A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-05221304 IN ADULT SUBJECTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO SUBJECTS WITHOUT HEPATIC IMPAIRMENT

Investigational Product Number:	PF-05221304
Investigational Product Name:	Not applicable
United States (US) Investigational New Drug (IND) Number:	130418
European Clinical Trials Database (EudraCT) Number:	2017-003034-86
Protocol Number:	C1171006
Phase:	1

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes

Amendment 1	18 September 2017	This amendment is making the following substantial changes to align with the Pfizer Enterprise-level revision to appropriate measures to prevent pregnancy in the population of childbearing potential enrolled who are sexually active ***and*** align with the Clinical Trial Facilitation Group (CTFG) 2014 European Guidance –
		• Section 4.4.4 revised to –
		  • Remove mandate to use highly effective contraception in female partners of male subjects of childbearing potential;
		  • CCI [redacted]
		  • Define sexual abstinence in the context of this research study.
		• Of note, this amendment keeps elements below (in Section 4.4.4) included in prior version of the protocol –
		  • Use of male or female condom alone is viewed as an effective method of contraceptive but must continue to be used with a highly effective method of contraceptive;
		  • In applicable female subjects, method of contraception must include a combination of a highly effective method with an additional method;
		  • In applicable male subjects, use of barrier method to prevent seminal transfer of investigational product to their female partner(s) of childbearing potential must be used;
		In addition, the following changes are made –
		• Text in Section 1.3.1, Section 4.2.2 and Appendix 2, revised to more clearly articulate that subjects who are pharmacologically managed for encephalopathy are permitted – so long as they do not have signs of clinically active Grade 3 or 4 hepatic encephalopathy and as such can still provide informed consent; encephalopathy grading applied at screening should be while on treatment (not pre-treatment) for encephalopathy to derive total score and Child-Pugh Classification;
		• In the Schedule and Activities and Section 4.3, while protocol permits unplanned assessments for subjects' well-being and safety, on Day -1, allowance added for sites to undertake local assessment of safety-related laboratory tests to ensure population remains stable prior to dosing on Day 1;

Document	Version Date	Summary of Changes
		• In Section 4.2.2 and Section 4.3, in subjects with severe hepatic impairment, allowance permitted to enroll and progress with dosing on Day 1 with SBP ≤160 mmHg and DBP ≤105 mmHg, as long as subject is otherwise medically stable. • In Table 2 assessment of mean platelet volume has been deleted considering this study will utilize a sponsor-identified central laboratory hence not permitting assessment of this parameter which requires fresh blood sample.
Original protocol	08 August 2017	Not applicable

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PROTOCOL SUMMARY

Background and Rationale:

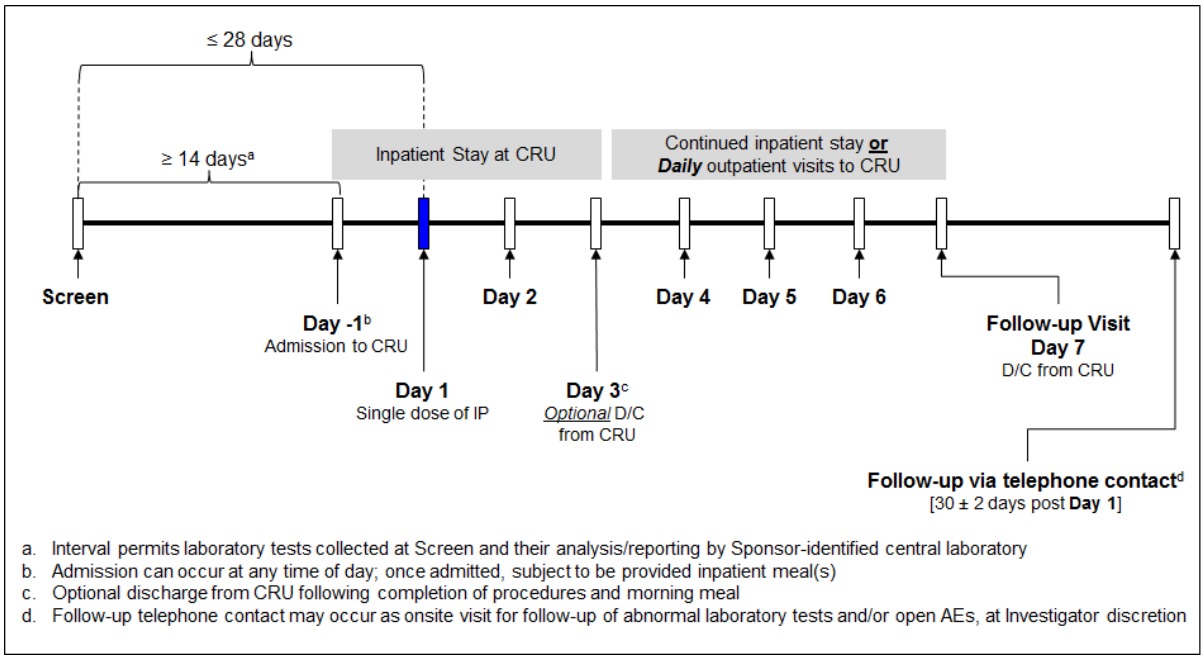
The current study is designed to evaluate the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics of PF-05221304.

Objectives and Endpoints:

Primary Objective:	**Primary Endpoints:**
To compare the pharmacokinetics of PF-05221304 (both total and unbound) following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment.	PF-05221304 PK parameters derived from plasma: • C_{max}, AUC_{inf}, f_u, $C_{max,u}$, and $AUC_{inf,u}$.
Secondary Objectives:	**Secondary Endpoints:**
To compare additional pharmacokinetic parameters (both total and unbound) of PF-05221304 following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment.	PF-05221304 PK parameters derived from plasma: • T_{max}, AUC_{last}, $AUC_{last,u}$, CL/F, CL_u/F, Vz/F, $V_{z,u}$/F and $t_{½}$, as data permit.
To evaluate the safety and tolerability of a single oral dose of PF-05221304 when administered to adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment	Assessment of treatment-emergent adverse events, clinical laboratory tests, vital signs, and 12-lead ECGs.
CCI [redacted]	

Study Design:

This is a non-randomized, open-label, single-dose, parallel-cohort, multisite study with overall design summarized below.



Study Treatment:

The investigational product is PF-05221304, provided as tablets, each containing 25 mg active drug. A single, oral, 25 mg dose of PF-05221304 will be administered with a standard morning meal.

Statistical Method:

A sample size of approximately 24 subjects with varying degrees of hepatic function (6 subjects per cohort) will provide enough precision to determine the 90% confidence interval to detect a 2-fold change in exposure (AUC_{inf}) with 80% tolerance probability between each of the Test (impaired) cohorts and the Reference (without hepatic impairment) cohort.

SCHEDULE OF ACTIVITIES:

Table A provides an overview of the protocol visits and procedures. Refer to Section 6 and Section 7 for detailed information on each procedure and assessment required for compliance with the protocol. The investigator ***may*** conduct unplanned visits, including safety-related laboratory tests on Day -1 with results reported by *local* laboratory prior to dosing on Day 1 *in addition* to those listed below, to conduct procedures to protect the well-being of the subject.

TABLE A. All procedures occurring at same nominal time as meals will occur prior to meal *except* dosing at 0H on Day 1 which is to occur with meal

Visit Identifier/Day [for list of abbreviations refer to Appendix 1]	**Screen** ≤-28	**-1**	**1**									**2**		**3[a]**	**4**	**5**	**6**	**Follow-Up**	
																		7	**30±2**
Hours Post Dose		--	**0**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**16**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	--
Informed consent & demography	x																		
Outpatient visit	x														x[a]	x[a]	x[a]	x[a]	
Inpatient stay at Clinical Research Unit		x	→	→	→	→	→	→	→	→	→	→	→	x	x	x	x	x	
Eligibility assessment with CPC at Screen, ***only*** (Appendix 2)	x	x																	
(Update) Medical history	x	x																	x
Physical exam (height & body weight at Screen, ***only***)[b]	x	x												x				x	
Breath alcohol test	x	x																	
(Update) alcohol/tobacco & contraception use	x	x													x[c]	x[c]	x[c]	x[c]	x[d]
(Update) prior/concomitant treatments	x	x													x[c]	x[c]	x[c]	x[c]	x
Single, *supine* 12-lead ECG	x		x				x							x				x	
Single, *seated* vital sign assessment (BP and pulse rate)	x		x				x							x				x	
Serious and non-serious adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x
Standard meals[e]		x	x				x			x		x		x	x	x	x	x	
Investigational product administration			x[f]																
Blood Samples for –																			
Clinical laboratory tests - after ≥4-hr fast (see Section 7.2.1)	x		x											x				x	
Serum FSH in females amenorrheic ≥12-months ***only***	x																		
Pregnancy (females only)	x		x															x	
CCI [redacted]																			
PF-05221304 PK			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PF-05221304 unbound fraction for protein binding							x												
Urine Samples for –																			
Urine drug test	x																		
Urinalysis (and microscopy, if needed)	x		x											x				x	
On-site pregnancy test (WOCBP, ***only***)			x															x	

a. Subjects can be discharged post completion of procedures (with subsequent outpatient visits) **or** remain inpatient from Day -1 to Day 7, inclusive, at Investigator discretion.
b. Full physical (PE) exam at Screen; at all other time points, limited PE for findings during previous PE or new/open AEs *only*, at Investigator discretion.
c. Procedure to be completed *only* if subject was discharged on Day 3 and returning for outpatient visits on each of these days.
d. Confirmation of appropriate contraception use, *only*.
e. Meals to be served, at clock times matching approximately 0H, 4H, 7H, and 10H relative to dosing on Day 1 (while inpatient) ***and*** at 0H (while outpatient).
f. Dosing to occur with standard morning meal provided approximately 30 minutes prior to 0H, and completed approximately 10 minutes prior to dosing.

1. INTRODUCTION

PF-05221304 is a potent, selective, orally bioavailable, and reversible dual acetyl-CoA carboxylase 1 and 2 (ACC1/2) inhibitor designed to have asymmetric distribution to the liver, CCI [redacted] as such PF-05221304 is expected to inhibit de novo lipogenesis (DNL) and stimulate fatty acid oxidation in the liver to a greater extent than in peripheral tissues. In humans, administration of PF-05221304 has been shown to suppress hepatic DNL in a Phase 1 study in healthy adult subjects; in addition, the drug is expected to stimulate hepatic fatty acid oxidation, and consequently reduce fat accumulation in the liver. This inhibition of hepatic DNL is postulated to result in a decrease and normalization of the excessive DNL observed in nonalcoholic fatty liver disease (NAFLD). In addition, the inhibition of ACC via administration of PF-05221304 also has the potential for anti-inflammatory effects in nonalcoholic steatohepatitis (NASH).

The current study is designed to evaluate the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics of PF-05221304.

1.1. Mechanism of Action/Indication

PF-05221304 is a potent, selective, orally bioavailable, and reversible dual ACC1/2 inhibitor, designed to have asymmetric distribution to the liver. It is being developed for the treatment of NASH with fibrosis.

1.2. Background

The World Health Organization lists NAFLD and NASH as the most important of conditions contributing to the global health burden due to liver diseases, with NASH acknowledged as a potentially fatal condition leading to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1] NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing degrees of fibrosis, with cirrhosis developing in a subset of patients[2,3] with the most common complication of cirrhosis being HCC.[3] Patients with NASH may be asymptomatic or have non-specific symptoms such as fatigue, despite having significant disease on liver biopsy and associated risk for progression to cirrhosis and liver-related mortality.

NASH is a clinical and histological subset of NAFLD (defined as presence of ≥5% hepatic steatosis) that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and non-liver related cancers.[2,3] In a recent meta-analysis, the global prevalence of NAFLD is estimated at 25%, with the prevalence of NASH in the subset with biopsy-proven NAFLD assessed at 59%.[5] The majority of the population with NAFLD has simple steatosis which has, in general, a benign clinical course. A proportion of patients with NAFLD progress to having hepatocellular ballooning and lobular inflammation – taking close to a decade to progress from 1 stage to the next and 30-40 years to develop cirrhosis; however, a smaller subset of patients progress very rapidly (within 10 years) to liver cirrhosis from NAFLD.[6] The 5-year (67%) and 10-year (38%) survival rates in patients with NASH is significantly

different than in those with NAFLD.[7] The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.8 and 15.4, respectively, per 1,000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[5] With the progression of NAFLD disease continuum from steatosis, inflammation, fibrosis, cirrhosis and HCC, varying degrees of impairment of liver function is noted with recent data suggesting potential implications of changes in drug transport and metabolism in this patient population.[8]

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigators' Brochure (IB) for PF-05221304. A summary of the components relevant to this study are presented below.

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1.3. Rationale for Study

The primary purpose of this non-randomized, single dose, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics of PF-05221304 following administration of a single, oral, 25 mg dose. Recognizing that the target population of PF-05221304 are patients with liver disease (NASH with fibrosis) and that the major clearance mechanism of PF-05221304 is predicted to be active uptake into liver the current study is proposed to evaluate whether there is any clinically meaningful effect of hepatic impairment on the plasma pharmacokinetics of PF-05221304.

1.3.1. Rationale for Study Population

The reference set of subjects (Cohort 1, demographic-matched subjects without hepatic impairment) will be characterized as subjects with no chronic medical conditions, and no significant abnormalities in clinical laboratory tests and other procedures conducted at Screening.

The Child-Pugh classification system (refer to Appendix 2) will be used to define the three cohorts of subjects with varying degrees of hepatic impairment (Cohorts 2 to 4, inclusive), in this study; with the reference being subjects without hepatic impairment. All three categories of hepatic impairment will be assessed as this represents the likely population in later phase studies for the proposed indication (treatment of NASH with fibrosis). In addition to alanine aminotransferase (ALT), total bilirubin and aspartate aminotransferase (AST) will be assessed in this study as per the recommendations of the National Cancer Institute Organ Dysfunction Working Group Criteria for assessment of hepatic impairment.[9] Notably, the historical requirement of an encephalogram for encephalopathy grading will not be required. This study will include subjects with mild (Child-Pugh Class A, Cohort 2), moderate

(Child-Pugh Class B, Cohort 3), and severe (Child-Pugh Class C, Cohort 4) hepatic impairment as well as demographic-matched control subjects, without hepatic impairment. 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 Appendix 2) will be excluded. However, subjects who have a *previous* history of Grade 3 or 4 encephalopathy but are ***currently*** receiving an intervention [for example: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to control their encephalopathy-related signs and symptoms are eligible provided the ***on-treatment*** encephalopathy grading at the Screening visit is Grade 2 or lower thereby permitting them to provide informed consent. Acknowledging the medical state of the population enrolled, certain eligibility criteria for subjects with hepatic impairment are purposefully, distinctly different, including assessment of Hepatitis B and Hepatitis C, with no specific exclusion of those who have these conditions planned for subjects classified in Cohorts 2, 3, or 4 (refer to Section 4.1.2 and Section 4.2.2).

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CCI patients with hepatic impairment (Cohorts 2 to 4, inclusive) 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-05221304 disposition.

Both females of childbearing potential, as well as those who are of non-childbearing potential, will be enrolled given the availability of EFD toxicity studies with PF-05221304. However, CCI

measures will be taken to limit the risk of pregnancy in the female population enrolled [refer to Schedule of Activities (Table A) as well as Section 4.4.4 and Section 7.2.1.1].

1.3.2. Rationale for Design

This study is a Phase 1, non-randomized, open-label, single-dose, parallel-group study of PF-05221304 in subjects with varying degrees of hepatic impairment and subjects without hepatic impairment, matched for age as well as body weight (and as much as practically possible gender). Details on age- and body weight- matching criteria are specified in Section 3.1. This study is proposed following a single dose of PF-05221304 considering that single dose plasma PK of PF-05221304 is generally predictive of exposure upon repeated dosing.

The current study will include subjects without hepatic impairment who have been demographically-matched to subjects with mild, moderate, and severe hepatic impairment as defined by Child-Pugh Classification (refer to Appendix 2). All subjects enrolled in this study will receive one single oral 25 mg dose of PF-05221304 in the fed state. To adequately characterize the elimination phase of the plasma PF-05221304 concentration-time profile in the cohorts with varying degrees of hepatic impairment, where the elimination half-life of PF-05221304 may be prolonged, the PK sampling will be collected serially up to 144 hours post-dose. To assess the in vivo protein binding of PF-05221304 with varying degrees of hepatic impairment, the fraction unbound (f_u) of PF-05221304 will be determined at approximately the expected time of maximum concentration (T_{max}) in each subject. CCI [redacted] In this study, PF-05221304 administration is planned to occur with the morning standard meal (refer to Section 4.4.1) to ensure consistency with the intended dosing scheme in the target patient population.

1.3.3. Rationale for PF-05221304 Dose Selected

A single oral dose of 25 mg will be used in this study. This dose has been selected based on prior experience in healthy subjects and also taking into account safety considerations for the subjects with varying degrees of hepatic impairment in whom an increase in plasma PF-05221304 exposure may be observed. CCI [redacted] While the proposed dose (25 mg) is half the highest dose selected for evaluation in the Phase 2a dose-ranging study (50 mg QD), repeated dosing at 25 mg QD, CCI [redacted] likely to be an efficacious dose thus viewed as an appropriate for the current study.

The dose proposed in the current study (25 mg single dose) reflects adequate safety margin compared to nonclinical toxicity studies. CCI [redacted]

Based on a review of effect of hepatic impairment on human pharmacokinetics for compounds cleared in a similar manner to PF-05221304 CCI [redacted] mild hepatic impairment generally results in less than 2-fold increases in plasma exposure. In the same group of compounds, moderate hepatic impairment results in less than 3-fold increases in plasma exposure; however, overall, very limited clinical data is available regarding the effect of severe hepatic impairment on the pharmacokinetics of CCI substrates.[10] CCI [redacted]

CCI [redacted]

CCI [redacted]

1.4. Summary of Benefit Risk Assessment

Study C1171006 entails administration of a single oral dose of PF-05221304 in patients with varying degrees of hepatic impairment and demographic-matched subjects without hepatic impairment, to assess the plasma PK of the investigational product. CCI [redacted] For the subjects participating in the current study, no clinical benefit is expected. The data from this study are envisioned to provide basis for development of dosing recommendations for the target patient population, including those with varying degrees of hepatic impairment. CCI [redacted] However, to ensure subject safety, standard, intensive, inpatient monitoring of subjects following administration of the single oral dose for at least 48 hours is included.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoints:**
To compare the pharmacokinetics of PF-05221304 (both total and unbound) following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment.	PF-05221304 PK parameters derived from plasma: • C_{max}, AUC_{inf}, f_u, $C_{max,u}$, and $AUC_{inf,u}$.
Secondary Objectives:	**Secondary Endpoints:**
To compare additional pharmacokinetic parameters (both total and unbound) of PF-05221304 following administration of a single oral dose in adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment.	PF-05221304 PK parameters derived from plasma: • T_{max}, AUC_{last}, $AUC_{last,u}$, CL/F, CL_u/F, Vz/F, $V_{z,u}$/F and $t_{½}$, as data permit.
To evaluate the safety and tolerability of a single oral dose of PF-05221304 when administered to adult subjects with varying degrees of hepatic impairment relative to age- and body weight-matched subjects without hepatic impairment.	Assessment of treatment-emergent adverse events, clinical laboratory tests, vital signs, and 12-lead ECGs.

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3. STUDY DESIGN

3.1. Study Overview

This is a non-randomized, open-label, single-dose, parallel-cohort, multisite study to investigate the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (total and unbound) of PF-05221304 after a single oral 25 mg dose administered in the fed state. A total of approximately 24 subjects with varying degrees of hepatic function will be enrolled into the study to ensure that up to 6 evaluable subjects in each of the 4 hepatic function cohorts complete the study. Subjects will be selected based on their Child-Pugh score as shown in Table 1.

Table 1. Hepatic Function Categories Based on Child Pugh Score

Cohort	Description	Child-Pugh Score	Number of Subjects
1	Without hepatic impairment	Not Applicable	6[a]
2	Mild hepatic impairment	Class A (5 to 6 points)	6
3	Moderate hepatic impairment	Class B (7 to 9 points)	6
4	Severe hepatic impairment	Class C (10 to 15 points)	6[b]

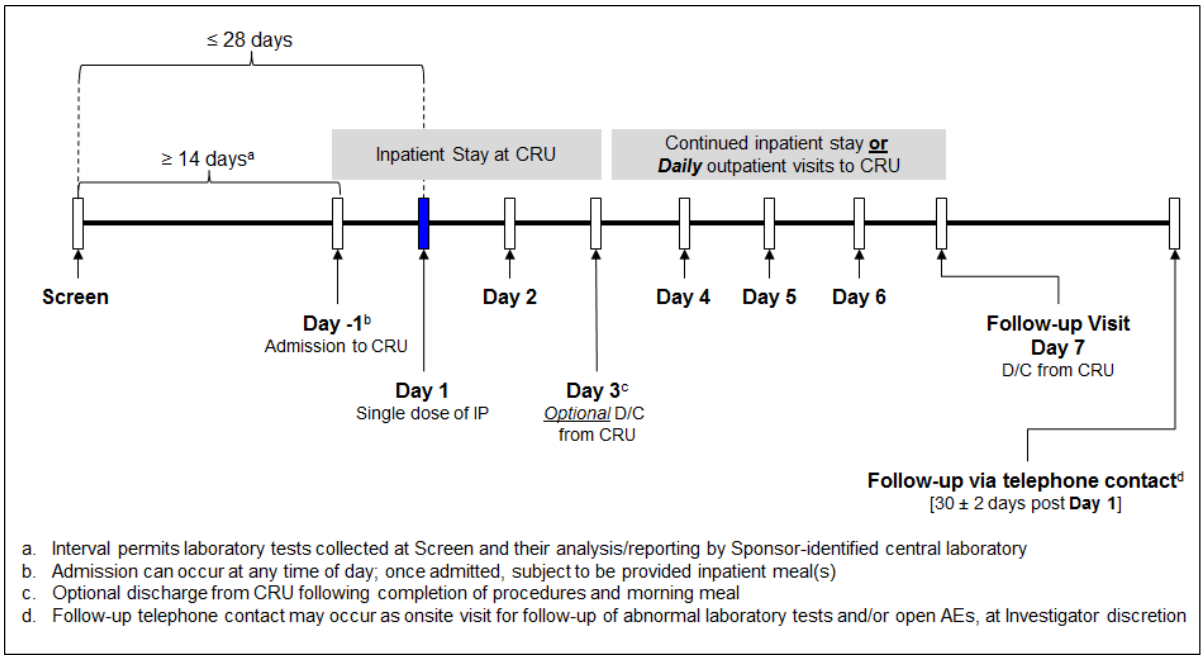
a. Additional subjects ***may*** be dosed to a maximum of 10 subjects to ensure mean age is ±5 years and mean body weight ±10 kg of this cohort is in line with pooled average assessed when ≥75% of subjects are dosed across other 3 cohorts.

b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 subjects in this cohort.

Child-Pugh scores will be determined as described in Appendix 2, at the screening visit. Recruitment for subjects meeting the criteria for Cohorts 3 and 4 will initiate first. Recruitment for subjects in Cohort 2 will start when approximately 50% of total subjects across Cohorts 3 and 4 (ie, 6 of 12) have been dosed. Subjects in Cohort 1 will be recruited last to match the average demographics (at a minimum, age and weight; and as much as practically possible gender) across the pooled Cohorts 2 through 4. Approval from the Sponsor must be garnered ***before*** proceeding with dosing subjects in Cohort 1.

The overall study design is summarized below in Figure 1. For individual subjects, the total duration of participation from the Screening Visit to the on-site Follow-up Visit (Day 7) will be a minimum of approximately 3 weeks and a maximum of approximately 5 weeks.

Figure 1. C1171006 Study Design



In this study, subjects who prematurely discontinue for non-safety related reasons ***may*** be replaced, at the discretion of the principal investigator (PI) and Sponsor study team.

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

1. Male or female subjects between the ages of 18 (*or* the minimum country-specific age of consent if >18) and 70 years, inclusive, at the Screening visit:

   - **Male and female subjects of childbearing potential** must agree to use highly effective method(s) of contraception [refer to Section 4.4.4]. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children **and** is sexually active.

     - Female subjects of childbearing potential must **not** be pregnant, breastfeeding, or planning to become pregnant for the duration of their participation in this study and **within 28-days** following the single dose of investigational product.

- **Female subjects of non-childbearing potential** must meet **at least 1** of the following criteria:

  a. 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, with a single repeat assessment, via the sponsor-identified central laboratory, permitted to assess postmenopausal state, if needed;

  b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

  c. 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 and ≤35.4 kg/m^2; and a total body weight >50 kg (110 lbs);

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 plans, laboratory tests, and other study procedures.

4.1.1. *Additional* Inclusion Criteria for Subjects without Hepatic Impairment (Cohort 1, *only*)

1. Male and/or female subjects –

   a. No clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests, as assessed by the sponsor-identified central laboratory;

   b. Breath alcohol test at Screen must be negative;

2. Subjects must fit the demographic-matching criteria, including –

   a. A body weight that is ±10 kg of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

   b. An age that is ±5 years of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

c. ***Attempts will be made*** to ensure that the male-to-female distribution in Cohort 1, is comparable, to that in the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4);

3. No known or suspected hepatic impairment; including at Screening, meet **all** the following criteria, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed:

   - ALT ≤ upper limit of normal (ULN);
   - 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;
   - Prothromin time ≤ ULN.

4.1.2. *Additional* Inclusion Criteria for Subjects with Impaired Hepatic Function (Cohorts 2, 3, and 4, *only*)

1. Satisfy the criteria for Class A, B, ***or*** C of the modified Child-Pugh classification (refer to Appendix 2);

2. 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);

3. 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 [PT] by more than 50%);

4. Stable concomitant medications (as defined in Section 5.8.2) for the management of individual subjects medical history; ***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;

5. **Previous** history of alcohol abuse is permissible provided that the subject is willing and able to abide by the lifestyle guidelines described in Section 4.4.2 of this protocol ***and*** breath alcohol test, at Screen, is negative.

4.2. Exclusion Criteria

Subjects in all 4 Cohorts with **any** of the following characteristics/conditions will ***not*** be included in the study:

1. 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;

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

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

3. Participation in other studies involving investigational drug(s) within **30 days** (or as determined by the local requirement) or 5 half-lives prior to study entry (Screening) and/or during study participation;

4. Subjects with known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-05221304;

5. At Screening, subjects with a positive result for human immunodeficiency virus (HIV) antibodies, as assessed by sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed;

6. Male subjects with partners who are currently pregnant, pregnant female subjects, breastfeeding female subjects, as well as fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use highly effective methods of contraception as outlined in Section 4.4.4 for the duration of the study and for **at least 28 days** after the dose of investigational product;

7. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within **60 days** prior to the dose of investigational product and until the on-site Follow-up visit (Day 7);

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

9. Unwilling or unable to comply with the Lifestyle Requirements outlined in Section 4.4;

10. 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.

4.2.1. *Additional* Exclusion Criteria for Subjects without Hepatic Impairment (Cohort 1, *only)*

In addition, subjects without hepatic impairment (Cohort 1) presenting with any of the following will ***not*** be included in the study:

1. Evidence of chronic liver disease including history of hepatitis, hepatitis B, or hepatitis C **or** evidence of **any** of the following, as assessed by sponsor-identified central laboratory, with a single repeat, permitted to assess eligibility, if needed –

    - Hepatitis B virus, defined by presence of hepatitis B surface antigen (HBsAg);

        - *NOTE*: while *not* part of the tests assessed in this study, subjects with a previously positive HBsAb result due to vaccination, are deemed eligible;

    - Hepatitis C virus (HCV), defined by presence of hepatitis C antibody (HCVAb) and HCV RNA (when reflexed based on a positive result for HCVAb);

2. History of regular alcohol consumption exceeding 14 drinks/week for female subjects or 21 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 of before Screening;

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

4. Screening ***supine*** 12-lead ECG demonstrating QTcF interval >450 msec *or* a QRS interval >120 msec. If QTcF exceeds 450 msec, *or* QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the ***three*** QTcF or QRS values should be used to determine the subject's eligibility;

5. Screening ***seated*** systolic blood pressure (SBP) ≥140 mm Hg *or* diastolic blood pressure (DBP) ≥90 mm Hg, following ≥5 minutes of seated rest. If SBP is ≥140 mm Hg *or* DBP ≥90 mm Hg, the BP assessment should be repeated 2 more times and the average of the ***three*** BP values should be used to determine the subject's eligibility;

6. Use of ***chronic*** prescription medications within **7 days or 5 half-lives** (whichever is longer) prior to Day 1 –

    - ***NOTE***: use of selected, limited prescription and non-prescription medications is permitted – refer to Section 5.8.1 for details;

7. 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.

4.2.2. *Additional* Exclusion Criteria for Subjects with Impaired Hepatic Function (Cohorts 2, 3, and 4, *only*)

In addition, subjects in the hepatic impairment cohorts (Cohorts 2, 3 and 4) presenting with ***any*** of the following will **not** be included in the study:

1. Hepatic carcinoma **or** hepatorenal syndrome **or** limited *predicted* life expectancy (defined as less than 1 year in Cohorts 2 & 3 and less than 6-months for Cohort 4 *only*);

2. History of surgery that would be expected to alter Absorption, Distribution, Metabolism and Excretion (ADME) properties of PF-05221304 – *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;

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

4. At Screening, subjects with an estimated glomerular filtration rate (eGFR) of ≤60 mL/min using the Modification of Diet in Renal Disease (MDRD) equation, and serum creatinine (SCr), as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed;

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

6. Severe ascites and/or pleural effusion, ***except*** for those categorized in Cohort 4 who may be enrolled provided subject is medically stable, per Investigators' medical judgment;

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

8. 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;

9. At Screening, persistent severe, uncontrolled hypertension; for example: ***seated*** systolic blood pressure (SBP) ≥180 mm Hg and/or diastolic blood pressure (DBP) ≥105 mm Hg after ≥5-minute of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits:

    - For subjects with SBP ≥160 mm Hg **or** DBP ≥100 mm Hg, the period between Screening and Day -1 must be used to refine the doses of the agents used for management of blood pressure (refer to Section 5.8.2) with the aim to have stable BP on Day 1 [refer to Section 4.3];

10. Subjects with ALT **or** AST >5x ULN on clinical laboratory tests at Screening, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed.

4.3. Criteria for Dosing on Day 1

Subjects will progress to dosing on Day 1 provided they have satisfied ***all*** the following criteria –

- Eligibility criteria outlined in Section 4.1 and Section 4.2;
- Breath Alcohol test on Day -1 is negative;
- In females of childbearing potential, *urine* pregnancy test on Day 1 prior to dosing as reported by *on-site* pregnancy test using supplies offered by sponsor-identified central laboratory, is negative for pregnancy – refer to Section 7.2.1.1;
- Safety-related laboratory tests collected and analyzed by sites' *local* laboratory on Day -1, *if performed* at investigator discretion, upon review on Day 1 must reflect subject to be in stable medical condition;
- ***Cohorts 2, and 3, only:*** patients with elevated BP at Screening must have measurement on Day 1 of SBP ≤159 mm Hg **and** DBP ≤99 mm Hg with repeat permitted, if needed, to confirm stable BP;
- ***Cohort 4, only:*** patients with elevated BP at Screening must have measurement on Day 1 of SBP ≤159 mm Hg **and** DBP ≤105 mm Hg with repeat permitted, if needed, to confirm stable BP.

4.4. Lifestyle Requirements

After confirmation of eligibility and starting on Day -1, the subjects will be instructed to maintain the guidelines described below for the duration of participation in the study.

4.4.1. Meals and Dietary Restrictions

While inpatient, the meals consumed are expected to follow the restrictions outlined below with subjects encouraged to complete each meal.

- Subjects must abstain from all food and drink (except water) for ≥4-hours prior to all fasting clinical laboratory evaluations;

- Water may be consumed as desired (ad libitum);

- Investigational product must be administered with the morning meal;

- ***While inpatient***, meals including on non-dosing days – will be standardized as follows –

    - Standard morning meal, lunch, afternoon snack, and evening meal (and an optional evening snack) will be provided at a similar clock time to the clock time when these meals are offered on Day 1 (ie, 0H, 4H, 7H, 10H, and 14H);

    - 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;

        - The morning meal (matching 0H), afternoon snack, ***and*** optional evening snack is ***each*** envisioned to constitute 300-400 calories ***and*** a macronutrient composition of approximately 55% carbohydrates, 30% fat and 15% protein;

        - Lunch and evening meal ***each*** is envisioned to constitute less than 1000 calories;

    - The nutritional macronutrient composition consumed by each subject should be maintained, as much as practically possible;

        - If subjects cannot complete the meals, the portion consumed in 25% increments will be documented and potential impact on results assessed by the Sponsor study team on a case-by-case basis;

    - ***On Day 1***, the morning meal will be provided at approximately 30 minutes prior to dosing at 0H (or similar clock time on non-dosing days) and is expected to be completed approximately 10 minutes prior to dosing;

- ***During the outpatient visits*** on Days 4 through 7, inclusive, as applicable, a morning meal will be consumed at the site following completion of the other procedures at this nominal time point [with the meal *either* provided by the site *or* the subject provided a voucher (or similar) by the site to purchase the meal before arriving to the site for each visit].

4.4.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for ≥24 hours prior to the single dose of investigational product (IP) on Day 1 (*plus* have a negative breath alcohol test on Day -1) and continue abstaining from alcohol until the on-site Follow-up visit (Day 7);
    - Subjects will undergo a breath alcohol test at time points indicated in the Schedule of Activities (Table A);
- Consumption of caffeinated drinks and nicotine-containing products is permitted during participation in the study; however, there may be a need for brief interruption while at the site, depending on local site policy.

4.4.3. Activity

- Subjects will **not** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within **48-hours** before each blood sample collection for clinical laboratory tests while participating in the study; physical activity at an individual subject's normal pace is permitted.

4.4.4. Contraception

CCI [redacted]

Female subjects who, ***in the opinion of the investigator*** are sexually active ***and*** at risk for pregnancy must agree to use, with their partner(s), highly effective contraception throughout the study and continue use for **at least 28 days** after receiving the single dose of the investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected the appropriate method of contraception for the individual subject from the list of permitted contraception methods below and instruct the subject in their consistent and correct use. At time points indicated in the Schedule of Activities (Table A), the investigator or designee will inform the female subject of the need to use the highly effective method of contraception consistently and correctly and document such conversation, and the subject's affirmation, in the subject's chart.

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). **One** of the below options must be used to satisfy the requirement for highly effective contraception in female subjects participating in this study:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, inserted, injected, implanted; *and* including oral, as well as transdermal methods unless prohibited by local regulations or ethics committee decision), with *either*:

    a. Male *or* female condom;

    b. Male sterilization.

2. Correctly placed copper-containing intrauterine device (IUD) or intrauterine system combined with *either*:

    a. Male *or* female condom;

    b. Male sterilization.

3. Male sterilization with absence of sperm in the post-vasectomy ejaculate in the female subjects' partner combined with *either*:

    a. Male *or* female condom;

    b. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedures.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label) **combined with one** of the following:

    a. IUD *or* intrauterine system;

    b. Male *or* female condom;

    c. Male sterilization.

All sexually active male subjects must agree to prevent potential transfer to and exposure of female partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the dose of investigational product (Day 1) and continuing for **at least 28 days** after the dose of investigational product.

In female subjects, pregnancy testing will be performed at time points indicated in the Schedule of Activities (Table A). The specific contraceptive method(s) in the females of childbearing potential will be documented, and ***at every visit*** their consistent and correct use will be ascertained and documented in the subject's source document. For additional details, refer to Section 7.2.1.1.

In addition, the investigator or designee will instruct *all subjects of childbearing potential* to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the female subject or male subjects' female partner.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with this study) *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 supporting study documentation.

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 clinical research unit (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 is PF-05221304, provided as tablets, each containing 25 mg active drug.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should ***not*** influence the decision to enroll a particular subject.

Following completion of informed consent at the Screening visit, each subject will be assigned a single 8-digit study-specific subject identification (SSID) number, by the site staff. The first four digits of the SSID will reflect the sponsor-assigned site number and the remaining four-digits will reflect each subjects' unique number assigned in chronological order of when informed consent is obtained.

5.2. Breaking the Blind

Not applicable, this is an open-label study.

5.3. Subject Compliance

The single dose of the 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 swallowed.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

The investigational product (PF-05221304) will be supplied by the Sponsor. PF-05221304 will be supplied to the sites as single strength tablets of 25 mg, in bulk. PF-05221304 will be presented to the subjects in individual dosing containers for oral ingestion.

5.4.2. 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-05221304 for witnessed dosing in this study will be prepared by the site staff.

Investigational product should be prepared and dispensed by the site into individual dosing containers by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.5. Administration

Administration of investigational product (PF-05221304), will occur at 8:30 AM (±1 hour) with the morning meal – refer to Section 4.4.1. A single, oral, 25 mg dose of PF-05221304 will be administered. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing. Investigator site personnel will administer investigational product to subjects with ambient temperature water **of approximately 120 mL**.

5.6. 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.

5.7. 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 will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

At the end of the study, 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.

5.8. Concomitant Treatments

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 (Table A).

Treatments taken **within 28 days** before the dose of investigational product (PF-05221304) will be documented as a prior treatment. Treatments taken after dosing of investigational product will be documented as concomitant treatments.

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study.

5.8.1. Subjects with Healthy Hepatic Function (Cohort 1, Only)

In general, subjects will abstain from all concomitant treatments, except for the treatment of adverse events. Of note, the following ***restrictions*** –

- Acetaminophen/paracetamol may be used at doses of ≤1 g/day;
- Herbal supplements must be discontinued **at least 28 days** prior to Day 1 and until the on-site Follow-up visit;
- Limited use of prescription and non-prescription medications that are not believed to affect the overall results of the study may be permitted on a case-by-case basis ***after*** approval by the Sponsor study team.

5.8.2. Subjects with Impaired Hepatic Function (Cohorts 2, 3, and 4)

Subjects are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s). ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the on-site Follow-up visit (on Day 7).

Subjects on the following medications, at the Screening Visit, are *excluded* from the study –

- CCI [redacted] (eg, cyclosporine, gemfibrozil, rifampin, erythromycin, clarithromycin);
- CCI [redacted] (eg, ketoconazole, itraconazole);
- CCI [redacted] (eg, rifampin);
- CCI [redacted] (eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadin);
- (Medical-grade) marijuana, regardless of medical indication.

Herbal supplements must be discontinued **at least 28 days** prior to Day 1 and until the on-site Follow-up visit (on Day 7).

5.9. Rescue Medication

There is no rescue therapy to reverse any adverse events (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 Section 7.2.4).
- *Vital Signs (blood pressure and pulse rate*: obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (refer to Section 7.2.3).
- ***If*** an intravenous catheter is placed for serial blood sample collections, ECGs and vital signs (blood pressure and pulse rate) assessments should be ***either*** collected prior to the insertion of the catheter ***or*** sufficient rest period after catheter insertion introduced to minimized 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 Section 7.2.1.
- *Serial blood samples for plasma PK* (refer to Section 7.1): as close as practically possible to the nominal time.
- *Other pre-dose 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 post-dose 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 Section 5.5): should occur as close as possible to the scheduled nominal time with a meal (refer to Section 4.4.1), **and 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 Section 12.3. Refer to Schedule of Activities Table A for the study procedures to be completed at the Screening visit.

In ***this study,*** subjects may be re-screened. This is permitted when, due to ***logistical constraints***, the maximum period between Screening Visit and Day 1, of **28 days,** is exceeded. In addition, for subjects in Cohorts 2-4, inclusive, ***only***, re-screening may be appropriate following mild intercurrent illness after the condition has resolved. In such cases, all screening procedures must be repeated and the subject assigned a new 8-digit SSID number. Subjects must be deemed to meet all the eligibility criteria under the new 8-digit SSID *before* progressing to Day 1.

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements (Section 4.4) and Concomitant Treatments (Section 5.8).

6.3. Study Period

Refer to Schedule of Activities Table A for the study procedures to be completed starting on Day -1 to Day 6, inclusive.

If a subject has any clinically significant, study-related abnormalities at the conclusion of the scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain at the site until such abnormalities are deemed not clinically significant, or it is safe for outpatient Follow-up. If the subject is unable or unwilling to remain at the site and/or when outpatient Follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange Follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.4. Follow-up

6.4.1. Follow-up Visit

In this study, there are two Follow-up visits, as follows:

- **1st is an on-site visit** which will occur **on Day 7** following dosing of investigational product on Day 1;
- **2nd is a telephone contact** to occur **30 ±2 days** following dosing of investigational product on Day 1;
- Refer to Schedule of Activities- Table A for the study procedures to be completed at each of the two Follow-up visits.

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 (refer to Section 8.1.3) 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, site 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:

- Conduct an inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Perform a limited physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit at PI discretion;
- Obtain supine, single, standard, 12-lead ECG (refer to Section 7.2.4);
- Obtain seated, single set of blood pressure and pulse rate measurements (refer to Section 7.2.3);
- Collect blood and urine specimens, following a ≥ 4-hour fast, for clinical laboratory tests (refer to Section 7.2.1);
- Undertake on-site urine pregnancy testing (in females of childbearing potential only) – refer to Section 7.2.1.1;
- Collect blood sample for pharmacokinetic analysis of PF-05221304 – refer to Section 7.1.1.

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 investigator upon consultation with 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 post treatment 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. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. 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 via a manual developed by the sponsor-identified central laboratory to the investigator site prior to initiation of the study.

7.1. Pharmacokinetics (PK)

Pharmacokinetic sampling time points in this study may be adjusted to adequately assess the plasma PK profile based on emerging data from this study; and while the actual times may change, the total number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic 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) **relative to 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).

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- 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.
- CCI [redacted]
- Refer to Section 6.1 for proposed chronology of procedures for nominal time points when PK collections coincide with other procedures.

Additional details regarding the collection, processing, storage and shipping of the blood samples will be offered, prior to study start, in a manual developed by the sponsor-identified central laboratory.

7.1.1. Plasma for Analysis of total PF-05221304 concentrations

During the study, blood samples (**3 mL**) to provide sufficient ***plasma*** for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K_2EDTA as defined in the Schedule of Activities Table A.

7.1.2. Plasma for Determination of PF-05221304 Unbound Fraction

During the study, a blood sample (**12 mL**) to provide sufficient ***plasma*** for unbound fraction determination will be collected into an appropriately labeled tube containing K_2EDTA as defined in the Schedule of Activities Table A.

7.2. Safety

7.2.1. Laboratory Tests

The clinical laboratory tests outlined in Table 2 will be performed, *by the sponsor-identified central laboratory*, as defined in the Schedule of Activities Table A. Blood and urine samples for clinical laboratory tests will be collected following ≥4-hour fast.

Table 2. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Reticulocyte count (Abs) MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine (***and*** eGRF via MDRD) *Plasma* Glucose (fasting) Calcium Sodium Potassium Chloride Phosphorus Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT Total bile acids Total bilirubin Direct bilirubin[a,b] Indirect bilirubin[a,b] Creatine Kinase[a,c] Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	Other tests as part of clinical laboratory tests: • aPTT, PT, INR • Serum FSH[e] • Serum and urine pregnancy test (refer to Section 7.2.1.1) • Urine drug test[f] • Serology[g]: HBsAg, HBcAb, HCVAb (and if positive, reflex HCV RNA), HIV
Additional Tests (Needed for Hy's law) – also refer to Section 8.4.2.			
AST ALT Total bilirubin Albumin Alkaline phosphatase Direct bilirubin	Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug levels and/or protein adduct level		

a. At Screening and Day 1, ***only.***
b. *After* Day 1, direct and indirect bilirubin assessed when total bilirubin is > ULN, ***only.***
c. *After* Day 1, creatine kinase assessed when ALT is > ULN, ***only.***
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
e. At Screening; and in females, only.
f. At Screening, ***only***; with minimum requirements including cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
g. At Screening, ***only.***

For list of abbreviations refer to Appendix 1.

In all cases, samples will be collected *prior to* initiation of a meal. 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 sponsor-identified 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. Additional details regarding sample collection, processing, and shipment will be provided in the manual developed by the sponsor-identified central laboratory and provided to the sites prior to the start of the study.

7.2.1.1. Pregnancy Testing

All pregnancy tests (serum *and* urine) used in this study must have a sensitivity of **at least 25 mIU/mL,** and must be performed using supplies offered by the sponsor-identified central laboratory.

For female subjects of childbearing potential, following a negative serum pregnancy test result ***and*** after confirmed eligibility based on Screening tests(s), appropriate contraception must be used (either continued or commenced) and the subject will require a negative *urine* pregnancy test on Day 1 before receiving IP on Day 1. The female subject should have used highly effective method of contraception (refer to Section 4.4.4) for **at least 28-days** before Day 1.

Pregnancy tests will be performed as defined in the Schedule of Activities (Table A) to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever a potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.2.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation as defined in the Schedule of Activities Table A.

- A ***full physical examination*** will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.

- A ***limited physical examination*** will be focused on general appearance, the respiratory, cardiovascular, and neurological systems, as well as towards subject reported symptoms, performed at Investigator discretion.

For measuring body 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.

7.2.3. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured as defined in the Schedule of Activities Table A. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

- **Single, seated** blood pressure/pulse rate will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg, following a rest of **≥5-minutes**; the assessment at Visit 5 (Day 1) will serve as each subject's baseline;
- Same arm (preferably the dominant arm) will be used for blood pressure/pulse rate assessment throughout the study;
- Blood pressure/pulse rate assessment should not be taken from the arm with an intravenous catheter, if placed;
- Subjects should be instructed not to speak during blood pressure/pulse rate measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for **≥30 seconds**.

Refer to Section 6.1 for proposed chronology of procedures for nominal time points when vital sign assessments coincide with other procedures.

7.2.4. Electrocardiogram

As defined in the Schedule of Activities Table A, 12-lead electrocardiograms (ECGs) should be collected.

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

Refer to Section 6.1 for proposed chronology of procedures for nominal time points when 12-lead ECG assessments coincide with other procedures.

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

CCI

CCI

CCI

CCI

[redacted]

7.5.1. Additional Research

CCI

[redacted]

7.6. Blood Volume

The total blood sampling volume for individual subjects in this study will be **approximately** CCI [redacted] Table 3 below reflects approximate sample volumes needed for each measured endpoint.

[redacted]

Table 3. Blood Volume Collected in Study C1171006

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screen	Days 1-6, inclusive	Follow-Up	
Clinical Laboratory Tests	30	1	--	--	30
Clinical Laboratory Tests	25	--	2	1	75
PF-05221304 PK, total concentrations	3	--	15	1	48
Samples for plasma protein binding to assess unbound plasma PF-05221304 concentrations	12	--	1	--	12
CCI					
TOTAL					CCI

Total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable

The actual collection times of blood sampling may change, but the total blood volume collected will not increase. 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) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (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 (see Section 8.2.3 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 Section 6.5)

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 Section 8.1 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 tuberculosis 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;
- Admission exclusively for the administration of blood products.

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. Protocol-Specific Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

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

The threshold of laboratory abnormalities for a potential DILI case depends on the 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 (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels – refer to Table 2. 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 liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

8.4.3. 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.

8.4.3.1. Exposure During Pregnancy

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

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

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

If a 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.

8.4.3.2. 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.

8.4.3.3. 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.

8.4.4. 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

8.4.4.1. 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

A sample size of approximately 24 subjects with varying degrees of hepatic function (6 subjects per cohort) will provide 90% confidence interval to detect a 2-fold change in exposure (AUC_{inf}) with 80% tolerance probability. Table 4 presents the precision of the estimated effects with the associated width of 90% confidence intervals with increasing standard deviation.

Table 4. Precision for 2-fold Change in AUC_{inf} as Function of Assumed Variability

Level of Precision	Assumed SD*= 0.16 CCI [redacted]	Assumed SD* = 0.23 CCI [redacted]	Assumed SD* = 0.28 CCI [redacted]
n=6/cohort	18% (1.65; 2.43)	24% (1.51; 2.64)	29% (1.42; 2.81)

*SD = Standard Deviation calculated on natural logarithmic scale

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-05221304 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 1 of the PK parameters of primary interest.

9.3.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-05221304 following single dose administration will be derived from the concentration-time profiles as detailed in Table 5. Actual PK sampling times will be used in the derivation of PK parameters. The fraction of PF-05221304 unbound in plasma (f_u) will be determined and reported for each subject by the analytical lab.

Table 5. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
$AUC_{last,u}$	Unbound area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	f_u* AUC_{last}
AUC_{inf}*	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
$AUC_{inf,u}$*	Unbound area under the plasma concentration-time profile from time zero extrapolated to infinite time	f_u* AUC_{inf}*
C_{max}	Maximum plasma concentration	Observed directly from data
$C_{max,u}$	Unbound maximum plasma concentration	f_u* C_{max}
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
CL_u/F*	Unbound apparent clearance	f_u* CL/F
Vz/F*	Apparent volume of distribution	$Dose/(AUC_{inf}\text{-}k_{el})$
Vz_u/F*	Unbound apparent volume of distribution	f_u* Vz/F

*As data permits

For list of abbreviations refer to Appendix 1

9.3.3. Statistical Methods

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (impaired) cohorts and the Reference (without hepatic impairment) cohort using a one-way ANOVA model based on natural log transformed data.

One-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-05221304 AUC_{inf}, AUC_{last} and C_{max}, unbound AUC_{inf} ($AUC_{inf,u}$), unbound AUC_{last} ($AUC_{last,u}$), and unbound C_{max} ($C_{max,u}$), as data permit, for each of the hepatic impairment classification cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

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The PF-05221304 PK parameters C_{max}, AUC_{last}, AUC_{inf}, f_u, T_{max}, $t_{½}$, CL/F, V_z/F, $AUC_{inf,u}$, $AUC_{last,u}$, $C_{max,u}$, CL_u/F, and V_{zu}/F will be summarized descriptively by hepatic function cohort. Individual PF-05221304 concentrations will be listed and summarized descriptively by nominal PK sampling time and hepatic function cohort. Individual subject and summary profiles (median and means) of the concentration-time data will be plotted by treatment for both total plasma PF-05221304 and unbound PF-05221304. 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. PF-05221304 AUC_{inf}, AUC_{last}, C_{max}, $AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$ individual subject parameters will be plotted by hepatic function cohort.

Linear regression may be used to analyze the potential relationship between appropriate PK parameters (eg CL/F and V_Z/F) and hepatic function (eg, serum albumin concentration, or prothrombin time). Estimates of the slope and intercept, together with their precision (90% confidence interval [CI]), and the coefficient of determination will be obtained from the model.

Plots of PK parameters (CL/F and V_Z/F) versus hepatic function (eg, serum albumin concentration, or prothrombin time) will be constructed. A regression line and 90% confidence region for the PK parameters and hepatic function will be included.

9.4. Pharmacodynamic Analysis

Not applicable for this study.

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9.6. Safety Analysis

During the study conduct, adverse events, ECGs, blood pressure, pulse rate, 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 pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. **In the study report,** for vital signs and ECGs, comparison will be made to the predose collections on Day 1.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted.

9.6.1. Electrocardiogram Analysis

During study conduct as well as reporting of study results, baseline will be defined as 12-lead ECGs data collected on Day 1 prior to dosing of IP. Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval and QRS interval, will be summarized by time.

The number (%) of subjects with maximum post dose QTcF values and maximum increases from baseline in the following categories will be tabulated by regimen:

Categorical Assessment of QTcF Interval

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

9.7. Interim Analysis

No formal interim analysis will be conducted for this study. The sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

9.8. 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.

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 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.

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 Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. 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 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 and possible risks associated with participation.

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 a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all *other* participating countries is defined as last subject last visit (LSLV) reflected by completion of the 2nd Follow-up visit for the last subject randomized in the study.

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-05221304** 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 **14 calendar 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 (clinical study report [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

1. LaBrecque D, Abbas Z, Anania F, et al. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. In: WGO Global Guidelines NAFLD/NASH (long version). Milwaukee, WI: World Gastroenterology Organisation; 2012: 29 pages.

2. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology 2015; 61(4):1392-405.

3. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64(6):1388-402.

4. Khan FZ, Perumpail RB, Wong RJ, et al. Advances in hepatocellular carcinoma: Nonalcoholic steatohepatitis-related hepatocellular carcinoma. World J Hepatol 2015; 7(18):2155-61.

5. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease – meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64(1):73-84.

6. Noureddin M, Anstee Q, Loomba R. Review article: emerging anti-fibrotic therapies in the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2016;43(11):1109-23.

7. LaBrecque D, Abbas Z, Anania F, et al. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. In: WGO Global Guidelines NAFLD/NASH (long version). Milwaukee, WI: World Gastroenterology Organisation; 2012: 29 pages.

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CCI [redacted]

[redacted]

Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	absolute
ACC	acetyl-CoA carboxylase
ADR	adverse drug reaction
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under curve (used when referring to PK)
AUC_{24}	area under concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the curve to infinity
$AUC_{inf,u}$	area under unbound plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under concentration-time curve from time 0 to time of last quantifiable concentration
$AUC_{last,u}$	area under unbound plasma concentration-time profile from time zero to time of last quantifiable concentration (C_{last})
CCI [redacted]	
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance
CL_u/F	unbound apparent clearance
C_{max}	peak or maximum observed concentration
$C_{max,u}$	maximum unbound plasma concentration
CO_2	carbon dioxide (bicarbonate)
CP	coproporphyrin
CPC	child-pugh classification
CPT	carnitine-palmitoyl transferase
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
DBP	diastolic blood pressure
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EFD	embryo-fetal development
eGFR	Estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FFA	free fatty acid
FSH	follicle-stimulating hormone
f_u	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HDL-C	high density lipoprotein cholesterol
HCVAb	hepatitis C antibody
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HCV	hepatitis C virus
hr	hour
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL-C	low density lipoprotein-cholesterol
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
CCI [redacted]	[redacted]
MedDRA	medical Dictionary for Regulatory Activities
min	minute
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
N/A	not applicable
CCI [redacted]	
PCD	primary completion date

Abbreviation	Term
PD	pharmacodynamics
PE	physical exam
PG	pharmacogenomic
CCI	[redacted]
PI	principal investigator
PK	pharmacokinetics
PR	pulse rate
PT	prothrombin time
Q12H	once every 12 hours
QD	quaque die, once a day
QTcF	QT interval corrected for heart rate using Fridericia's formulae
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCr	serum creatinine
SRSD	single reference safety document
SSID	study subject identification
$T_{1/2}$	terminal half-life
T_{max}	time to reach maximum concentration
TBili	total bilirubin
TEAE	treatment-emergent adverse event
Th17	T helper 17
THC	tetrahydrocannabinol
TIPS	transjugular intrahepatic portosystemic shunt
Treg	regulatory T
CCI	[redacted]
ULN	upper limit of normal
US	United States
VLDL	very low density lipoprotein
$V_{z,u}/F$	unbound apparent volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	Women/females of childbearing potential

Appendix 2. Child-Pugh Classification (CPC) of Liver Dysfunction

Table 2-1: Scoring for Child-Pugh Classification

Cohort	CPC	Level of dysfunction	**Total Score** (tally based on assessment of parameters in **Table 2-2**)
1	Not Applicable	Without hepatic impairment	Not Applicable
2	A	Mild	5-6
3	B	Moderate	7-9
4	C	Severe	≥10

Table 2-2: Derivation of Child-Pugh Classification Score

Assessment Parameters	**Assigned score for observed findings**		
	1 point	**2 point**	**3 point**
Encephalopathy grade [a] (refer to **Table 2-3** below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Asymptomatic	Requiring intervention
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, sec prolonged	<4	4 to 6	>6

a. Subjects with a prior history of Grade 3 or 4 encephalopathy who are *currently* receiving an intervention [*for example*: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to manage encephalopathy-related signs and symptoms should be scored for encephalopathy grading *based on their presentation while on intervention at the Screening visit* and can be included in Study C1171006 so long as they do ***not*** have clinically active Grade 3 or 4 encephalopathy.

Table 2-3: Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4[a]	Unrousable coma, no personality/behavior, decerebrate

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

CPC should be assessed at Screening, *only* to determine the classification of a given subject.