test (LFT) results.

Table 1. Hepatic Function Categories Based on Child-Pugh Score

Cohort	Description	Child-Pugh Score	Number of Subjects
1	Moderate hepatic impairment	Class B (7 to 9 points)	8
2	Mild hepatic impairment	Class A (5 to 6 points)	8
3	Normal hepatic function	Not Applicable	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
Prothrombin time, seconds prolonged	<4	4 to 6	>6

Table 3. Determination of Encephalopathy Grade

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

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

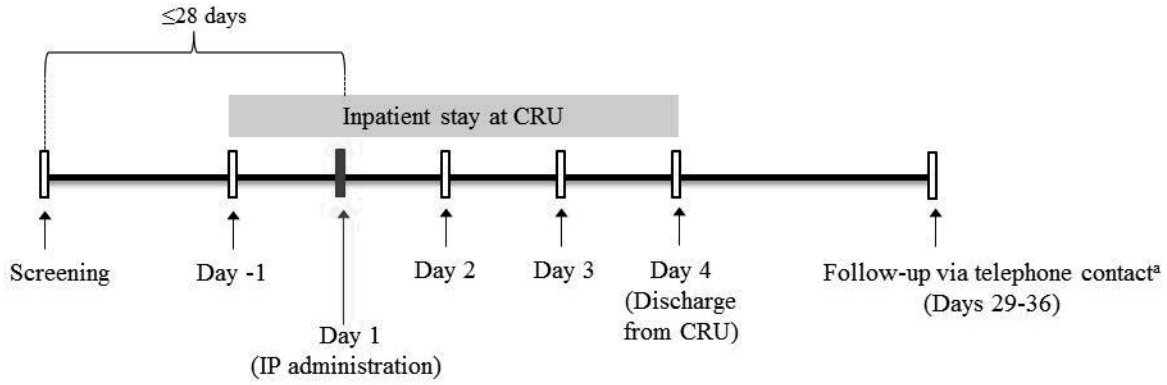
A minimum of 24 subjects with varying degrees of hepatic function will be enrolled into the study, with approximately 8 subjects in each cohort. Subjects who withdraw/discontinue early from the study may be replaced at the discretion of the sponsor.

Recruitment for subjects with moderate and mild hepatic impairment (Cohorts 1 and 2) will initiate first and these subjects will be enrolled in parallel. Subjects with normal hepatic function (Cohort 3) will be enrolled after the completion of subjects in Cohorts 1 and 2 (in-patient portion of the study) to match the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; and as much as practically possible gender) across the pooled Cohorts 1 and 2. Approval from the sponsor must be obtained ***before*** proceeding with dosing subjects in Cohort 3.

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

The overall study design is summarized below in Figure 1. For individual subjects, the total maximum duration of study participation from the Screening visit to the end of clinical research unit (CRU) stay is approximately 31 days and approximately 63 days from the Screening visit to the Follow-up contact.

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.

4. SUBJECT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria

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

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

- Female subjects of nonchildbearing potential must meet at least one of the following criteria:

  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; ***and*** have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

  - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

  - Have medically confirmed ovarian failure.

  All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

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

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

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

4.1.1. *Additional* Inclusion Criteria for Subjects with Normal Hepatic Function (Cohort 3, *only*)

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

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

7. Subjects must fit the demographic-matching criteria, including:

   - A body weight that is ±15 kg of the median of the pooled hepatic impairment cohorts, as provided by the sponsor;

   - An age that is ±10 years of the median of the pooled hepatic impairment cohorts, as provided by the sponsor;

   - ***Attempts will be made*** to ensure that the male-to-female distribution in Cohort 3 is comparable to that in the pooled hepatic impairment cohorts;

- Given that [redacted] of metabolism is mediated by [redacted] attempts will be made to match the number of [redacted] subjects in Cohort 3 as closely as practically possible to the pooled hepatic impairment cohorts.

8. Normal hepatic function with no known or suspected hepatic impairment.

4.1.2. *Additional* Inclusion Criteria for Subjects with Impaired Hepatic Function (Cohorts 1 and 2, *only*)

9. Screening medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests; abnormal findings that are related to the subject's underlying condition are acceptable.

10. 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 14 days of investigational product administration.

11. 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, computerized tomography scan, ***or*** magnetic resonance imaging (MRI).

12. Stable hepatic impairment, defined as no clinically significant change in disease status within the 28 days prior to the Screening visit, as documented by the subject's recent medical history (for example: no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or PT by more than 50%). If subjects do not have such records, 2 screening visits (at least 14 days apart) will be performed to demonstrate stability of the disease.

13. Stable concomitant medications (as defined in Concomitant Treatment(s) section) for the management of an individual subject's medical history for at least 28 days. ***On a case-by-case basis***, with input from the sponsor, subjects receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

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

4.2. Exclusion Criteria

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

1. Subjects with clinically significant infections within the past 3 months (for example, those requiring hospitalization, or as judged by the Investigator), evidence of any infection (including influenza) within the past 7 days, history of disseminated herpes simplex infection or recurrent (>1 episode) or disseminated herpes zoster.

2. Subjects with a personal or family history of hereditary immunodeficiency (eg, severe combined immunodeficiency disorder [SCID], Wiskott-Aldrich syndrome, X-linked agammaglobulinemia).

3. Subjects who have been vaccinated with live or attenuated vaccines within 6 weeks of dosing, or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of dosing.

4. Have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) (refer to details in Tuberculosis Testing section).

5. Subjects with a malignancy or with a 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.

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

    - ***NOTE***: subjects 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.

7. A positive urine drug test, for illicit drugs, at Screening;

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

    - Hepatic impairment subjects may be eligible to participate after approval from sponsor if their drug screen is positive with a prescribed substance that is not expected to interfere with the PK of PF-04965842.

8. Subjects with a history of or current positive results for: human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (refer to Hepatitis Testing section). However, hepatic impairment subjects shown to have been adequately treated for hepatitis C with positive antibodies and negative mRNA may be eligible to participate in the study (refer to Hepatitis Testing section).

9. Use of CCI ***inhibitors*** CCI [redacted] ***inducers*** CCI [redacted] within 14 days or 5 half-lives (whichever is longer) prior to Day 1.

   - ***NOTE:*** the CCI [redacted] inhibitor and inducer examples above are not exhaustive, consult the sponsor if additional guidance is need.

10. Use of CCI ***inhibitors*** CCI [redacted] ***inducers*** CCI [redacted] within 14 days or 5 half-lives (whichever is longer) prior to Day 1.

    - ***NOTE:*** the CCI [redacted] inhibitor and inducer examples above are not exhaustive, consult the sponsor if additional guidance is need.

11. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1. Limited use of nonprescription medications that are not believed to affect subject 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 hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs], vaginal ring, and postcoital contraceptive methods) and hormone replacement therapy must have been discontinued at least 28 days prior to the first dose of investigational product; Depo-Provera® must have been discontinued at least 6 months prior to dosing of investigational product.

    For subjects with ***mild and moderate hepatic impairment***, stable concomitant medications may be given if they are considered necessary for the welfare of the study subjects (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 Treatment(s) section).

12. Treatment with an investigational drug(s) within 28 days or 5 half-lives (whichever is longer) prior to Day 1.

13. Use of immunosuppressant agents, eg, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil, mycophenolate sodium within 7 days or 5 half-lives (whichever is longer) prior to Day 1.

14. An estimated glomerular filtration rate (eGFR) of ≤60 mL/min based on the Modification of Diet in Renal Disease (MDRD) equation (refer to Table 4), and serum creatinine measured with a standardized assay, with a single repeat permitted to assess eligibility, if needed.

15. Female subjects of childbearing potential who are unwilling or unable to use highly effective methods of contraception as outlined in Contraception section for the duration of the study and for at least 28 days after the dose of investigational product; male subjects with partners who are currently pregnant, pregnant female subjects, female subjects planning to become pregnant, breastfeeding female subjects.

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

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

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

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

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

4.2.1. *Additional* Exclusion Criteria for Subjects with Normal Hepatic Function (Cohort 3, *only*)

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

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

22. Evidence or history of clinically significant dermatological condition including atopic dermatitis (or eg, contact dermatitis or psoriasis) or visible rash present during physical examination.

23. Known or suspected hepatic impairment; including at Screening, meet ***any*** of the following criteria, 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*:** Subjects with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ ULN ***plus*** ALT and AST are ≤ ULN ***plus*** alkaline phosphatase, hemoglobin, and reticulocyte count are all ≤ ULN;
    - Albumin > ULN;
    - Prothrombin time (PT) > ULN.

24. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (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.

25. 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 subject's eligibility.

26. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the subject's eligibility.

4.2.2. *Additional* Exclusion Criteria for Subjects with Impaired Hepatic Function (Cohorts 1 and 2, *only*)

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

27. Hepatic carcinoma ***or*** hepatorenal syndrome ***or*** limited *predicted* life expectancy (defined as less than 1 year).

28. History of surgery that would be expected to alter absorption, distribution, metabolism and excretion properties of PF-04965842 – ***for example***: status post porta-caval shunt surgery.

- ***NOTE:*** Subjects with a transjugular intrahepatic portosystemic shunt (TIPS) are permitted provided that they meet the Child-Pugh criteria.

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

30. Signs of clinically active Grade 3 or 4 hepatic encephalopathy (ie, > Grade 2 Portal Systemic Encephalopathy score) – refer to Table 3.

31. Severe ascites and/or pleural effusion.

32. Child-Pugh scores >9 points.

33. Subjects who have previously had a transplanted kidney, liver, or heart.

34. Screening ***supine*** 12-lead ECG demonstrating a QTcF interval >470 msec ***or*** a QRS interval >120 msec. If QTcF exceeds 470 msec, ***or*** QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the subject's eligibility.

35. At Screening, persistent severe, uncontrolled hypertension; for example: ***supine*** systolic BP (SBP) ≥180 mm Hg and/or diastolic BP (DBP) ≥105 mm Hg after ≥5-minute of seated rest, with a single repeat permitted to assess eligibility, if needed.

36. Subjects with ALT or AST >5× ULN at Screening, with a single repeat permitted to assess eligibility if needed, may be considered for inclusion on a case-by-case basis if, in the opinion of the Investigator and sponsor, these levels will not affect subject safety.

4.3. Enrollment Criteria

This is a non-randomized, open-label, single-dose, parallel-cohort study. Subjects will be enrolled into the study and assigned to the respective cohorts provided they have satisfied all subject eligibility criteria.

4.4. Lifestyle Requirements

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations, and 10 hours prior to the collection of the predose PK sample. Water is permitted until 1 hour prior to 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 subjects (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 subject should not exceed approximately 3200 kcal;

- Breakfast will be provided on all days except on Day 1 (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;

- Subjects 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.

4.4.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for ≥24 hours prior to the single dose of investigational product on Day 1 (*plus* have a negative breath alcohol test on Day -1) and continue abstaining from alcohol until the collection of the final PK sample on Day 4;

- Subjects will undergo a breath alcohol test at time points indicated in the SCHEDULE OF ACTIVITIES;

- Consumption of caffeinated drinks and nicotine-containing products (≤5 cigarettes per day or equivalent) is permitted during participation in the study; however, subjects will abstain from nicotine- or caffeine-containing products for at least 2 hours prior to any scheduled electrocardiogram or blood pressure determinations.

4.4.3. Activity

- Subjects 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.

4.4.4. Contraception

All fertile female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. Although female subjects with tubal ligation are considered to be of childbearing potential, no highly effective contraception is required if bilateral tubal ligation was performed.

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the SCHEDULE OF ACTIVITIES, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least one of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Females of childbearing potential cannot use hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing IUDs, vaginal ring, and postcoital contraceptive methods).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Correctly placed copper-containing intrauterine device (IUD).

2. Male sterilization with absence of sperm in the postvasectomy ejaculate.

3. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Male condom or female condom used ***WITH*** a separate spermicide product (ie, foam, gel, film, cream, or suppository) is not considered a highly effective method of contraception.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the

subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

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

For this study, the investigational product(s) is PF-04965842, provided as 100 mg tablets.

5.1. Allocation to Treatment

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

The investigator will assign subject identification numbers sequentially to the subjects as they are screened for the study. All subjects enrolled will receive the same study treatment.

5.2. Subject Compliance

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

PF-04965842 will be supplied to the CRU by the sponsor as 100 mg tablets in high density polyethylene bottles. PF-04965842 will be presented to the subjects in individual dosing containers.

5.3.2. Preparation and Dispensing

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

authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-04965842 tablets will be prepared at the CRU for individual dosing by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

5.4. Administration

Following an overnight fast of at least 10 hours, subjects will receive a single oral 200 mg dose of PF-04965842 at approximately 0800 hours (±2 hours). Investigator site personnel will administer investigational product to subjects with ambient temperature water of approximately 240 mL. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

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

5.5. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

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

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

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

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

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products (PF-04965842 oral tablets) will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s)

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment as defined in the SCHEDULE OF ACTIVITIES.

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

Females using hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing IUDs, vaginal ring, and postcoital contraceptive methods), or taking hormone replacement therapy are ***not eligible*** to participate in this study. However, females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue hormone therapy at least 28 days prior to dosing of investigational product and remain off hormonal therapy for the duration of

the study. Depo-Provera® must be discontinued at least 6 months prior to dosing of investigational product.

Subjects on the following medications, at the Screening visit, are ***excluded*** from the study:

- Use of CCI ***inhibitors*** CCI [redacted] or ***inducers*** CCI [redacted] within 14 days or 5 half-lives (whichever is longer) prior to Day 1.
- Use of CCI ***inhibitors*** CCI [redacted] or ***inducers*** CCI [redacted] within 14 days or 5 half-lives (whichever is longer) prior to Day 1.
  - ***NOTE***: the CCI [redacted] inhibitor and inducer examples above are not exhaustive, consult the sponsor if additional guidance is needed.
- Use of immunosuppressant agents, eg, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil, mycophenolate sodium within 7 days or 5 half-lives (whichever is longer) prior to Day 1.

Herbal supplements must be discontinued **at least 28 days** prior to Day 1 and until the end of CRU stay on Day 4.

5.7.1. Subjects with Normal Hepatic Function (Cohort 3, Only)

In general, subjects 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 subject safety or the overall results of the study may be permitted on a case-by-case basis ***after*** approval by the sponsor.

5.7.2. Subjects with Impaired Hepatic Function (Cohorts 1 and 2)

Subjects are permitted to be on stable doses of background medications if they are considered necessary for the welfare of the study subjects (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 on Day 4.

- Allowed concomitant medications should be administered to hepatic impairment subjects at least 2 hours prior to dosing or withheld to 4 hours after dosing on Day 1.

5.8. Rescue Medication

There is no rescue therapy to reverse any AEs observed with administration of investigational product; standard medical supportive care must be provided to manage the AEs.

6. STUDY PROCEDURES

6.1. Proposed Chronology of Procedures

For the procedures described below, where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the following chronology of events should be adhered to**, *where possible*:**

- *12-lead ECG*: obtain prior to vital signs assessment, blood samples, and prior to dosing (refer to Electrocardiogram section).

- *Vital Signs (BP and PR)*: obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (refer to Blood Pressure and Pulse Rate section).

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

- *Fasting blood samples for clinical laboratory tests*: after assessment of 12-lead ECG and vital signs but *prior* to start of meal (and dosing, when applicable) - refer to Laboratory Tests section.

- *Serial blood samples for plasma PK* (refer to Pharmacokinetics section): as close as practically possible to the nominal time.

- *Other predose procedures*: should be obtained/performed as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

- If the postdose blood collection nominal time coincides with the nominal time of a meal, these blood samples should be collected ***prior*** to start of the meal.

- *Dosing* (refer to Administration section): should occur **as close as practically possible** following pre-dose blood sample collection.

6.2. Screening

Subjects will be screened within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in Subject Information and Consent section. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require rescreening if the Day -1 laboratory results meet the eligibility criteria. CCI [redacted]

For subjects with hepatic impairment, Child-Pugh classification will be assessed at the Screening visit. If a subject is not able to provide documentation of stable hepatic impairment, ***2*** screening visits (**at least 14 days apart**) will be performed to demonstrate stability of the disease. Stable hepatic impairment is defined as no clinically significant change in disease status within the 28 days prior to the Screening visit, as documented by the subject's recent medical history (eg, no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time (PT) by more than 50%). At the second Screening visit, the Child-Pugh classification will be repeated to ensure eligibility and document stability of the disease.

Refer to the SCHEDULE OF ACTIVITIES for the study procedures to be completed at the Screening visit.

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements and Concomitant Treatment(s) sections of the protocol.

6.3. Study Period

Refer to the SCHEDULE OF ACTIVITIES for the study procedures to be completed during the study.

CCI [redacted]

6.4. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (refer to the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (refer to the Contraception section). Contact with the subject may be done via a phone call. However, follow-up contact may occur as an onsite visit for follow-up of clinically significant abnormal laboratory tests and/or ongoing AEs.

6.5. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are dosed and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Limited physical examination, if there is a new or ongoing AE or clinically significant abnormal physical finding from the last visit;
- Supine BP and PR measurements;
- Single 12-Lead ECG measurement;
- Blood and urine specimens for safety laboratory;
- Pregnancy test (female of childbearing potential);
- Blood sample for PK analysis.

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

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

Subjects who withdraw from the study may be replaced at the discretion of the sponsor.

Withdrawal of consent:

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

Lost to follow-up:

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

7. ASSESSMENTS

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 subject. 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.

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

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SCHEDULE OF ACTIVITIES section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 4. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Indirect, direct bilirubin[a] Alkaline phosphatase Uric acid Albumin Total protein PT	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[b]	β-hCG[c] FSH[d,e] Hepatitis B core antibody[d] Hepatitis B surface antibody[d] Hepatitis B surface antigen[d] Hepatitis C antibody (HCVAb)[d,f] Human immunodeficiency virus[d] QuantiFERON-TB Gold Test or PPD[d] Urine drug screening[d] eGFR based on the MDRD equation[g]
	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 Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only performed when total bilirubin is > ULN.
b. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
c. Serum or urine β-hCG for female subjects of childbearing potential.
d. Screening only.
e. Only females who are amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
f. Hepatitis C virus ribonucleic acid (HCV RNA) reflex testing required if HCVAb is positive.
g. Estimated glomerular filtration rate (eGFR) will be calculated based on the calculations below:

1. Obtain the MDRD-derived eGFR
   - eGFR (mL/min/1.73m^2) = 175 × ($S_{cr, std}$)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay.
2. Convert the MDRD-derived, body surface area (BSA)-adjusted eGFR obtained above to absolute eGFR (mL/min) for ***eligibility assessment***:
   - **eGFR (mL/min)** = eGFR (mL/min/1.73m^2) ×subject's BSA where BSA is calculated as
     - $BSA = (Weight^{0.425} \; x \; Height^{0.725})$ x 0.007184

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

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

Clinically significant abnormal laboratory findings at the final assessment should be followed to resolution or until determined by the investigator to be stabilized. Repeat tests may be indicated to establish this.

7.1.1.1. Hepatitis Testing

The hepatitis B core antibody (HepBcAb), hepatitis B surface antibody (HepBsAb), hepatitis B surface antigen (HepBsAg), and hepatitis C antibody (HCVAb) tests will be performed. The hepatitis C virus ribonucleic acid (HCV RNA) reflex testing is required only if HCVAb is positive.

Interpretation of Hepatitis B Testing Results:

- HepBsAg negative and HepBcAb negative: Subject is eligible for the study;
- HepBsAg positive and HepBcAb negative: Subject is excluded from study participation;
- HepBsAg negative, HepBcAb positive and HepBsAb positive: Subject is eligible for study;
- HepBsAg negative, HepBcAb positive and HepBsAb negative: Subject is excluded from study participation.

Interpretation of Hepatitis C Testing Results:

- HCVAb positive and HCV RNA positive: Subject is excluded from study participation. However hepatic impairment subjects shown to have been adequately treated for hepatitis C with positive antibodies and negative mRNA may be eligible to participate in the study.

7.1.1.2. Tuberculosis Testing

The active or latent or inadequately treated infection with *Mycobacterium TB* is evidenced by any of the following:

a. A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test.

   A negative QFT-G or Mantoux/PPD tuberculin skin test is required unless the subject has previously received a documented adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale.

b. Chest x-ray taken at Screening with changes suggestive of active TB infection as determined by a qualified radiologist. A chest x-ray is required if a positive QFT-G or PPD, unless previously performed and documented within 12 weeks prior to Screening.

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

QFT-G In-Tube Test is the preferred testing method.

A blood sample (approximately 3 mL) will be collected at Screening for QFT-G In-Tube testing.

7.1.1.2.1. Purified Protein Derivative Test

If the QFT-G In-Tube test cannot be performed, or if the results cannot be determined to be positive or negative, then subjects may be screened using the PPD Tuberculin Test (Mantoux method).

Subjects must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study. The test should be performed according to local standards with induration of <5 mm required for inclusion.

7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed as outlined in the SCHEDULE OF ACTIVITIES. Serum pregnancy test must be used at the Screening visit, serum or urine pregnancy test may be used on Day -1 and Day 4.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the site(s), local laboratory, or central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

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

7.1.4. Blood Pressure and Pulse Rate

BP and PR will be measured at times specified in the SCHEDULE OF ACTIVITIES section of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject'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. Subjects 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 PR is acceptable; however, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

7.1.5. Electrocardiogram

12-Lead ECGs should be collected at times specified in the SCHEDULE OF ACTIVITIES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Refer to Proposed Chronology of Procedures section for nominal time points when 12-lead ECG assessments coincide with other procedures.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of PF-04965842 [redacted]

During the study, blood samples (10 mL) to provide approximately 5 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at times specified in the SCHEDULE OF ACTIVITIES section of the protocol.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/ data collection tool [DCT]).

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

Details regarding the collection, processing, aliquoting, storage and shipping of PK samples will be provided in the laboratory manual. The shipment addresses and assay laboratory contact information will be provided to the investigator site prior to initiation of the study.

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

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

CCI

CCI

[redacted]

7.5. Blood Volume

The total blood sampling volume for individual subjects in this study is estimated to be approximately 268 mL. The actual collection times/volume of blood sampling may change and 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.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (refer to the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal/Early Termination section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

8.2.3. Serious Adverse Events

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

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a TB

unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), PT/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a 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) may be warranted.

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

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

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

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

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

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

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

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

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

8.4.2.2. Exposure During Breastfeeding

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

8.4.2.3. Occupational Exposure

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

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

8.4.3. Medication Errors

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

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

8.4.3.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

This is an estimation study. Hepatic impairment subjects will be enrolled based on their Child-Pugh scores at Screening. Eight (8) subjects will be enrolled into each of the three study groups (moderate hepatic impairment, mild hepatic impairment and subjects with normal hepatic function). The sample size is based on recommendations from the FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."[7]

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

9.3.1. Analysis Populations

The PK concentration population will be defined as all subjects who received 1 dose of PF-04965842 and in whom at least 1 plasma concentration value is reported.

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

9.3.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-04965842 following single dose administration will be derived from the concentration-time profiles as detailed in Table 5. CCI [redacted] Actual PK sampling times will be used in the derivation of PK parameters.

Table 5. Plasma Pharmacokinetics Parameters

Parameter	Definition	Method of Determination
CCI [redacted]	[redacted]	[redacted]
AUC_{inf}*	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*As data permits

For list of abbreviations refer to Appendix 1

9.3.3. Statistical Methods

The effect of hepatic impairment on PK parameters for PF-04965842 will be assessed by constructing 90% CIs around the estimated difference between each of the Test (hepatic impairment cohorts) and the Reference (normal hepatic function cohort) using a one-way analysis of variance (ANOVA) model based on natural log transformed data.

ANOVA will be used to compare the natural log transformed AUC_{inf}, CCI [redacted] and C_{max}, for each of the hepatic impairment cohorts (Test) to the normal hepatic function cohort (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

The PK parameters for PF-04965842 and CCI [redacted] will be summarized descriptively by hepatic function cohort. CCI [redacted]

Boxplots for AUC_{inf}, CCI [redacted] and C_{max} will be generated by hepatic function cohort. Individual plasma concentrations for PF-04965842 CCI [redacted] will be listed and summarized descriptively by nominal PK sampling time and hepatic function cohort. Individual subject and summary profiles (means and medians) of the concentration-time data will be plotted by cohort. For summary statistics and summary plots by sampling time, the

nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

CCI [redacted]

[redacted]

9.4. Safety Analysis

All subjects who receive the investigational product will be included in the safety analyses and listings.

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

- Physical examination collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward findings identified on physical exams conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data and medical history collected at Screening will be included in the study database.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, 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, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct

access to source documents to perform this verification. This verification may also occur after study completion.

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

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

For studies conducted at non-Pfizer investigator sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for GCP, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site 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, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

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

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

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject 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 investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

At the end of the study, the investigational product in this study will ***not*** be provided to the subjects who participated.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-04965842 at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical 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 all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

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

for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients 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.

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

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4. Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. Semin Cutan Med Surg 2012;31:S3-5.

5. Leicht S, Hanggi M. Atopic dermatitis. How to incorporate advances in management. Postgrad Med 2001;109(6):119-27.

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7. Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function - Study design, data analysis, and impact on dosing and labeling. FDA Guidance, March 2011.

Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
ANOVA	analysis of variance
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinite time
CCI	[redacted]
[redacted]	[redacted]
CCI	[redacted]
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BA	bioavailability
BID	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CI	confidence interval
CCI	[redacted]
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	Clinical Trial
CCI	[redacted]
DBP	diastolic blood pressure
DCT	data collection tool
DDIs	drug-drug interactions
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EFD	embro-fetal development
eGFR	estimated glomerular filtration rate
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

Abbreviation	Term
C[redacted]	[redacted]
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HepBcAb	hepatitis B core antibody
HepBsAb	hepatitis B surface antibody
HepBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	identification
IFN-α	interferon alpha
IFN-γ	interferon gamma
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
JAK	janus kinase
C[redacted]	[redacted]
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LSLV	last subject last visit
CCI [redacted]	[redacted]
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI [redacted]	[redacted]
MDRD	modification of diet in renal disease
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
N/A	not applicable
CCI [redacted]	[redacted]
NOAEL	no-observed-adverse-effect level
CCI [redacted]	[redacted]
PCD	primary completion date
CCI [redacted]	[redacted]
PPD	purified protein derivative
PI	principal investigator
PK	pharmacokinetic(s)
POC	proof of concept
PR	pulse rate
PT	prothrombin time
QD	once daily
QFT-G	QuantiFERON®-TB Gold

Abbreviation	Term
QTc	corrected QT
QTcF	QT interval corrected for heart rate using Fridericia's correction
qual	qualitative
[redacted]	[redacted]
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCID	severe combined immunodeficiency disorder
$S_{cr, std}$	serum creatinine measured with a standardized assay
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
STATs	signal transducers and activators of transcription
[redacted]	[redacted]
TB	Tuberculosis
TBili	total bilirubin
TEAEs	treatment emergent adverse events
[redacted]	[redacted]
THC	tetrahydrocannabinol
TIPS	transjugular intrahepatic portosystemic shunt
TYK2	tyrosine kinase 2
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
WBC	white blood cell
WOCP	women of childbearing potential