Title Page

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS OF PF-07923568 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	143479
EudraCT/CTIS Number:	NA
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241012
Phase:	1

Brief Title: A Study to Investigate the Effects of Hepatic Impairment on the Pharmacokinetics of PF-07923568

Document History

Document	Version Date
Original protocol	23 February 2023

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Single-Dose, Parallel Group Study to Compare the Pharmacokinetics of PF-07923568 in Adult Participants With Varying Degrees of Hepatic Impairment Relative to Participants Without Hepatic Impairment

Brief Title:

A Study to Investigate the Effects of Hepatic Impairment on the Pharmacokinetics of PF-07923568

Regulatory Agency Identification Number(s):

US IND Number:	143479
EudraCT/CTIS Number:	NA
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241012
Phase:	1

Rationale:

The primary purpose of this study is to characterize the effect of varying degrees of HI on the plasma PK of PF-07923568 following administration of a single oral dose of PF-07923568.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary:	**Primary:**
• To compare the PK of PF-07923568 following administration of a single oral dose in adult participants with varying degrees of HI relative to age- and body weight-matched participants without HI.	• Plasma: C_{max}, AUC_{last} or AUC_{inf}*, as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-07923568 when administered to adult participants with varying degrees of HI and in age- and body weight-matched participants without HI.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, ECG parameters.

* AUC_{last} will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf}, otherwise they will be treated as tertiary endpoints.

Overall Design:

This is an open-label, single-dose, parallel-group, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-07923568 after a single, oral CCI mg dose administered in the fed state (standard breakfast). Safety and tolerability will be evaluated throughout the study.

Number of Participants:

Approximately 28-32 participants will be enrolled to receive study intervention.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Key Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for study enrollment:

<u>All Groups</u>

- Males or females between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive at the screening visit.
- Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
- BMI of 17.5 to 38.0 kg/m^2, inclusive, and a total body weight >50 kg (110 lb).
- Capable of giving signed informed consent.

<u>*Additional* for Group 1 *Only* (without HI)</u>

- At screening, no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, including BP and pulse rate measurement, standard 12-lead ECG and clinical laboratory tests.

- At screening, meet the demographic-matching criteria, including body weight within ±15 kg and age within ±10 years, of the average of the pooled hepatic impairment groups, as provided by the sponsor.

- No known or suspected hepatic impairment and meet all the following criteria based on screening laboratory tests: ALT ≤ ULN, AST ≤ ULN, T bili ≤ ULN, albumin ≤ ULN, and PT ≤ ULN.

Additional for Groups 2-4 *Only* (Mild, Moderate, and Severe HI)

- Stable hepatic impairment that meets criteria for Class A, B, or C of the Child-Pugh classification with no clinically significant change in disease status within 28 days before screening.

- Stable concomitant medications for the management of individual participant's medical history.

Key Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

All Groups

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

- At screening, a positive result for HIV antibodies.

- History of surgery that would be expected to alter absorption, distribution, metabolism, or excretion properties of PF-07923568 (eg, status post portacaval shunt surgery).

- Other medical or psychiatric condition or laboratory abnormality that may increase the risk of study participation or make the participant inappropriate for the study.

- Use of specific prohibited prior/concomitant therapies as outlined in the protocol including use of an investigational product within 30 days (or local requirement) or 5 half-lives (whichever longer), or 14 days plus 5 half-lives for moderate and strong CYP3A inducers or time-dependent inhibitors, before study dose.

- eGFR <60 mL/min/1.73m^2 (calculated with the 2021 CKD-EPI Scr-Scys combined equation) at screening.

- A positive urine drug test at screening or Day -1; however, ***participants in Groups 2-4, only***, who have been medically prescribed medications and report use at screening may be allowed after sponsor approval.

- At screening ***or*** Day -1, a positive breath alcohol test.

- For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in women of childbearing potential at Day -1.

Additional Group 1 *Only* (without HI)

- Evidence of chronic liver disease including history of hepatitis, hepatitis B, or hepatitis C.

- History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of screening.

- Screening ***supine*** standard 12-lead ECG demonstrating QTcF interval >450 ms or a QRS interval >120 ms.

- Screening ***seated*** SBP ≥140 mmHg or DBP ≥90 mmHg, following ≥5 minutes of seated rest.

- Use of ***chronic*** prescription medications within 7 days or 5 half-lives (whichever is longer) before Day 1, or for prohibited medications, use within the required washout/restriction period in the protocol.

Additional Exclusion Criteria for Groups 2-4 *Only* (Mild, Moderate, and Severe HI)

- Hepatic carcinoma ***or*** hepatorenal syndrome ***or*** limited predicted life expectancy (defined as <1 year).

- A diagnosis of hepatic dysfunction secondary to any acute ongoing hepatocellular process that is documented by medical history, PE, liver biopsy, hepatic ultrasound, CT scan, or MRI.

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

- Signs of clinically active Grade 3 or 4 hepatic encephalopathy (ie, > Grade 2 Portal Systemic Encephalopathy score).

- Severe ascites and/or pleural effusion, except for those categorized in **Group 4** who may be enrolled provided participant is medically stable, per the investigators' medical judgment.

- Previously received a kidney, liver, or heart transplant.

- Screening ***supine*** 12-lead ECG demonstrating a QTcF interval >470 ms or a QRS interval >120 ms.

- At screening, Day -1, or pre-dose on Day 1, persistent severe, uncontrolled hypertension.
- ALT ***or*** AST >5x ULN on clinical laboratory tests at screening.

Study Arms and Duration:

A total of approximately 28-32 participants with varying degrees of hepatic function will be administered a single, oral CCI mg dose of PF-07923568 in the fed state as shown in the table below.

Hepatic Function Categories Based on Child-Pugh Score

Group	Description	Child-Pugh Score	Number of Participants
1	Without hepatic impairment	Not Applicable	8[a]
2	Mild hepatic impairment	Class A (5 to 6 points)	8
3	Moderate hepatic impairment	Class B (7 to 9 points)	8
4	Severe hepatic impairment	Class C (10 to 15 points)	4-8[b]

a. Additional participants may be dosed to a maximum of 10 participants to ensure mean age ±10 years and mean body weight ±15 kg of this group is aligned with the pooled average assessed when approximately ≥75% of participants are dosed across the other 3 groups.

b. The total number of participants enrolled that are classified as having severe HI will be a minimum of 4 to a maximum of 8 depending on recruitment rates.

Categorization of participants into Groups 2-4 will be done based on Child-Pugh scores determined at the screening visit.

Staged Enrollment of Study Groups

Participants will be dosed in a staged manner as follows:

- Participants with moderate HI (Group 3) and severe HI (Group 4) will be enrolled first.
- Recruitment of participants with mild HI (Group 2) will initiate when approximately 50% of the participants in Group 3 have been dosed.
- ***Sponsor approval is required before proceeding with recruitment of Group 2.***
- An average value for age and weight for the 3 HI groups (Groups 2-4) will be determined and participants without HI (Group 1) will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 2-4.

- Recruitment for healthy participants in Group 1 (without HI) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 15 to 18 participants) have been dosed.

- ***Sponsor approval is required before proceeding with recruitment of Group 1.***

For individual participants, the total duration of participation from the screening visit to the follow-up visit will range from approximately 5 weeks (minimum) to approximately 8 weeks (maximum). The study consists of an initial screening period of up to 28 days (while allowing for the return and review of all results, including laboratory tests), a 6-day inpatient stay at the CRU which includes administration of a single oral dose of PF-07923568, and a follow-up contact that will occur 28-35 days after PF-07923568 administration.

PF-07923568 will be supplied by Pfizer as CCI mg capsules in open-label bulk bottles along with individual dosing containers, as necessary, for unit dosing. For the CCI mg dose administered in this study, participants will take 4 PF-07923568 CCI mg capsules orally with the morning meal.

Study Intervention(s)	
Intervention Name	PF-07923568
Arm Name (group of participants receiving a specific treatment or no treatment)	Group 1, Group 2, Group 3, Group 4
Unit Dose Strength(s)	CCI mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP

Arm Title	Group 1	Group 2	Group 3	Group 4
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants without HI will receive a single CCI mg dose of PF-07923568 administered orally as 4 PF-07923568 CCI mg capsules	Participants with mild HI will receive a single CCI mg dose of PF-07923568 administered orally as 4 PF-07923568 CCI mg capsules	Participants with moderate HI will receive a single CCI mg dose of PF-07923568 administered orally as 4 PF-07923568 CCI mg capsules	Participants with severe HI will receive a single CCI mg dose of PF-07923568 administered orally as 4 PF-07923568 CCI mg capsules

Statistical Methods:

A sample size of approximately 28-32 participants (approximately 8 participants per Groups 1-3, and 4-8 participants in Group 4 based on recruitment rate, with varying degrees of hepatic function in each of the 4 groups) has been selected based on recommendation from

the "FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".[1] Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

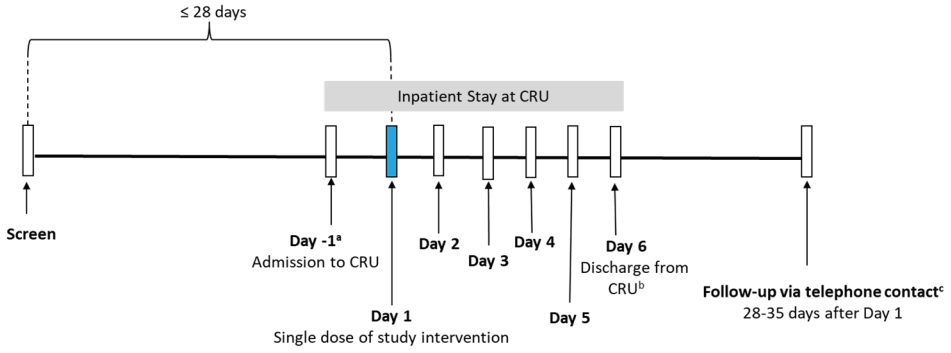
The effect of varying degrees of HI on PK parameters will be assessed by constructing 90% CI around the estimated difference between each of the Test (hepatic impaired) groups and the Reference (without hepatic impairment) group. A one-way ANOVA will be used to compare the natural log transformed PF-07923568 AUC_{inf}, C_{max}, and AUC_{last}, as data permit, for each of the hepatic impairment groups (Test) to the group without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test /Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

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

Ethical Considerations:

A single dose of PF-07923568 administered in this study is not expected to provide any clinical benefit to study participants. This study is designed primarily to characterize the effect of varying degrees of HI on the PK of PF-07923568. Results from this study will be used in conjunction with collective safety, tolerability, efficacy, and PK/PD data from other PF-07923568 studies to develop dosing recommendations for the target patient populations with varying degrees of hepatic function.

1.2. Schema



a. Admission can occur at any time of day; once admitted, participant to be provided inpatient meal(s).
b. Following completion of procedures and morning meal, participant will be discharged from the CRU.
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion, in the window of 28 to 35 days after Day 1.

1.3. Schedule of Activities

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

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

Table 1. Study Schedule of Activities

Visit Identifier/Day *[list of abbreviations in Appendix 11]*	Screen ≤-28 to -2	Day -1	Day 1											Day 2	Day 3	Day 4	Day 5	Day 6	ET	Follow-up[a] Day 29-36
Hours Post Dose		--	0	1	2	3	4	5	6	8	10	12	14	24	48	72	96	120	--	--
Informed consent & demography	x																			
Outpatient visit	x																			
Inpatient stay at CRU		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x		
COVID-19 assessment[b]																				
Eligibility assessment	x	x	x																	
Medical history	x																			
Child-Pugh Classification scoring	x																			
PE (height & weight at screening only)[c]	x	x																x	x	
Breath alcohol & Urine drug test	x	x																		
Alcohol/tobacco & contraception use[d]	x	x																x	x	x
(Update) Prior/concomitant treatments	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Single, *supine* 12-lead ECG[e]	x	x	x[e]											x				x	x	
Single, *seated* vital signs (BP, pulse rate)[e]	x	x	x[e]											x				x	x	
AE monitoring (non-serious & SAEs)	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Standard meals/optional snacks[f]		x[f]	x				x		x		x		x	x	x	x	x			
Study intervention administration[g]			x																	
Blood & Urine for clinical laboratory tests[h]	x		x[j]															x	x	
Serology for FSH (all females), HIV, HBsAg, HCVAb/RNA	x																			
Serum pregnancy test (all females)	x																			
Urine pregnancy test (WOCBP only)[i]		x																x	x	
Blood for PK sampling for PF-07923568 and Blood:Plasma			x[j]	x	x	x	x	x[k]	x	x		x[k]		x	x	x	x	x	x	
Retained Research Sample for Genetics (Prep D1)[l]			x[j]																	

Table 1. Study Schedule of Activities

Visit Identifier/Day *[list of abbreviations in Appendix 11]*	Screen ≤-28 to -2	Day -1	Day 1											Day 2	Day 3	Day 4	Day 5	Day 6	ET	Follow-up[a] Day 29-36
Hours Post Dose		--	0	1	2	3	4	5	6	8	10	12	14	24	48	72	96	120	--	--
Retained Research Sample for Biomarkers (Prep B2)[m]			x[j]																	

a. Follow-up visit to be performed as telephone contact and must occur in the window of 28 to 35 days (ie, Day 29-36) from administration of study intervention. A clinic visit may be performed in place of telephone contact, if deemed necessary by the investigator, eg, for follow-up of abnormal laboratory tests and/or open AEs.

b. Assessment of risk for, symptoms of or testing for COVID-19 may be performed at screening, admission to the CRU, and/or at other times during the study at investigator discretion and according to local site policies.

c. Complete PE at screening; at all other time points limited PE, at investigator discretion (see Section 8.3.1).

d. In confirmation of appropriate contraception use only.

e. If done around the time of a blood draw, ECG and vital sign assessments (BP and pulse rate) should be collected before the blood draw. ECG and vital signs on Day 1 at Time 0H must be done before collection of the pre-dose blood samples. If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (BP and pulse rate) should be collected before insertion of the catheter.

f. Meals/snacks to be served at clock times matching approximately 0H, 4H, 6H (optional snack), 10H, and 14H (optional snack) relative to dosing on Day 1, while inpatient. Meals/snacks on Day -1 must be timed such that there is at least an 8 hour fast prior to collection of the pre-dose PK sample on Day 1 (see Section 5.3.2).

g. Dosing to occur with standard morning meal provided approximately 30 minutes prior to 0H, and meal completed approximately 10 minutes prior to dosing.

h. Safety related laboratory tests collected on Day -1, ***if performed*** at investigator discretion, must be reviewed prior to dosing and must reflect the participant to be in stable medical condition.

i. Test result must be reviewed and deemed acceptable (ie, negative) to continue participation in the study.

j. Samples at 0H on Day 1 must be collected pre-dose.

k. Whole blood aliquot (approximately 0.15 mL) will be collected from PK samples for in vivo blood:plasma ratio assessment.

l. Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

m. Prep B2 Retained Research Samples for Biomarkers: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

2. INTRODUCTION

PF-07923568 (sisunatovir) is being developed to act as a highly potent, selective, orally available agent to treat and prevent RSV infection. PF-07923568 is an inhibitor of CCI [redacted] that is currently being investigated for the treatment of RSV infection.

2.1. Study Rationale

The primary purpose of this study is to characterize the effect of varying degrees of HI on the plasma PK of PF-07923568 following administration of a single oral dose of PF-07923568.

2.2. Background

RSV, a member of the Pneumovirus family, is a significant pathogen of the very young, immunocompromised, and the elderly. RSV is ubiquitous and is known to infect almost all children by 2 years of age.[2] The clinical manifestation of RSV infection is typically mild upper respiratory tract illness.[3] However, in infants, young children, the immunocompromised, and the elderly, it can cause serious LRTI.[4] Infants <6 months of age are at the highest risk of severe RSV infection which can lead to hospitalization, ICU admission, and even death.[5]

The current management of RSV infection includes a combination of preventative and limited treatment measures, primarily consisting of supportive care. Ribavirin, a nucleoside analogue, is currently the only licensed antiviral for the treatment of RSV in children (Virazole®).[6] There is no approved antiviral for the treatment of RSV in other age groups. Most current guidelines make either no recommendation or do not recommend routine use of ribavirin due to its weak antiviral capacity, inherent toxicity and teratogenic potential.[7] Thus, a placebo-controlled design is considered appropriate for trials of new antiviral agents for the treatment of RSV. Palivizumab (Synagis®) is a prophylactic monoclonal antibody that has been shown to protect infants against RSV disease and is used in specified high risk infant groups. Despite the availability of these agents, their limited use means that treatment of RSV infection remains an area of unmet need.

PF-07923568 is a potent inhibitor of CCI [redacted] The RSV F protein is essential for the entry of the virus to the host cell. Cell surface expression of the F protein also causes CCI [redacted] leading to the giant syncytia characteristic of RSV infection.

The PF-07923568 preclinical profile, as well as the safety and tolerability data from the first human dosing studies, provide a strong rationale for the clinical development of PF-07923568.

2.2.1. Nonclinical Pharmacology

CCI [redacted]

[redacted] An in vitro secondary pharmacology study did not reveal any significant off-target activity for PF-07923568.

Details of the nonclinical pharmacology program are included in the IB which is the SRSD for this study.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In animal PK studies, PF-07923568 showed slow oral absorption, moderate-high CL, high volume of distribution, and oral bioavailability of 46%, 42-132%, and 44% in mouse, rat, and dog, respectively.

Plasma protein binding of PF-07923568 was low to moderate across species, with average fraction unbound of 67%, 38%, 52%, 27%, and 48% in human, mouse, rat, dog, and guinea pig, respectively. Repeat dosing studies in the rat show that extensive distribution of PF-07923568 to the lungs occurs, resulting in high lung-to-plasma ratio. This effect is greater than dose proportional from 50 mg/kg to 150 mg/kg.

Consistent with the results of the midazolam DDI study (C5241004), *in vitro* studies indicate that CYP3A4 is the main CYP isoform that metabolizes PF-07923568 with minor contribution from CYPs 2C9 and 2D6.

In vitro studies indicate a DDI risk exists for OATP1B1/1B3, OCT1, MATE1, OCT2, and OAT3. However, ratios of unbound hepatic inlet concentrations relative to Ki values are low, and DDI risk is considered unlikely for OATPs, OCT2, and OAT3.

Additionally, in vitro studies indicate there is a risk of inhibition of CYPs 1A2, 2B6, 2C9, 2C19, and 3A4. The DDI with CYPs 1A2, 2C9, and 2C19 is predicted to be minimal (predicted less than 25% increase in AUC of a sensitive substrate) and DDI with CYP2B6 is predicted to be weak. A DDI study conducted with sisunatovir (CCI [redacted] and CCI [redacted] as a sensitive CCI [redacted] probe substrate (C5241004) indicate that sisunatovir is CCI [redacted]

In vitro studies indicate that sisunatovir is a P-gp substrate; therefore, co-administration of inhibitors for the transporter (P-gp) may result in increased exposure to sisunatovir (approximately 2-fold). A clinical DDI study (C5241004) indicated that CCI [redacted] coadministration produced an approximately CCI [redacted] in exposure to sisunatovir.

The major metabolites produced in all species appeared to be hydroxylated metabolites although some Phase 2 metabolites were also detected in all species. The metabolite profile in the rat, mouse, dog, guinea pig, and human were similar with the exception of M4, an apparent double hydroxylation only apparent in human at low levels.

Further details of the nonclinical PK and metabolism program are included in the IB.

2.2.3. Nonclinical Safety

In the repeat dose toxicity studies in adult (up to 28 days) and neonatal/juvenile rats and dogs, the MTDs were defined by body weight loss and reduced food consumption accompanied by adverse clinical observation of varying severity. In dogs, there was dose-related incidence of emesis and liquid feces at ≥15 mg/kg/day. The key target organ for toxicity in adult animals was the hepatobiliary system, which included both degenerative and inflammatory changes in bile duct, in rats (≥60 mg/kg/day) and dogs (≥45 mg/kg/day). In dogs, the hepatobiliary findings correlated with elevated plasma levels of ALP, ALT, and GGT. In addition, the findings observed only in rats were in kidney (degeneration/regeneration of medullary tubules) at ≥120 mg/kg/day, lung (vascular degeneration/necrosis) at 240 mg/kg/day (non-tolerated dose), and trachea (epithelial degeneration and subepithelial inflammation [predominantly in females]) at 120 mg/kg/day in 14 and/or 28-day studies. In the 28-day dog repeat dose toxicity study, the NOAEL was 15 mg/kg/day corresponding to C_{max} of 729 ng/mL and AUC_{tau} of 9510 ng.h/mL. In the 28-day rat repeat dose toxicity study, the NOAEL was 60 mg/kg/day corresponding to C_{max} of 322 ng/mL and AUC_{tau} of 4725 ng.h/mL.

In the embryo-fetal toxicity studies in rat (GD6-17) and rabbit (GD6-18), there were no effects on pregnancy or embryo-fetal development. In rat, the NOAEL for maternal toxicity was 45 mg/kg/day based on the transient initial body weight loss followed by dose-related decreased body weight gain at ≥45 mg/kg/day. The NOAEL for embryo-fetal toxicity in rat was 60 mg/kg/day, corresponding to systemic maternal exposure (AUC_{24}) of 9830 ng.h/mL on Day 15 of gestation. In rabbit, maternal toxicity was limited to lower body weight gain and food intake at 45 mg/kg/day. The NOAEL for embryo-fetal development in rabbit was 45 mg/kg/day, corresponding to a systemic maternal exposure (AUC_{24}) of 220 ng.h/mL on Day 16 of gestation.

Further details of the nonclinical toxicology program are included in the IB.

2.2.4. Clinical Overview

Table 2. Completed PF-07923568 Studies

Study Number (Status)	Study Type/Key Design Features	Study Population	Dose, Dosing Regimen	Formulation Used
C5241001-previously REVC001[a] (completed)	Phase 1, randomised, double-blind, placebo-controlled, safety, tolerability, PK, food-effect of single ascending dose (SAD) and multiple ascending dose (MAD)	Healthy participants	Dose range: 10 mg – 525 mg (SAD); 36 participants Dose range: 175 mg – 350 mg; BID (MAD), food effect; 24 participants	Liquid Formulation DIC
C5241002-previously REVC002 (completed)	Phase 2a, randomised, double-blind, placebo-controlled	Healthy participants inoculated with RSV CV	200 mg or 350 mg BID for a total 10 doses; 66 participants	DIC
C5241004-previously REVC004 (completed)	Phase 1, adaptive, part-randomised, part open-label, drug interactions, safety and tolerability	Healthy participants	200 mg; BID; 62 participants	DIC
C5241005-previously REVC005 (completed)	Phase 1, open-label, single-dose, PK, safety, and tolerability	Healthy participants	200 mg, 4 single doses total; 9 participants 1 ×: DIC (fed) 1 ×: DPB (fed) 1 ×: DPB dispersed in H_2O (fed) 1 ×: DPB dispersed in H_2O (fasted) [wash-out: 3 days between each of the 4 dosing days]	DIC DPB

a. A total of 8 participants received the liquid dosage formulation of PF-07923568 in a solution, at a concentration of 5 mg/mL, containing hydroxypropyl-β-cyclodextrin (HBP cyclodextrin), Lycasin, flavoring agent (strawberry) benzoic acid and water, and 68 subjects received DIC in the study.

Abbreviations: BID = twice-daily dosing; DIC = PF-07923568 drug in capsule; DPB = PF-07923568 dry powder blend; MAD = multiple ascending dose; PK = pharmacokinetic; RSV = respiratory syncytial virus; RSV CV = RSV challenge virus; SAD = single ascending dose.

A total of 201 adult healthy participants have received PF-07923568 in 4 completed clinical studies (C5241001, C5241002, C5241004, and C5241005) investigating the PK profile, effects of food on PK, effects of formulation on PK (C5241001, C5241005), DDIs (C5241004), and the efficacy in an RSV Viral Challenge Study (C5241002) at doses ranging

from 10 mg to 525 mg. In addition, as of 14 November 2022, 49 pediatric patients hospitalized due to RSV LRTI have been enrolled into the ongoing C5241003 study.

The administration of PF-07923568 was well tolerated at all doses, dosage forms, and dosing regimens tested. In the adult healthy participants treated to date, the occurrence of TEAEs considered related to PF-07923568 has been low. Most commonly reported treatment-related TEAEs were in the GI disorders SOC; nausea, diarrhea, and abdominal pain. These TEAEs have been mild to moderate in intensity and resolved without sequelae. Most events attributed to IMP involved the GI tract with nausea, diarrhea, and abdominal pain/discomfort/distension being the most common and occurring more commonly with the 350 mg dose of PF-07923568 than with the 200 mg PF-07923568 dose, where the number of participants reporting these events were lower and similar to those on placebo. In children, PF-07923568 is required to be suspended in a solution to enable oral administration, there has been evidence of poor tolerability when PF-07923568 was suspended in water as a single dose of 2.0 mg/kg in children aged 6-36 months, resulting in expulsion of the oral dose. Suspension in breast milk, formula milk, or saline appeared to improve the palatability, with all doses being successfully administered to children aged 1-36 months in study C5241003.

As of 22 November 2022, there have been no SAEs attributable to PF-07923568 and no deaths in the clinical studies.

In adults, under both fasting and fed conditions, PF-07923568 is slowly absorbed reaching maximum plasma concentrations (t_{max}) at 5-6 hours (hrs) with a relatively moderate clearance, resulting in a half-life of 7-10 hrs in healthy participants. Dosing to steady state resulted in steady state concentrations being reached after approximately 2 days of dosing resulting in 2-4 fold accumulation of exposure. AUC and C_{max} values increased in a greater than dose proportional manner across single and multiple dose studies. Following 5 days of dosing, the variability in PK parameters was high, with % CV ranging from 67.4-84% for C_{max} and 71.9-144% for AUC_{12}.

The effect of food on the single dose PK was assessed for the DIC formulation and DPB formulation dispersed in water. For the DIC the extent of systemic exposure to PF-07923568 (geometric mean AUC_{inf} under fed and fasted conditions) was 357 and 221 ng.h/mL, respectively, with the between-subject variability being lower under fed conditions (CV 64.1% compared with 198%). The ratio of fed/fasted was 218% (90% CI 94.2 - 502%) for C_{max} and 162% (90% CI 83.0 – 316%) for $AUC_{0\text{-}inf}$. It should be noted that the DIC fasted results from C5241001 were lower than typically seen in other studies with 200 mg administered under fasting conditions resulting in an artificially higher ratio of fed/fasted in this study. For the DPB dispersed in water the extent of systemic exposure to PF-07923568 (geometric mean AUC_{inf}) under fed and fasted conditions was 371 and 337 ng.h/mL, respectively, with the between-subject variability being slightly lower under fasted conditions (CV 49.0% compared with 61.6%). The ratio of fed/fasted was 107.7% (90% CI 78.0 – 148.8%) for C_{max} and 110.0% (90% CI 85.6 – 141.4%) for AUC_{inf}.

Clinical DDI Study C5241004 demonstrated that the disposition of PF-07923568 is expected to be affected by moderate to strong inhibitors and inducers of CYP3A4. Furthermore,

PF-07923568 was demonstrated to be a moderate inhibitor of CYP3A4, so dose adjustments for compounds that are sensitive substrates for CYP3A4 may need to be considered.

In an RSV challenge study, PF-07923568 treatment resulted in a statistically significant reduction in AUC of RSV viral load compared with placebo; 55.25% (p=0.007) and 63.05% (p=0.002) for the 200 mg and 350 mg PF-07923568 dose groups, respectively (dosed every 12 hrs [Q12H] for 5 days). Results for the AUC of total symptom score were consistent with the viral load AUC. Geometric mean AUCs of total symptom score were 195.56, 30.79, and 31.76 hrs for placebo, 200 mg PF-07923568 and 350 mg PF-07923568, respectively. The reduction in AUCs of total symptom score compared with placebo was statistically significant for both PF-07923568 treatment groups; p=0.009 (70.84%) and p=0.002 (74.42%), (Wilcoxon Rank-Sum test) for the 200 mg and 350 mg PF-07923568 dose groups, respectively.

More detailed information about results of clinical studies for PF-07923568 may be found in the IB.

2.3. Benefit/Risk Assessment

PF-07923568 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

For healthy participants participating in this study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of PF-07923568 as a potential new, pharmacological agent for the treatment of RSV. As of 14 September 2022, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.3. The clinical impact of these potential risks will be minimized through standard, intensive, inpatient monitoring of the participants following administration of multiple oral doses of the study intervention.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sisunatovir may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07923568		
Hepatobiliary system effects	Degenerative and inflammatory changes in the bile duct of both rats (≥60 mg/kg/day) and dogs (≥45 mg/kg/day) in studies of up to 28 days, with elevated plasma levels of ALP, ALT, and GGT in dogs only. Evidence of recovery for all findings following a 14-day treatment-free period.	Standard monitoring including laboratory (ie, transaminases, ALP, GGT) and AE monitoring.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal effects	Transient dose-related incidence of emesis and liquid feces in dogs at doses ≥15 mg/kg/day in studies up to 28 days. Additionally, inflammation in the duodenum, gall bladder, and liver at 45 mg/kg/day noted in 28-day dog study. In previous clinical studies sisunatovir has been associated with mild GI AEs in fasted state.	As this is an investigational agent, there is some risk that is mitigated by close observation of AEs, etc. Participants will be closely evaluated in an inpatient setting to monitor for GI AEs. If needed, palliative alleviating measures such as antiemetics may be provided.
Renal effects	Degeneration/regeneration of medullary tubules was noted in rats at ≥120 mg/kg/day in studies of up to 28 days; considered non-adverse based on lack of clinical pathology changes.	Standard monitoring including laboratory and AE monitoring.
Cardiovascular effects	Myocardial degeneration and necrosis were noted at 240 mg/kg/day (non-tolerated dose) in a 14-day rat study. No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days. Phase 1 first-in-human (FIH) study (C5241001) showed no adverse clinically significant changes in safety laboratory parameters (including troponin), ECGs, and VS.	Monitoring will include VS, including heart rate and ECG assessments.
Pulmonary effects	Vascular degeneration/necrosis in lung at 240 mg/kg/day and epithelial degeneration/necrosis in trachea at 120 mg/kg/day in 14-day rat study. No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days. Phase 1 FIH study (C5241001) showed no adverse clinically significant changes in safety laboratory parameters (including troponin), ECGs, and VS.	There will be standard safety monitoring including VS and AEs.
Thymus effects	Lymphoid atrophy and decreased thymus weight and reduced size of thymus in both rats (≥120 mg/kg/day) and dogs ≥15 mg/kg/day) in studies of up to 28 days. Evidence of recovery following a 14-day treatment-free period. These findings are secondary to stress and not directly sisunatovir-related.	Standard monitoring including laboratory (ie, complete blood count with differential) and AE monitoring. Single dose regimen should further limit this potential risk.
Other		
Risk of COVID-19 exposure during study	During the pandemic, study participants could be exposed to the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Assessment of risk for, symptoms of, or testing for COVID-19 may be performed at screening, admission to the CRU, and/or at other times during the study at investigator discretion and according to local site policies.

2.3.2. Benefit Assessment

A single dose of PF-07923568 is not expected to provide any clinical benefit to study participants. This study is designed primarily to characterize the effect of varying degrees of hepatic impairment on the PK of PF-07923568 to support further clinical development of PF-07923568 as a potential treatment of RSV. Results from this study will be used in conjunction with collective safety, tolerability, efficacy, and PK/PD data from other PF-07923568 studies to develop dosing recommendations for the target patient population with varying degrees of hepatic function.

2.3.3. Overall Benefit/Risk Conclusion

PF-07923568 is not expected to provide any clinical benefit to healthy participants in this study.

Based on the profile of PF-07923568 observed in nonclinical and clinical studies to date, and taking into account the measures to minimize risk to study participants, the potential risk to the participants in this study is deemed to be minimal and is justified by the anticipated benefits that may be afforded to patients with varying degrees of HI receiving PF-07923568 in the future.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary:	**Primary:**
• To compare the PK of PF-07923568 following administration of a single oral dose in adult participants with varying degrees of HI relative to age- and body weight-matched participants without HI.	• Plasma: C_{max}, AUC_{last} or AUC_{inf}*, as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-07923568 when administered to adult participants with varying degrees of HI and in age- and body weight-matched participants without HI.	• Assessment of TEAEs, clinical laboratory abnormalities, VS, ECG parameters.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare additional PK parameters of PF-07923568 following administration of a single oral dose in adult participants with varying degrees of HI and in age- and body weight-matched participants without HI.	• Plasma: CL/F, V_z/F, T_{max} and $t_{1/2}$ as data permit.

* AUC_{last} will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf}, otherwise they will be treated as tertiary endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-dose, parallel-group, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-07923568 after a single, oral CCI mg dose administered in the fed state (standard breakfast). Safety and tolerability will be evaluated throughout the study. A total of approximately 28-32 participants with varying degrees of hepatic function will be administered as a single, oral CCI mg dose of PF-07923568 in the fed state as shown in Table 3.

Table 3. Hepatic Function Categories Based on Child-Pugh Score

Group	Description	Child-Pugh Score	Number of Participants
1	Without HI	Not Applicable	8[a]
2	Mild HI	Class A (5 to 6 points)	8
3	Moderate HI	Class B (7 to 9 points)	8
4	Severe HI	Class C (10 to 15 points)	4-8[b]

a. Additional participants may be dosed to a maximum of 10 participants to ensure mean age ±10 years and mean body weight ±15 kg of this group is aligned with the pooled average assessed when approximately ≥75% of participants are dosed across the other 3 groups.

b. The total number of participants enrolled that are classified as having severe HI will be a minimum of 4 to a maximum of 8 depending on recruitment rates.

Categorization of participants into Groups 2-4 will be done based on Child-Pugh scores determined, as described in Appendix 10 at the screening visit.

Staged Enrollment of Study Groups

Participants will be dosed in a staged manner as follows:

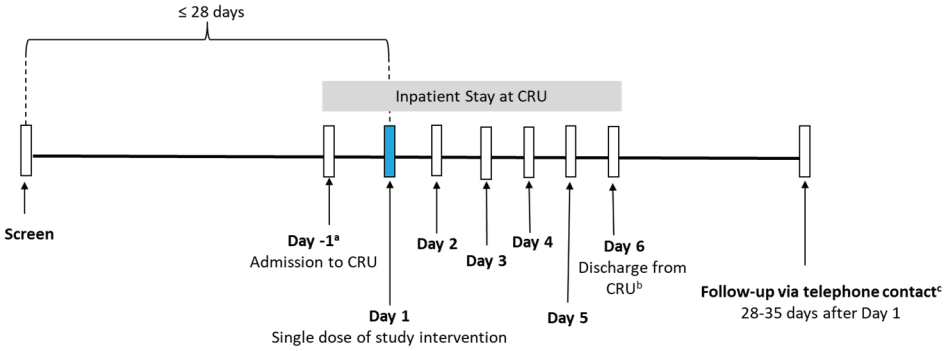
- Participants with moderate HI (Group 3) and severe HI (Group 4) will be enrolled first.
- Recruitment of participants with mild HI (Group 2) will initiate when approximately 50% of the participants in Group 3 have been dosed.
- ***Sponsor approval is required <u>before</u> proceeding with recruitment of Group 2.***
- An average value for age and weight for the 3 HI groups (Groups 2-4) will be determined and participants without HI (Group 1) will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 2-4.

- Recruitment for healthy participants in Group 1 (without HI) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 15 to 18 participants) have been dosed.

- ***Sponsor approval is required <u>before</u> proceeding with recruitment of Group 1.***

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

The overall study design is presented as a schematic in Section 1.2 and below. For individual participants, the total duration of participation from the screening visit to the follow-up visit will range from approximately 5 weeks (minimum) to approximately 8 weeks (maximum). The study consists of an initial screening period of up to 28 days (while allowing for the return and review of all results, including laboratory tests), a 6-day inpatient stay at the CRU which includes administration of a single oral dose of PF-07923568, and a follow-up contact that will occur 28-35 days after PF-07923568 administration.



a. Admission can occur at any time of day; once admitted, participant to be provided inpatient meal(s).
b. Following completion of procedures and morning meal, participant will be discharged from the CRU.
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion, in the window of 28 to 35 days after Day 1.

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of varying degrees of HI on the PK, safety and tolerability of PF-07923568. A single dose of PF-07923568 is proposed, as single dose plasma PK of PF-07923568 is generally predictive of exposure upon repeated dosing. Mean predicted accumulation index for a single dose of 175-350 mg comparable to the mean observed accumulation after multiple doses of 175-350 mg BID for 5 days.

There is uncertainty of the effect of HI on PF-07923568 PK. *In vitro* and *in vivo* studies indicate that PF-07923568 is predominantly eliminated through hepatic metabolism. CYP3A4 is the main CYP isoform that metabolizes PF-07923568 with minor contribution from CYPs 2C9 and 2D6. Based on review of the effect of hepatic impairment on human PK for compounds cleared in a similar manner to PF-07923568 (CYP3A-mediated metabolism), impaired hepatic function is generally associated with increased drug exposures in plasma (internal data and data cited in University of Washington Drug Interaction Database).

However, the magnitude of this increase in exposure is variable between compounds with some being only modestly impacted, while others exhibit increases in exposure even greater than 2-fold when participants with severe hepatic impairment are considered. As such, this study will enroll participants with varying degrees of hepatic impairment, and participants without hepatic impairment (matched for age as well as body weight and gender, as much as practically possible) in order to allow a robust assessment of PK across the entire spectrum of hepatic function.

Nonclinical studies indicate that the clearance of sisunatovir following oral administration to rats is predominantly hepatic. A rat bile-duct cannulated study showed negligible renal excretion (Study PPN70-058.04). Furthermore, an ADME (absorption, distribution, metabolism, and excretion) study in male Sprague-Dawley rats that received a single oral administration of [^{14}C]-sisunatovir showed that excretion was predominantly via the fecal route and urine accounted for <4% of the dose (Study RVL/01). It is anticipated that renal excretion will be similarly low in humans.

Given the elimination of sisunatovir via hepatic enzymes with minimal contribution by renal elimination, it is expected that HI could have an effect on the clearance of sisunatovir. Following administration of single doses of PF-07923568, the arithmetic mean terminal t½ of PF-07923568 ranged from 7-10 hours. Even with a possible modest increase in half-life, serial PK samples will be collected over 120 hours post-dose, which is expected to adequately characterize the elimination phase of the plasma concentration-time profile in the cohorts with varying degrees of HI. The protein binding of PF-07923568 in humans is 33%, resulting in a high fu of 67%.

Available PK data with PF-07923568 administered under fasted or fed conditions indicate that PF-07923568 may be administered without regard to food. Overall, adminstration of PF-07923568 with food results in a slight reduction in observed variability and trended towards having fewer GI TEAEs. In this study, a single dose of CCI mg PF-07923568 will be administered with a standard breakfast to reflect the conditions for anticipated use of PF-07923568 in future trials.

In general, participants with normal hepatic function (Group 1) will abstain from concomitant treatments, except for the treatment of AEs. Use of selected limited prescription and non-prescription medications may be permitted (refer to Section 6.9 for details). Participants with impaired hepatic function (Groups 2-4) are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s) with some exclusions (see Appendix 9). According to the DDI risk assessment for PF-07923568 as described in Section 2.2.2, sisunatovir is a moderate inhibitor of CYP3A4 and is projected to be a weak inhibitor of CYP2B6. For this reason sensitive and narrow TI CYP3A4 substrates and sensitive narrow TI CYP2B6 substrates are prohibited in this study. Since PF-07923568 is a P-gp and CYP3A4 substrate, strong and moderate CYP3A4 inhibitors and strong P-gp inhibitors are also prohibited. Lastly, due to risk of MATE1 and OCT1 inhibition, sensitive substrates of these transporters are prohibited.

To minimize the risks of COVID-19 related complications to participants and the study site personnel, assessment of risk for, symptoms of or testing for COVID-19 may be performed at screening, admission to the CRU, and/or at other times during the study at investigator discretion and according to local site policies.

The Child-Pugh Classification (refer to Appendix 10) will be used to define the 3 groups of participants with varying degrees of HI. This study will include participants with mild (Child-Pugh Class A, Group 2), moderate (Child-Pugh Class B, Group 3), and severe (Child-Pugh Class C, Group 4) HI as well as demographically matched control participants without HI (Group 1). All participants will be required to provide their own consent to participate in this study, hence participants with clinically active Grade 3 or Grade 4 encephalopathy will be excluded. However, participants who have a previous history of Grade 3 or 4 encephalopathy but are currently receiving an intervention (eg, lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin) to manage 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 their own informed consent. Acknowledging the medical state of the population enrolled, certain eligibility criteria for participants with hepatic impairment are distinctly different, with no specific exclusion of participants with Hepatitis B and Hepatitis C in Groups 2-4.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for sisunatovir, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore the use of a highly effective method of contraception is required for all fertile participants (see Appendix 4).

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

While there is uncertainty of the effects of HI on the exposure of PF-07923568 and the metabolism by CYP3A4, the proposed dose of CCI mg is expected to be safe and well-tolerated in participants with HI.

This dose has been selected based on prior experience in clinical studies with PF-07923568 (Section 2.2.4) demonstrating that it is safe and well tolerated. The clinical program for PF-07923568 has evaluated doses up to 350 mg twice daily (BID) for 5 days to date

The clinical program for PF-07923568 has evaluated doses up to 350 mg twice daily (BID) for 5 days to date. PF-07923568 was generally well tolerated in the viral challenge study (C5241002) as well as other Phase 1 studies conducted to date. However, under fasting conditions an increased incidence of GI AEs, primarily mild and moderate HI, were observed

at the 350 mg dose relative to the 200 mg dose. Higher rates of GI AEs were also observed at higher doses within the Phase 1 program. In these studies, sisunatovir was dosed in a fasted state. Although improved GI tolerability has been observed for some anti-infective agents when dosed with food, it is not clear if GI tolerability of sisunatovir will improve with food. The effect of food on the PK of sisunatovir has been variable in Phase 1 studies. However, the effect of food on the PK of sisunatovir using the formulation to be used in this study (DPB in capsules) showed minimal food effect accompanied by a decrease in observed variability. Given the above, it is anticipated that with a single CCI mg dose potential increases in plasma exposure in participants with varying degrees of hepatic impairment in the current study, if encountered, are not anticipated to pose an undue safety risk.

4.4. End of Study Definition

The end of the study is defined as the date of the follow-up as shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if they have completed all phases of the study, including the follow-up visit (telephone contact or onsite visit per investigator discretion) as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

5.1.1. Participants in All Groups

Age and Sex:

1. Male or female between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive, at the screening visit.

   WOCBP, however, cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Other Inclusion Criteria:

2. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations (as described in Section 5.3), and other study procedures.

3. BMI of 17.5 to 38.0 kg/m^2, inclusive; and a total body weight >50 kg (110 lb), at the screening visit; with a single repeat assessment of total body weight (and hence BMI), *on a separate day* before Day -1 permitted to assess eligibility, if needed.

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

5.1.2. *Additional* Inclusion Criteria for Group 1 *Only* (without HI)

1. At screening, no clinically relevant abnormalities identified by a detailed medical history, complete PE, including BP and pulse rate measurement, 12-lead ECG and clinical laboratory tests, as assessed by the sponsor approved laboratory.

2. At screening, participants must meet the demographic-matching criteria, including:

   - A body weight that is within ±15 kg of the average of the pooled hepatic impairment groups (Groups 2-4), as provided by the sponsor;
   - An age that is within ±10 years of the average of the pooled hepatic impairment groups (Groups 2-4), as provided by the sponsor;
   - ***Attempts will be made*** to ensure that the male-to-female distribution in Group 1 is comparable to that in the pooled hepatic impairment groups (Groups 2-4).

3. No known or suspected hepatic impairment, and meet **all** the following criteria at screening, as assessed by the sponsor approved laboratory, with a single repeat permitted to assess eligibility, if needed:

   - ALT ≤ ULN;
   - AST ≤ ULN;
   - T bili ≤ ULN.

   NOTE: Participants with a history of Gilbert syndrome (and hence elevated T bili) 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;
   - PT ≤ ULN.

5.1.3. ***Additional*** Inclusion Criteria for Groups 2-4 *Only* (Mild, Moderate, and Severe HI)

1. Stable hepatic impairment that meets the criteria for Class A, B, or C of the Child-Pugh classification (refer to Appendix 10) with no clinically significant change in disease status within the 28 days prior to the screening visit, as documented by the participant's recent medical history (eg, no worsening clinical signs of hepatic impairment, no worsening of T bili or PT by more than 50%).

2. Stable concomitant medications for the management of individual participant's medical history; ***on a case-by-case basis***, with approval from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

5.2. Exclusion Criteria

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

5.2.1. Participants in All Groups

Medical Conditions:

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

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

2. At screening, a positive result for HIV antibodies, as assessed by sponsor approved laboratory, with a single repeat permitted to assess eligibility, if needed.

3. History of surgery that would be expected to alter absorption, distribution, metabolism, or excretion properties of PF-07923568 (eg, status post portacaval shunt surgery).

   NOTE: Participants with a trans-jugular intrahepatic portosystemic shunt are permitted provided that they meet the Child-Pugh criteria.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy

5. Use of specific prohibited prior/concomitant therapies as outlined in Section 6.9, Appendix 9. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Investigational products which are strong CYP3A inducers or time-dependent inhibitors are prohibited within 14 days plus 5 half-lives prior to the dose of study intervention.

Prior/Concurrent Clinical Study Experience:

6. Known prior participation (ie, received at least 1 dose of study intervention) in a study involving PF-07923568.

Diagnostic Assessments:

7. eGFR <60 mL/min/1.73m^2 (calculated with the 2021 CKD-EPI Scr-Scys combined equation, see Appendix 7), at the screening visit, as assessed by the sponsor approved laboratory, and confirmed by a single repeat test, if deemed necessary.

8. A positive urine drug test at screening or Day -1. However, ***participants in Groups 2-4, only***, who have been medically prescribed medications, eg, opiates/opioids, cannabinoids, benzodiazepines, methylphenidate (or similar), and report the use of these drugs to the investigator at the screening visit may be allowed to participate, after approval from the sponsor, and if in line with protocol specifications regarding prohibited medications (see Section 6.9, Appendix 9).

   NOTE: Repeat urine drug testing to assess study eligibility at screening or Day -1 is not permitted in this study.

9. At screening ***or*** Day -1, a positive breath alcohol test, as assessed using kits approved by sponsor; for the screening test, a single repeat (which may be on a separate day) before Day -1 is permitted to assess eligibility, if needed.

10. For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in WOCBP at Day -1.

11. ***If performed*** at investigator discretion, safety related laboratory tests collected on Day -1, upon review prior to dosing reflect the participant not to be in stable medical condition.

Other Exclusion Criteria:

12. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing and until the follow-up contact.

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

14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.2.2. ***Additional*** Exclusion Criteria for Group 1 *Only* (without HI)

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 approved 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, a previously positive hepatitis B surface antibody result due to vaccination is permissible.

   - Hepatitis C infection, defined by presence of HCVAb ***and*** HCV RNA.

2. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine.

3. Screening ***supine*** standard 12-lead ECG demonstrating QTcF interval >450 ms or a QRS interval >120 ms. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

4. Screening ***seated*** SBP ≥140 mmHg or DBP ≥90 mmHg, following ≥5 minutes of seated rest. If SBP is ≥140 mmHg or DBP ≥90 mmHg, the BP assessment should be repeated 2 more times and the average of the 3 BP values should be used to determine eligibility.

5. Use of ***chronic*** prescription medications within 7 days or 5 half-lives (whichever is longer) prior to Day 1, or for prohibited medications, use within the required washout/restriction period provided in Appendix 9.

   NOTE: Use of selected, limited prescription and non-prescription medications may be permitted ***on a case-by-case basis*** after approval from the sponsor (refer to Section 6.9 for details).

5.2.3. ***Additional*** Exclusion Criteria for Groups 2-4 *Only* (Mild, Moderate, and Severe HI)

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

2. A diagnosis of hepatic dysfunction secondary to any acute ongoing hepatocellular process that is documented by medical history, PE, liver biopsy, hepatic ultrasound, CT scan, or MRI.

3. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than **4 weeks** prior to the screening visit.

4. Signs of clinically active Grade 3 or 4 hepatic encephalopathy (ie, >Grade 2 Portal Systemic Encephalopathy score; refer to Appendix 10).

5. Severe ascites and/or pleural effusion, except for those categorized in Group 4 who may be enrolled provided participant is medically stable, per the investigators' medical judgment.

6. Previously received a kidney, liver, or heart transplant.

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

8. At screening, Day -1 or pre-dose on Day 1, persistent severe, uncontrolled hypertension as outlined below:

   - ***Seated*** SBP ≥180 mmHg or DBP ≥105 mmHg after ≥5 minutes of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits; if done, the repeat assessment overrides initial results.

     NOTE: For participants with SBP ≥160 and ≤179 mmHg ***or*** DBP ≥100 and ≤104 mmHg at screening, the period between screening and Day 1 may be used to refine the doses of the agents used for management of BP with the aim of having stable BP by Day -1.

   - **Day 1**: ***seated*** SBP ≥160 mmHg or DBP ≥100 mmHg after ≥5 minutes of seated rest, with a single repeat permitted to assess eligibility, if needed; if done, the repeat assessment overrides initial results.

9. ALT ***or*** AST >5x ULN on clinical laboratory tests at screening, as assessed by the sponsor approved laboratory, with a single repeat permitted to assess eligibility, if needed.

5.3. Lifestyle Considerations

After confirmation of eligibility, participants will be instructed to maintain the guidelines described below for the duration of participation in the study.

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to all fasting clinical laboratory evaluations and pre-dose PK sample (0.5 hrs prior to dosing) on Day 1.
- Water may be consumed as desired (ad libitum).
- While inpatient, all meals will be standardized as follows:
    - On Day 1, following a fast of at least 4 hours, participants should begin breakfast approximately 30 minutes prior to PF-07923568 administration. The breakfast will be consumed over approximately a 20-minute period with PF-07923568 administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to complete the entire breakfast. There will be no water restrictions prior to dosing.
    - Standard morning meal, lunch, an optional afternoon snack, an evening meal, and an optional evening snack will be provided at a similar clock time to the clock time when these meals are provided relative to dosing on Day 1 while inpatient ie, approximately 0, 4, 6 (optional snack), 10, and 14 hrs (optional snack).
    - The total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The nutritional macronutrient

composition consumed by each participant should be maintained, as much as practically possible.

- The daily caloric intake per participant should not exceed approximately 3200 kcal.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to Day 1 and until collection of the final PK blood sample.

- When a meal or snack is scheduled at the same time as an ECG and/or VS assessments, the meal will be provided after the ECG and/or VS assessments are completed.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for ≥24 hrs prior to admission for inpatient stay (and for red wine abstain for at least 7 days prior to Day 1), plus have a negative breath alcohol test on Day 1 and continue abstaining from alcohol until collection of the final PK blood sample.

    - Participants will undergo breath alcohol tests at timepoints indicated in the SoA, additional tests may be conducted at investigator discretion

- Consumption of caffeinated drinks and tobacco (or 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.

  In addition:

- Participants must abstain from caffeine-containing products for a minimum of 2 hrs prior to all vital signs and ECG measurements conducted throughout study participation (from screening to the final follow-up).

- Smoking may not be permitted when it would interfere with the timing of scheduled study procedures. In addition, participants must abstain from use of tobacco- or nicotine-containing products: for a minimum of 2 hrs prior to all vital signs and ECG measurements, for a minimum of 2 hrs prior to and following administration of study intervention.

5.3.4. Activity

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

- In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except if required for study procedures, eg, ECG), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.4. Screen Failures

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

In this study, participants may be rescreened only after contact with a sponsor Clinical representative. This may be permitted when, for example due to logistical constraints or administrative reasons, the maximum period between screening visit and Day 1, of **28 days**, is exceeded. In addition, for participants in ***Groups 2-4 only***, rescreening may be appropriate following mild intercurrent illness after the condition has resolved. Otherwise, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

In cases where rescreening is permitted, all screening procedures must be repeated and the participant assigned a new 8-digit SSID number. Participants must be deemed to meet all the eligibility criteria under the new 8digit SSID ***before*** progressing to Day 1. Reconsent is required.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to PF-07923568.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	PF-07923568
Arm Name (group of participants receiving a specific treatment or no treatment)	Group 1, Group 2, Group 3, Group 4
Type	Drug
Dose Formulation	Capsule
Unit Dose Strength(s)	[redacted] mg
Dosage Level(s)	[redacted] mg, single dose
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IMP.

Study Intervention(s)	
Packaging and Labeling	Study intervention will be provided as open-label supply in bulk bottles along with individual dose containers, as necessary, for unit dosing.
Current/Former Name(s) or Alias(es)	PF-07923568 Sisunatovir RV521

Arm Title	Group 1	Group 2	Group 3	Group 4
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants without HI will receive a single CCImg dose of PF-07923568, administered orally as 4 PF-07081532 CCImg capsules	Participants with mild HI will receive a single CCImg dose of PF-07923568, administered orally as 4 PF-07081532 CCImg capsules	Participants with moderate HI will receive a single CCImg dose of PF-07923568, administered orally as 4 PF-07081532 CCImg capsules	Participants with severe HI will receive a single CCImg dose of PF-07923568, administered orally as 4 PF-07081532 CCImg capsules
Associated Intervention Labels	PF-07923568	PF-07923568	PF-07923568	PF-07923568

PF-07923568 will be supplied by Pfizer as CCImg capsules in open-label bulk bottles along with individual dosing containers, as necessary, for unit dosing. For the CCImg dose administered in this study, participants will take 4 PF-07923568 CCImg capsules, orally, with the morning meal as described in Section 5.3.2.

6.1.1. Administration

Following an overnight fast of at least 8 hrs, participants will receive breakfast as outlined in Section 5.3.2 (Meals and Dietary Restrictions). The participants will then receive study intervention at approximately 08:00 hrs (plus or minus 2 hrs) on Day 1. Investigator site personnel will administer study intervention with ambient temperature water to a total volume of ***approximately 120 mL***. Participants may receive additional ambient temperature water up to 120 mL, if needed. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for non-working days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

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

Capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

This is an open-label study in which each participant dosed will receive a single CCI mg dose of PF-07923568. Following completion of informed consent at the screening visit, each participant will be assigned a single 8-digit SSID number by the site staff. The first 4 digits of the SSID will reflect the sponsor-assigned site number and the remaining 4 digits will reflect each participant's unique number assigned in chronological order of when informed consent is obtained. Each participant who is dosed with study intervention will also be assigned a separate, distinct number (as provided to the site by the sponsor), to enable execution of the sponsor's standard processes for analysis of PK samples.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

A record of the number of study intervention capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

6.6. Dose Modification

Dose modification of PF-07923568 is not allowed.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of PF-07923568 greater than 1200 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hrs.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety only when associated with an SAE.
5. Obtain a blood sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

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

Treatments taken within 28 days before study intervention dosing on Day 1 will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study. See Appendix 4 for hormonal contraceptives that are permitted in this study.

Participants on certain medications are ***excluded*** from the study (see Appendix 9 for list of prohibited medications due to potential drug-drug interaction).

Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

6.9.1. Participants in Group 1 Only (without Hepatic impairment)

In general, participants in Group 1 (without HI) will abstain from all concomitant treatments, except for the treatment of AEs. Of note, are 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 follow-up;
- Limited use of prescription and nonprescription medications that are not believed to affect the overall results of the study may be permitted on *a case-by-case basis* ***after approval*** from the sponsor study team.

6.9.2. Participants in Groups 2-4 Only (Hepatic Impairment)

Participants in Groups 2-4 (with HI) are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s), as long as this is in line with protocol specifications regarding prohibited medications as described above in Section 6.9 and in Appendix 9. On a ***case-by-case basis,*** with approval from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control. ***Whenever possible***, attempts must be made to ***not*** add new medications or alter the doses and regimens of the concomitant medications after enrollment and for the duration of participation in this study, except in circumstances where a change is deemed medically necessary. Any changes must be captured in the CRF.

Participants may receive any permitted background medications according to their stable medication routine at their usual dosing times. This is with the exception of phosphate binders, antacids, and bile acid binding resins (eg, cholestyramine, colestipol), which must not be administered within the 8 hrs before study intervention dosing or within the 4 hrs after study intervention dosing on Day 1. **On Day 1**, the investigator will determine the appropriate time to administer medications that are to be taken on an empty stomach. Otherwise, permitted concomitant medications that may be administered under fed conditions can be taken with breakfast on the morning of Day 1. On all other study days, participants are to receive their background medications at their usual times.

6.9.3. Rescue Medicine

There is no rescue therapy to reverse AEs observed with PF-07923568; standard medical supportive care must be provided to manage any AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is NA.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following: safety, behavioral, compliance or administrative reasons, or if the study is terminated by sponsor.

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

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study intervention and the study at that time.

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants may be rescreened after contact with a sponsor Clinical representative as described in Section 5.4.

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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If done around the time of a blood draw, ECGs and vital sign assessments (BP and pulse rate) should be collected before the blood draw. If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (BP and pulse rate) should be collected before insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 95 m. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

NA.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

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

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

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

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

PE findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward PE findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

BP and pulse rate will be measured as defined in the SoA.

- ***Single, seated*** BP and pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg, following a rest of **≥5 minutes**;
- Same arm (preferably the dominant arm) will be used for BP/pulse rate assessment throughout the study;
- BP/pulse rate assessment should not be taken from the arm with an IV catheter, if placed;
- Participants should be instructed not to speak during BP/pulse rate measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

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

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Single, supine standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a post-dose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a post-dose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hrs of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5. COVID-19 Specific Assessments

Assessment of risk for, symptoms of or testing for COVID-19 may be performed at screening, admission to the CRU and/or at other times during the study at investigator discretion and according to local site policies.

8.3.6. Pregnancy Testing

A serum pregnancy test is required in at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention on Day 1. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.2).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon

awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention;
- A male participant who is receiving or has discontinued study intervention inseminates a female partner;
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a liveborn 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 including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

NA.

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

NA.

8.4.8. Adverse Events of Special Interest

NA.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

NA.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

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

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

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

In the event of a medication dosing error, the sponsor should be notified within 24 hrs.

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07923568

Blood samples of approximately 2 mL, to provide a minimum volume of 0.8 mL plasma, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07923568 as specified in the SoA. Whole blood aliquot (approximately 0.15 mL) will collected from PK samples for *in vivo* blood/plasma ratio assessment. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Samples will be used to evaluate the PK of PF-07923568. Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07923568 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and hepatic impairment. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7. Biomarkers

8.7.1. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 10 mL whole blood Prep B2 optimized for serum.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s) and hepatic impairment. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documentation.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No formal statistical hypothesis testing will be performed in this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety analysis set	All participants assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Set	The PK concentration population is defined as all participants who received at least 1 dose of PF-07923568 and in whom at least 1 plasma concentration value is reported.
PK Parameter Set	The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-07923568 and have at least 1 of the PK parameters of interest calculated.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Endpoints will be reported and analyzed according to the hepatic function group that participants fall into based upon their Child-Pugh score at screening.

9.3.1.1. Analyses for PK Endpoints

Natural log-transformed PK parameters (AUC_{inf}, C_{max}, and AUC_{last}, as data permit) will be analyzed using an ANOVA model including hepatic function group as fixed effect. Estimates of the adjusted means and of the adjusted mean differences (Test-Reference) with their corresponding 90% CIs will be obtained before being exponentiated to provide estimates of the adjusted geometric means and of the ratio of adjusted geometric means (Test/Reference).

9.3.2. Primary Endpoint(s) Analysis

9.3.2.1. Definition of Endpoint(s)

The plasma PK parameters for PF-07923568 following single dose administration will be derived from the concentration-time profiles as detailed in Table 4. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 4. Plasma PK Parameters

Parameter	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_{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.
C_{max}	Maximum plasma concentration	Observed directly from data.
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	$Dose/AUC_{inf}$.
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \cdot k_{el})$.

* as data permit

The plasma concentrations of sisunatovir will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Data permitting, the PK parameters listed in Table 4 will be summarized descriptively by treatment.

9.3.2.2. Main Analytical Approach

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% CIs around the estimated difference between each of the Test (hepatic impaired) groups and the Reference (without hepatic impairment) group. A one-way ANOVA will be used to compare the natural log transformed PF-07923568 AUC_{inf}, C_{max}, and AUC_{last}, as data permit, for each of the hepatic impairment groups (Test) to the group without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test /Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Individual PF-07923568 concentrations will be listed and summarized descriptively by nominal PK sampling time and hepatic function group. Individual participant and summary profiles of the concentration-time data (using actual and nominal times, respectively) will be plotted by hepatic function group for total plasma PF-07923568.

Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, and C_{max}, if data permit) will be constructed by hepatic function group and overlaid with geometric means. PK parameters of PF-07923568 will be summarized descriptively by hepatic function group.

9.3.2.3. Supplementary Analyses

Additional analysis using linear regression may be used to analyze the potential relationship between appropriate PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}, if data permit) and hepatic function (eg, serum albumin concentration, PT or T bili). Plots of PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}) versus hepatic function will be constructed, with a regression line and 90% confidence region included. Estimates of the slope and intercept, together with a 90% CI, and the coefficient of determination (ie, R-squared and adj-R-squared) may be obtained from the model.

Additionally, as an exploratory analysis, age and body weight may be explored as additional covariates/factors in the models, as appropriate.

9.3.3. Secondary Endpoint Analysis - Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and PE and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported. COVID-19 specific assessments data will be considered source data and will not be required to be reported.

9.3.3.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

9.3.4.1. Biomarkers

Biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.3.5. Other Analyses

Pharmacogenomic data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

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

9.5. Sample Size Determination

A sample size of approximately 28-32 participants (approximately 8 participants per Groups 1-3, and 4-8 participants in Group 4 based on recruitment rate, with varying degrees of hepatic function in each of the 4 Groups) has been selected based on recommendation from the "FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling". Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

The expected widths of the 90% CIs with 80% coverage probability are shown in Table 5 for a range of possible effects (Test vs Reference). The calculation assumes the selection of the default value (80%) of the tolerance parameter in the conventional calculation.[8] These estimates are based on an assumed conservative standard deviation of 0.6 for logAUC_{inf} (also applicable to logC_{max}) based on data from previous study C5241001 part C, fed condition.

Table 5. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects

Estimated ratio 100* Test/Reference	n=8 per group	
	AUC	
	90%CI	CI width
75%	(42.73,131.64)	88.91
100%	(56.97,175.52)	118.55
150%	(85.46,263.28)	177.82
200%	(113.95,351.04)	237.09
400%	(227.89,702.08)	474.19

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

A data monitoring committee (DMC) or independent oversight committee (IOC) will not be utilized.

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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

10.1.7. Data Quality Assurance

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

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered

closed when all required documents and study supplies have been collected and a study -site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. 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 upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide

comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) Coagulation aPTT,PT,INR PT control	BUN Creatinine (Scr) Cystatin C (Scys) eGFR[a] ***Plasma*** Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT T bili Direct bilirubin[b,c] Indirect bilirubin[b,c] Creatine kinase[b,d] Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[e]	Other tests as part of clinical laboratory tests: At times specified in SoA: 1. Urine pregnancy test (WOCBP ***only***)[f] At screening only: 2. Serology: HBsAg, HCVAb (if positive, HCV RNA) and HIV 3. Serum FSH (***all*** females) 4. Serum pregnancy test (βhCG) (***all*** females) 5. Reticulocyte count (Abs) 6. Total bile acids 7. Amylase 8. Lipase At screening and Day -1 only: 9. Breath alcohol test[g] 10. Urine drug test[h] For suspected DILI: 11. AST, ALT 12. T bili, direct and indirect bilirubin 13. Total bile acids, GGT 14. Albumin 15. Alkaline phosphatase 16. CK 17. PT, INR 18. Acetaminophen/paracetamol or protein adduct levels For suspected DICI/DIKI: 19. Creatinine (Scr) 20. Cystatin C (Scys) 21. eGFR[a] 22. Spot (dipstick) UACR

a. eGFR should be calculated using the 2021 CKD-EPI Scr-Scys combined equations, see Appendix 7.
b. At screening and Day 1 **only,** unless conditions for testing are met after Day 1 per notes "c" and "d" below.
c. After Day 1, direct and indirect bilirubin assessed only when T bili is > ULN.
d. After Day 1, creatine kinase assessed only when ALT is > ULN.
e. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
f. Performed on-site using kits approved by sponsor.
g. Performed on-site using kits approved by sponsor.
h. Minimum testing requirements include cocaine, THC, opiates and opioids, benzodiazepines and amphetamines.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

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

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom,and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction at least 35 days following the last dose of investigational product; and (c) at least 1 of the following conditions applies:

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

  OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (failure rate of <1% per year) with low user dependency during the intervention period and agrees to use it for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective non-estrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral + barrier*;

    - Injectable + barrier*.

7. Sexual Abstinence

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

* Acceptable barrier methods to be used concomitantly with options 6 for the study include any of the following:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

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

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

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

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

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

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine(Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only). In this study, eGFR will be determined using the 2021 CKD-EPI Scr-Scys combined equation (see Section 10.7.2.1 below) and both Scr and Scys will be measured as part of the protocol-required safety laboratory assessments at all times specified in the SoA.

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[9]

2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽0.7	if ⩽0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ⩽0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽0.9	if ⩽0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ⩽0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• Newonset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in Drug-Drug Interaction (DDI)

The prohibited concomitant medications listed below should not be taken with PF-07923568 for the period of time at least equal to 5 half-lives plus 14 days preceding the first dose of study intervention, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

Strong and moderate CYP3A4 and P-gp inhibitors or inducers are prohibited, as these medications may have meaningful impact on the pharmacokinetics of sisunatovir.

PF-07923568 is a CYP3A4 inhibitor and therefore sensitive and narrow therapeutic index CYP3A4 substrates are also prohibited in this study. Since based on in vitro data PF-07923568 may be a weak inhibitor of CYP2B6, sensitive narrow TI substrates of CYP2B6 are excluded.

PF-07923568 also may be an inhibitor of OCT1 and MATE1 transporters; therefore, sensitive substrates of these transporters are excluded.

Although his is not all-inclusive, a list of medications that are prohibited in this study is provided below. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Prohibited Concomitant Medications

CYP3A Inhibitors		CYP3A Inducers	
Moderate	**Strong**	**Moderate**	**Strong**
Aprepitant	Boceprevir	Bosentan	Apalutamide
Ciprofloxacin	Cobicistat	Efavirenz	Carbamazepine
Conivaptan	Danoprevir	Etravirine	Enzalutamide
Crizotinib	Dasabuvir	Phenobarbital	Mitotane
Cyclosporine	Elvitegravir	Primidone	Phenytoin
Diltiazem	Indinavir		Rifampin
Dronedarone	Itraconazole		St. John’s wort
Erythromycin	Ketoconazole		
Fluconazole	Lopinavir		
Fluvoxamine	Paritaprevir		
Imatinib	Ombitasvir		

Tofisopam	Posaconazole		
Verapamil	Ritonavir		
	Saquinavir		
	Telaprevir		
	Tipranavir		
	Telithromycin		
	Troleandomycin		
	Voriconazole		
Sensitive CYP3A Substrates		**CYP3A Substrates with Narrow Therapeutic Index**	
Alfentanil	Lovastatin	Alfentanil	
Atorvastatin	Lurasidone	Astemizole	
Avanafil	Maraviroc	Cisapride	
Budesonide	Midazolam	Cyclosporine	
Buspirone	Naloxegol	Dihydroergotamine	
Darifenacin	Nisoldipine	Ergotamine	
Darunavir	Quetiapine	Fentanyl	
Dasatinib	Sildenafil	Pimozide	
Dronedarone	Simvastatin	Quinidine	
Ebastine	Sirolimus	Sirolimus	
Eletriptan	Tacrolimus	Tacrolimus	
Eplerenone	Ticagrelor	Terfenadine	
Everolimus	Tolvaptan		
Ibrutinib	Tipranavir		
Indinavir	Triazolam		
Felodipine	Vardenafil		
Lomitapide			
Sensitive MATE1 Substrates			
Metformin			
Sensitive CYP2B6 Substrates		**CYP2B6 Substrates with Narrow Therapeutic Index**	
Velpatasvir		Cyclophosphamide	
P-gp Inhibitors		**P-gp Inducers**	
Atazanavir	Lopinavir	Apalutamide	
Boceprevir	Lumacaftor	Atazanavir	
Cobicistat	Mifepristone	Fosamprenavir	
Conivaptan	Nelfinavir	Lopinavir	
Cyclosporine	ombitasvir and paritaprevir and ritonavir and dasabuvir	Rifampin	
Darunavir	Posaconazole	St. John's wort (hypericum perforatum) extract	
Diltiazem	Ritonavir	Tipranavir	
elvitegravir and cobicistat and emtricitabine and tenofovir DF	Saquinavir	Verapamil	
Erythromycin	Telaprevir		
glecaprevir and pibrentasvir	Tipranavir		
Indinavir	Tucatinib		
Itraconazole	Verapamil		
Ketoconazole	vonoprazan and amoxicillin and clarithromycin		
Lonafarnib	Voxilaprevir		
Sensitive OCT Substrates			
Imatinib			

Not an all-inclusive list.

10.10. Appendix 10: Child-Pugh Classification of Liver Dysfunction

Table 7. Scoring for Child-Pugh Classification[10]

Group		Child-Pugh Score	Level of Dysfunction	Total Score (tally based on assessment of parameters in Table 8)
1		Not Applicable	Without hepatic impairment	Not Applicable
2		A	Mild	5-6
3		B	Moderate	7-9
4		C	Severe	≥10

Table 8. Derivation of Child-Pugh Classification Score

Assessment Parameters	Assigned score for observed findings		
	1 point	2 points	3 points
Encephalopathy grade[a] (refer to Table 9 below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Asymptomatic	Requiring intervention
Serum T bili, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
PT, sec prolonged	<4	4 to 6	>6

a. Participants with a prior history of Grade 3 or 4 encephalopathy who are *currently* receiving an intervention [*eg,* 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 C5241012 as long as they do ***not*** have clinically active Grade 3 or 4 encephalopathy.

Table 9. 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. Participants with clinically active Grade 3 or 4 encephalopathy are excluded.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{12}	area under the plasma concentration-time profile over 12 hrs
AUC_{24}	area under the plasma concentration-time profile over 24 hrs
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time profile over tau, the dosing interval, where tau = 24 hours
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BBS	Biospecimen Banking System
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	total clearance of drug from eg, plasma
CL/F	apparent clearance of drug from eg, plasma
C_{last}	last quantifiable concentration
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CPC	Child-Pugh Classification

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
CT scan	computed tomography scan
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DCT	data collection tool
DDI	drug-drug interaction
DIC	Drug in Capsule
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DPB	Dry Powder Blend
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
H	hour
HAE	hypoglycemic adverse event
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HI	hepatic impairment
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Term
hrs	hours
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
ICU	intensive care unit
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IV	intravenous(ly)
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
k_{el}	first-order elimination rate constant
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LRTI	lower respiratory tract infection
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MAD	multiple ascending dose
MATE1	multidrug and toxin exclusion protein 1
MQI	medically qualified individual
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	Not Applicable
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	octamer binding transcription factor
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P glycoprotein
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex

Abbreviation	Term
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RSV CV	respiratory syncytial virus challenge virus
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SSID	single subject identifier
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TI	therapeutic index
T_{max}	time to reach C_{max}
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
US	United States
VS	vital signs
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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