A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY IN HEALTHY ADULT MALE PARTICIPANTS TO ASSESS THE EXTENT OF EXCRETION, ABSOLUTE BIOAVAILABILITY, FRACTION ABSORBED, AND PHARMACOKINETICS OF [^{14}C]PF-06865571 USING A ^{14}C-MICROTRACER APPROACH

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Short Title: A Study in Healthy Adult Male Participants to Assess ADME Properties of [^{14}C]PF-06865571

Protocol Amendment Summary of Changes Table

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1. PROTOCOL SUMMARY

1.1. Synopsis

Not applicable.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

Visit Identifier	**Screening**	**Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]**																									**F/U Phone Call**	**ET**
Days Relative to Day 1	**-42 to -2**	**-1**	**1**															**2**			**3[b]**		**4**	**5**	**6**	**7-21[c]**	**≥28 - 35 days (P2 only)**	**-**
Hours After *Oral* PF-06865571 Dose	**-**	**-**	**0**	**0.5**	**1**	**2**	**3**	**3.08**	**3.17**	**3.25**	**3.5**	**3.75**	**4**	**6**	**9**	**12**	**16**	**24**	**27**	**36**	**48**	**51**	**72**	**96**	**120**	**144-504**		**-**
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			**-3**				**0**	**0.083 (5 min)**	**0.17 (10 min)**	**0.25 (15 min)**	**0.5 (30 min)**	**0.75 (45 min)**	**1**	**3**	**6**	**9**	**13**	**21**	**24**	**33**	**45**	**48**						
Informed Consent	X																											
Inclusion/Exclusion Criteria	X	X																										
Admission to the CRU (P1 only)		X																										
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[b,c]	→	→	→	X[c]		
Medical/medication history (update)	X	X																										
Height and Weight	X																											
Physical Examination[d]		X																				X[e]						X
Supine 12-lead ECG	X		X																			X[e]						X
Supine Vital Signs (Blood Pressure and Pulse Rate)	X		X																			X[e]						X
COVID-19 questionnaire[f]	X	X																										

Visit Identifier	Screening	Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]																								F/U Phone Call	ET
Days Relative to Day 1	**-42 to -2**	**-1**	**1**															**2**			**3[b]**		**4**	**5**	**6**	**7-21[c]**	**≥28 - 35 days (P2 only)**	**-**
Hours After *Oral* PF-06865571 Dose	**-**	**-**	**0**	**0.5**	**1**	**2**	**3**	**3.08**	**3.17**	**3.25**	**3.5**	**3.75**	**4**	**6**	**9**	**12**	**16**	**24**	**27**	**36**	**48**	**51**	**72**	**96**	**120**	**144-504**		**-**
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			**-3**				**0**	**0.083 (5 min)**	**0.17 (10 min)**	**0.25 (15 min)**	**0.5 (30 min)**	**0.75 (45 min)**	**1**	**3**	**6**	**9**	**13**	**21**	**24**	**33**	**45**	**48**						
COVID-19 temperature check[g]	X	X	X[h]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		X
Serious and Non-serious Adverse Event Monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Standard Meals[i]		X	X[i]										X		X			X		X	X		X	X	X	X		
Oral 300 mg [^{14}C]PF-06865571 Administration (P1 Only)			X																									
Oral 300 mg PF-06865571 Administration (P2 only)			X																									
IV infusion 100 µg [^{14}C]PF-06865571 Administration (P2 Only)							X	→	→	X																		
[redacted]			[redacted]	[redacted]																								
COVID-19 testing[k]	X	X																					X			X[k]		
Emesis Collection for Radioactivity Measurement, if Occurs (P1 Only)			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X										

Visit Identifier	Screening	Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]																								F/U Phone Call	ET
Days Relative to Day 1	**-42 to -2**	**-1**	**1**															**2**			**3[b]**		**4**	**5**	**6**	**7-21[c]**	**≥28 - 35 days**	**-**
Hours After *Oral* PF-06865571 Dose	**-**	**-**	**0**	**0.5**	**1**	**2**	**3**	**3.08**	**3.17**	**3.25**	**3.5**	**3.75**	**4**	**6**	**9**	**12**	**16**	**24**	**27**	**36**	**48**	**51**	**72**	**96**	**120**	**144-504**		**-**
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			**-3**				**0**	**0.083 (5 min)**	**0.17 (10 min)**	**0.25 (15 min)**	**0.5 (30 min)**	**0.75 (45 min)**	**1**	**3**	**6**	**9**	**13**	**21**	**24**	**33**	**45**	**48**					**(P2 only)**	
Blood Sample Collection for -																											
PK of PF-06865571 following oral [^{14}C] PF-06865571 in P1 and unlabeled PF-06865571 in P2[l]			X	X	X	X	X						X	X	X	X	X	X		X	X[l]		X	X	X			X
Total Radioactivity[m] (P1 only)	X		X	X	X	X	X						X	X	X	X	X	X		X	X		X	X	X[m]			X
Metabolite profiling/ID[m] (P1 only)			X	X			X							X		X		X		X	X		X	X	X[m]			X
PK of IV infusion [^{14}C]PF-06865571 (P2 Only)			X[n]				X	X	X	X	X	X	X	X	X	X	X	X		X	X							
Safety laboratory	X	X																				X[e]						X
HIV, HBsAg, HCVAb	X																											
Pfizer Genomic Prep D1.5 Banked Biospecimen (P1 Only)[o]			X																									
Pfizer Prep B1 Banked Biospecimen (P1 Only)[o]			X																									

Visit Identifier	Screening	Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]																								F/U Phone Call	ET
Days Relative to Day 1	**-42 to -2**	**-1**	**1**															**2**			**3[b]**		**4**	**5**	**6**	**7-21[c]**	**≥28 - 35 days (P2 only)**	**-**
Hours After *Oral* PF-06865571 Dose	**-**	**-**	**0**	**0.5**	**1**	**2**	**3**	**3.08**	**3.17**	**3.25**	**3.5**	**3.75**	**4**	**6**	**9**	**12**	**16**	**24**	**27**	**36**	**48**	**51**	**72**	**96**	**120**	**144-504**		**-**
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			**-3**				**0**	**0.083 (5 min)**	**0.17 (10 min)**	**0.25 (15 min)**	**0.5 (30 min)**	**0.75 (45 min)**	**1**	**3**	**6**	**9**	**13**	**21**	**24**	**33**	**45**	**48**						
Urine Sample collection for -																											
Spot Collection for Urine Drug Screening (P1 only)	X	X																									
Spot Collection for Urine Cotinine Screening (P1 only)	X	X																									
Spot Collection for Urinalysis (and Microscopy, if needed)[p]	X	X																				X[e]					X
Total Radioactivity and Metabolite profiling/ID[q] (P1 Only)		X[q]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	→	X	→	→	X	→	X	X	X	X[o]		X
Total Radioactivity[q] (P2 Only)							X	→	→	→	→	→	→	→	→	→	X	→	→	X	→	→	X[q]						
Feces Sample collection for -																											
Total Radioactivity and Metabolite ID[r] (P1 Only)		X[r]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	→	→	X	→	X	X	X	X[r]		X
[^{14}C]PF-06865571[r] (P2 Only)							X[r]	→	→	→	→	→	→	→	→	→	→	→	X	→	→	X[r]						

Abbreviations: →= ongoing/continuous event; AE = adverse event; COVID-19 = Coronavirus disease 2019; CRU = Clinical Research Unit; ECG = electrocardiogram; ET=early termination; F/U=follow-up; HCVAb = hepatitis C antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; P1 = Period 1; P2 = Period 2; PK = pharmacokinetics; SAE = serious adverse event; LC/MS = liquid chromatography tandem mass spectrometry; ET = early termination.

Visit Identifier	Screening	Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]																								F/U Phone Call	ET
Days Relative to Day 1	-42 to -2	-1	1															2			3[b]		4	5	6	7-21[c]	≥28 - 35 days (P2 only)	-
Hours After *Oral* PF-06865571 Dose	-	-	0	0.5	1	2	3	3.08	3.17	3.25	3.5	3.75	4	6	9	12	16	24	27	36	48	51	72	96	120	144-504		-
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			-3				0	0.083 (5 min)	0.17 (10 min)	0.25 (15 min)	0.5 (30 min)	0.75 (45 min)	1	3	6	9	13	21	24	33	45	48						

Note: Black color denotes oral dose administration and sampling post oral administration and Red color denotes IV dose administration and sampling post IV administration. IV samples may optionally be labeled with the corresponding time relative to the oral dose for sample collection; however, PK data for the IV administration will be analyzed relative to the start of the IV infusion.

a. There will be a wash-out period of 8-22 days from drug administration in Period 1 and Period 2. The day to start Period 2 is dependent on the duration for Period 1 but will be at least after all sample collection in Period 1 are complete.

b. In Period 2, participants will be discharged on Day 3 (ie, 48 hours IV dose administration).

c. Dosing in Period 2 (as 1 cohort) or Completion of Period 1 (1 participant at a time) when at least 1 of 3 criteria are met: (1) ≥90% of radioactive dose has been recovered in urine+feces+emesis (if any); (2) <1% of radioactive dose has been recovered in urine+feces during 24H interval over 2 consecutive days; (3) participant has reached Day 21 (in Period 1). At the latest, Period 2, Day -1 would occur on the same day as Period 1, Day 21.

d. Full physical examination will be conducted at Day -1 (Period 1); otherwise brief physical exam envisioned for findings during previous PE or new/open AEs, at Investigator discretion.

e. Procedures to be completed at time of discharge in Period 2 only.

f. A site-generated questionnaire checking suspected contact and COVID-19 related symptoms to be completed by participants.

g. Participant's body temperature will be checked at least twice daily (approximately 12 hours apart) during the CRU confinement.

h. The first body temperature check on Day 1 of each period will be performed before PF-06865571 dosing.

i. Standardized meals to be served at clock times matching approximately **–0.5H** (see Section 5.3.1), *and* at 4H and 9-10H relative to oral PF-06865571 dosing.

[redacted]

k. Testing for COVID-19 pathogen (SARS-CoV-2) by PCR will be performed at each visit to the CRU (Screening and Admission). For participants admitted for residence in the CRU, subsequent COVID-19 tests will be performed 2x/week at a minimum.

l. For Period 2, Plasma PK of PF-06865571 will only be assessed up to 48 hours.

m. Samples are to be collected up to 120 hours. Based on emerging data, up to 2 additional samples for total ^{14}C accelerator mass spectrometry (AMS) and metabolite profiling between Day 7 and Day 21 of Period 1 completion may be collected.

n. Sample will be used for sample dilution, if necessary, using matrix matched plasma. [^{14}C]PF 06865571 concentration will not be determined in this sample.

o. If not collected on the designated collection day, the banked biospecimen can be collected at the next available time point when biospecimens are being collected in conjunction with a participant visit.

Visit Identifier	Screening	Period 1 (P1) and Period 2 (P2), unless otherwise limited to 1 of these 2 Periods[a]																								F/U Phone Call	ET
Days Relative to Day 1	-42 to -2	-1	1															2			3[b]		4	5	6	7-21[c]	≥28 - 35 days (P2 only)	-
Hours After *Oral* PF-06865571 Dose	-	-	0	0.5	1	2	3	3.08	3.17	3.25	3.5	3.75	4	6	9	12	16	24	27	36	48	51	72	96	120	144-504		-
Hours After *IV* [^{14}C]PF-06865571 Dose (P2 Only)			-3				0	0.083 (5 min)	0.17 (10 min)	0.25 (15 min)	0.5 (30 min)	0.75 (45 min)	1	3	6	9	13	21	24	33	45	48						

p. Microscopy required only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

q. "Blank" sample collected within 24H prior to dosing in each period; and over intervals of 0-12H, 12-24H, 24-48H, 48-72H, 72-96H, 96-120H plus each 24H interval, relative to ***oral*** dosing in Period 1. In Period 2, samples will be collected over 0-12H, 12-24H and 24-48H following administration of ***IV*** radiolabeled drug.

r. "Blank" sample collected within 24H prior to dosing in each period; samples collected over 0-24H, 24-48H, 48-72H, 72-96H, 96-120H plus each 24H interval relative to ***oral*** dosing in Period 1. In Period 2, samples will be collected over 0-24H and 24-48H following administration of ***IV*** radiolabeled drug.

2. INTRODUCTION

PF-06865571 is a diacylglycerol acyltransferase 2 (DGAT2) inhibitor that is currently being developed for the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis.

2.1. Study Rationale

The purpose of this study is to assess the extent of excretion of PF-06865571 as well as the absolute bioavailability, fraction absorbed and pharmacokinetics of PF-06865571 in healthy male participants using a ^{14}C microtracer dose approach.

2.2. Background

Diacylglycerol acyltransferases (DGATs) catalyze the terminal step in triglyceride (TG) synthesis; specifically, the esterification of a fatty acid with diacylglycerol (DAG) resulting in the formation of TG.[1] In mammals, two structurally unrelated DGAT enzymes (DGAT1 and DGAT2) have been characterized. DGAT1 is highly expressed in the intestine and plays a central role in fat absorption.[2] DGAT2 is highly expressed in liver and adipose.[3] In preclinical models, blockade of hepatic DGAT2 using antisense oligonucleotides results in both down-regulation of the expression of multiple genes encoding proteins involved in lipogenesis and parallel induction in oxidative pathways.[4,5] The net result of these changes is a decrease in the levels of hepatic DAG and TG lipid which, in turn, reduces hepatocyte lipid burden and decreases hepatic very low density lipoprotein (VLDL) TG secretion.[5,6] PF-06865571 is a potent, reversible oral, small molecule DGAT2 inhibitor that is postulated to decrease hepatic TG synthesis and hepatic lipid burden in non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Based on observations in nonclinical studies conducted, it is hypothesized that DGAT2i will impact both physiological drivers contributing to NASH via direct inhibition of liver triglyceride synthesis, as well as adaptive responses leading to reduction in hepatic DNL. Following 2 weeks of dosing in participants with NAFLD, DGAT2i has been shown to reduce liver fat in a dose-responsive manner.

2.2.1. Nonclinical Pharmacokinetics and Metabolism

Nonclinical studies indicate that PF-06865571 was rapidly absorbed in rat and moderately absorbed in monkey with mean oral bioavailability of 31% and 48%, respectively. In vitro, PF-06865571 showed high passive permeability, and preliminary studies indicated that PF-06865571 was a substrate for multi-drug resistance protein (MDR)1 (also known as P-glycoprotein [P-gp]) and mouse breast cancer resistance protein (mBCRP) efflux transporters.

PF-06865571 was moderately bound to plasma proteins. The mean unbound fraction of PF-06865571 was 0.464, 0.213, 0.331, 0.419, 0.360, and 0.353 in rat, rabbit, dog, monkey, and human plasma, respectively, with PF-06865571 preferentially distributing into plasma relative to blood.

The major primary metabolic pathway identified from preliminary in vitro and in vivo metabolite profiling in human is O-de-ethylation with subsequent sulfation and glucuronidation. There was no evidence of human unique metabolites. Reaction phenotyping studies indicate the total cytochrome P450 (CYP) contribution to PF-06865571 metabolism was >96%, and CYP3A was the predominant isoform responsible for the metabolism of PF-06865571 suggesting a risk of clinical drug-drug interactions (DDI) with PF-06865571 as a victim upon co-administration with CYP3A inhibitors or inducers.

While in vitro data suggest that PF-06865571 has the potential to induce CYP3A4 and CYP2B6, in a clinical study (C2541002), there was no dose-response relationship of endogenous biomarkers of CYP3A4 induction with increasing repeated doses of PF-06865571 up to 1800 mg/day. PF-06865571 also has the potential to inhibit uridine diphosphate-glucuronosytransferase (UGT) 1A1, UGT1A9, and UGT2B15 based on in vitro data from human liver microsomes. In addition, in vitro evaluations suggest that PF-06865571 has the potential to inhibit CYP2C9, intestinal CYP3A, P-gp, breast cancer resistance protein (BCRP), organic cation transporter (OCT)1, OCT2, and multidrug and toxic compound extrusion transporter (MATE)1 at the highest planned clinical dose in the program going forward (ie, 300 mg twice daily [BID]).

2.2.2. Clinical Overview

2.2.2.1. Summary of Clinical Safety

As of the issuance of this protocol, 9 clinical studies with PF-06865571 have been completed. Across these 9 studies, a total of 306 unique participants have been randomized. This includes 141 unique healthy adult participants, 18 adults with hepatic impairment, and 165 adults with NAFLD. Of the 306 participants randomized, 231 (75%) were exposed to PF-06865571 - 65 unique participants (28%) to single oral doses of PF 06865571 and an additional 166 participants (72%) to repeated, oral, doses of PF-06865571 for up to 6 weeks.

Administration of PF-06865571 alone has been found to be well tolerated with the maximum tolerated dose not identified and no adverse drug reactions identified. Upon administration of single oral doses of PF-06865571, across the 300-fold dose range evaluated (ie, 5 to 1500 mg), TEAEs reported in ≥4 participants across all arms evaluated were headache (12%), and diarrhea (7%).

2.2.2.2. Summary of Clinical Pharmacology

Following administration of single oral doses of PF-06865571 under fed conditions in C2541001, median time for C_{max} (T_{max}) ranged from 1.5 to 4 hours across the dose groups. Approximate dose-proportional increases in C_{max} and AUC_{24} were observed between the 5 mg and 1500 mg doses. Under fed conditions, the mean terminal elimination half-life ($t_{½}$) ranged from 1.5 to 5.2 hours. At the 1000 mg dose level, exposures under fasted condition were approximately 2-fold lower than those in the fed state. Median PF-06865571 T_{max} occurred earlier in the fasted state, compared to dosing under fed conditions (1 h versus 4 h). In addition, the terminal elimination $t_{½}$ under fasted conditions was more variable than under fed conditions.

Following repeated administration of oral doses of PF-06865571 under fed conditions in C2541002, C_{max} values on Days 1, 7 and 14 were observed within a median T_{max} range of 1.5 to 3.0 hours post-dose across the 30 mg - 600 mg Q8H doses. Steady state appeared to have been reached by Day 4 based on PF-06865571 median trough plasma concentration-time profiles. Following a single dose on Day 1 and at steady state (Days 7 and 14), PF-06865571 plasma exposure across the 30 mg - 600 mg Q8H doses appeared to increase in a dose proportional manner based on geometric mean AUC_{tau} and C_{max} values. Mean $t_{½}$ on Day 14 ranged from 3.29 hours to 6.92 hours across the 30 mg - 600 mg Q8H doses with longer $t_{½}$ values observed at higher doses. Minimum drug accumulation was observed following multiple dose administration of PF-06865571 Q8H. Mean accumulation ratios ranged from 0.950 to 1.33 based on AUC_{tau} values and 0.990 to 1.44 based on C_{max} values across all doses on both Day 7 and Day 14. The proportion of drug excreted via renal elimination on Day 14 was low, with less than approximately 2% (mean Ae_{tau}% values ranged between 0.696% and 1.79%) of the dose excreted in urine as unchanged drug over the dosing interval across the 30 mg - 600 mg Q8H doses. Mean CLr values ranged between 0.293 to 0.630 L/hr.

2.3. Benefit/Risk Assessment

The current study is the first to administer radiolabeled, nCi doses of [14C]PF-06865571 – both orally and intravenously. The single doses of PF-06865571 administered in this study are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to evaluate the ADME properties of PF-06865571 along with absolute bioavailability and fractional absorbed following administration in healthy adult males.

As of the issuance of this protocol, no specific human risks have been identified with oral administration of PF-06865571; potential risks with PF-06865571 and the current study, are summarized in Section 2.3.1. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06865571 may be found in the investigator's brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06865571		
First time clinical administration of [^{14}C]PF-06865571 – both orally and intravenously	• Single *oral* doses up to 1500 mg of PF-06865571 observed to be well tolerated; single, oral dose of PF-06865571 in this study (300 mg) represents is 5-fold lower • IV dose of PF-06865571 in this study (100 µg) is 15,000-fold lower than the highest *oral* dose previously administered and observed to be well tolerated • Microtracer of [^{14}C]PF-06865571 identified for this study (300 nCi) is equivalent to 0.75 mrem, which represents radiation exposure which is well below the average dose (in US) per year from background radiation sources which is 610 mrem, and below common acute radiation doses (eg, Dental x-ray ~ 1.5 mrem; Transatlantic flight ~ 2.5 mrem; Mammogram ~ 72 mrem; Full body CT scan ~ 1000 mrem). Additionally, the radioactive dose to be administered is categorized as the lowest risk category of 1 by the ICRP.[7]	• Administration of PF-06865571 will occur in an inpatient setting under close supervision • Clear communication via ICD of negligible risk with the [^{14}C]PF-06865571 doses administered and PF-06865571 IV dose relatively to previously administered oral doses
Food effect resulting in change in PF-06865571 exposure, post oral dose	• Clinical data indicate that PF-06865571 exposure are lower in fasted state than in fed state	• Study intervention, when administered orally, administered with a meal
Exposure in utero	• In embryo-fetal development toxicity study ***in rats***, lower fetal body weight and skeletal anomalies observed at all doses with NOAEL for this developmental toxicity not identified • In embryo-fetal developmental toxicity study ***in rabbits***, no developmental toxicity observed	• Risk of fetal toxicity communicated through Section 7 of the PF-06865571 IB (Jan-2020) • Enrollment in this study, considering administration of [^{14}C]-study intervention, limited to healthy adult males • In males who are sexually active with female partner(s) of childbearing potential, use of barrier methods not required/mandated given safety margins >100-fold – refer to Section 10.4

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Number of ***serial and parallel*** procedures to ensure near complete collection of each radioactive dose administered carry risks for non-evaluable data	• Duration of washout between the 2 Periods in this study are pre-defined but rather guided by recovered radioactivity across plasma, urine, feces, and when applicable vomitus – which will likely vary between participants	• Feasibility of parallel evaluation of PK, radioactivity, safety is precedented at site selected for this study • A priori identified criteria for when dosing can occur in Period 2 outlined in Schedule of Activities • Clear communication in protocol and to participants (via ICD) about the *maximum* possible duration of inpatient stay with this stay reduced as guided by observed data in study
Other		
Risk COVID-19 contamination during study	• During the pandemic healthy participant could be infected with the SARS-COV-2 virus through study participation • Leading to increased health risk for study participants and others involved in study conduct, potentially confounding AE with study intervention	• COVID-19 specific assessments according to Schedule of Activities

2.3.2. Benefit Assessment

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need. They will receive close monitoring of their safety via study procedures undertaken (eg, PE, 12-lead ECGs, vital signs) which will occur as outlined in this protocol.

2.3.3. Overall Benefit/Risk Conclusion

Based on the safety profile of PF-06865571 observed in clinical studies to date, and the measures taken as part of the study designed outlined in this protocol, the risk to the participants in this study is deemed to be minimal. The overall benefit:risk profile for PF-06865571 supports continued clinical development and the conduct of this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the extent of excretion of total radioactivity in urine and feces following administration of a single oral dose of [^{14}C]PF-06865571.	• Total recovery of radioactivity in urine, feces and total excreta (urine + feces) as percentage of total radioactive dose administered.
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-06865571.	• Metabolic profiling/identification and determination of relative abundance of [^{14}C]PF-06865571 and the metabolites of [^{14}C]PF-06865571 in plasma, urine and feces.
Secondary:	**Secondary:**

• To quantify plasma PK parameters of PF-06865571 and total radioactivity following administration of a single oral dose of [^{14}C]PF-06865571.	• Period 1: AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf} and $t_{½}$ to describe single oral dose of:
	  • Total radioactivity in plasma
	  • PF-06865571 in plasma

• To quantify plasma PK parameters of PF-06865571 following administration of a single, IV, microtracer of [^{14}C]PF-06865571.	• [^{14}C]PF-06865571 (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permit, $t_{½}$, AUC_{inf}, CL and V_{ss}.
• To determine the absolute oral bioavailability (F) of PF-06865571 following administration of a single oral dose of PF-06865571 compared to a single IV microtracer of [^{14}C]PF-06865571.	• Plasma AUC_{inf} of oral unlabeled PF-06865571 and IV microtracer of [^{14}C]PF-06865571 in Period 2 only.
• To determine the fraction of the dose absorbed (Fa) following administration of a single oral dose of [^{14}C]PF-06865571.	• Total urinary radioactivity following oral administration of [^{14}C]PF-06865571 in Period 1 and IV microtracer administration of [^{14}C]PF-06865571 in Period 2.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize cumulative rate of excretion of total radioactivity in urine and feces over time following administration of a single oral dose of [^{14}C]PF-06865571.	• Cumulative recovery of radioactivity in urine and feces, and total excreta (urine + feces) over time as a percentage of total radioactive dose administered.

Objectives	Endpoints
• To quantify plasma PK parameters of PF-06865571 in plasma following administration of a single oral dose of unlabeled PF-06865571.	• PF-06865571 plasma (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permit, $t_{½}$, AUC_{inf}, CL/F, V_z/F.
[redacted]	[redacted]
• To evaluate the safety and tolerability of PF-06865571, administered as a single oral dose of [^{14}C]PF-06865571 or a single oral dose of PF-06865571 followed by administration of a single IV microtracer of [^{14}C]PF-06865571.	• AE monitoring, clinical laboratory measurements, vital signs and 12-lead ECG.

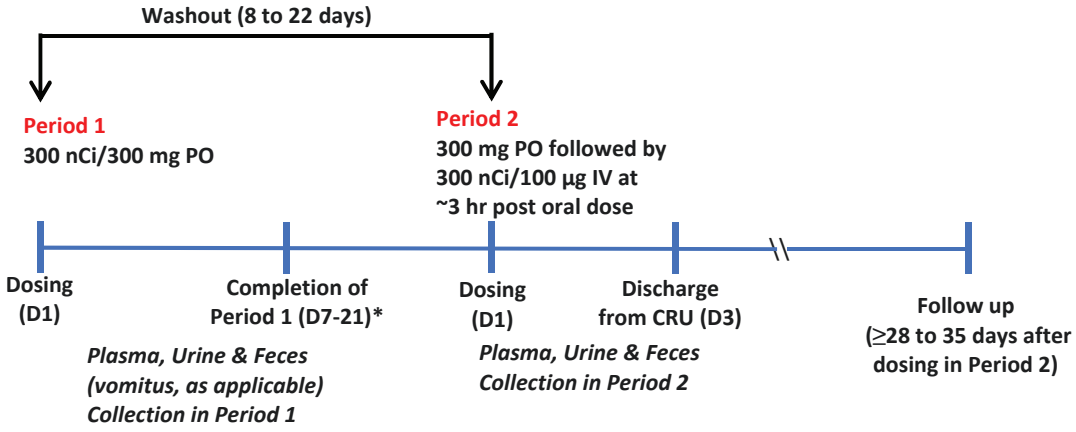
4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 1, open-label, non-randomized, 2-period, fixed-sequence, single-dose study of PF-06865571 in healthy male participants to characterize the ADME properties of [^{14}C]PF-06865571 following oral administration; and to evaluate the absolute oral bioavailability (F) and fraction absorbed (Fa) of PF-06865571 following oral administration of unlabeled PF-06865571 and IV administration of [^{14}C]PF-06865571.

In this study 6 participants will be enrolled to ensure evaluable data is acquired in at least 4 participants. Each participant will receive 2 regimens (A and B) in Periods 1 and 2, respectively, as outlined in Figure 1. Participants who withdraw from the study may be replaced if the number of evaluable participants is less than 4.

Figure 1. Two (2)-Period Fixed Sequence Study Design



* Completion of Period 1 (1 participant at a time) when at least 1 of 3 criteria are met: (1) ≥90% of radioactive dose has been recovered in urine+feces+emesis (if any); (2) <1% of radioactive dose has been recovered in urine+feces during 24H interval over 2 consecutive days; (3) participant has reached Day 21 (in Period 1). At the latest, Period 2, Day -1 would occur on the same day as Period 1, Day 21.

Regimen A in Period 1: An oral dose of 300 mg PF-06865571 containing approximately 300 nCi ^{14}C (ie, radiolabeled PF-06865571) will be administered within approximately 10 minutes of completion of a standard breakfast (see Sections 5.3.1 and 6.1.1).

Regimen B in Period 2: An oral dose of 300 mg unlabeled PF-06865571 followed at T_{max} by an IV dose of 300 nCi [^{14}C] in 100 µg of PF-06865571 (3 µCi/mg active drug). The [^{14}C] IV dose will be administered as an infusion over approximately 15 minutes. Oral unlabeled PF-06865571 will be administered within approximately 10 minutes of completion of a standard breakfast (see Sections 5.3.1 and 6.1.1).

Screening will occur within 42 days of the first dose of the investigational product in Period 1. All participants will provide informed consent and undergo screening evaluations to determine their eligibility.

Eligible participants will be admitted to the CRU on Day -1 of Period 1 and scheduled to remain in the CRU through the completion of Period 2. As such, inpatient stay will be for a total duration of 12 days (minimum) to 25 days (maximum). Each participant will have 1 -follow-up phone call that will occur at least 28 days and up to 35 days following the last dose of investigational product to assess for AEs and SAEs.

In exceptional cases, participants may leave the CRU for personal reasons, at the discretion of the investigator, for up to a maximum of 8 hours during Period 1 after Day 7, if the participant has completed Period 1 based on the completion criteria defined in Figure 1.

4.2. Scientific Rationale for Study Design

This study will investigate the ADME of [^{14}C]PF-06865571 and characterize plasma, fecal and urinary radioactivity and identify any metabolites, if possible, of [^{14}C]PF-06865571 in male participants (obtained from Periods 1 and 2). A 2-period design is being used to minimize variability and enable within -participant comparison of the urinary excretion of radioactivity with both routes for the estimation of Fa. Only male participants will be enrolled to also minimize variability. Only nonsmokers will be enrolled to minimize any potential effect on metabolism by smoking. In addition, this study will provide a better understanding of the PK disposition of PF-06865571 by obtaining IV clearance and delineating the extent of oral absorption (F and Fa), further assisting with BCS classification assessment for PF-06865571. This information will support the further formulation development. Oral dosing will be administered with a meal as food has been shown to significantly increase exposures of PF-06865571 and mimics how PF-06865571 is being administered in the clinical program.

Period 2 of this study will enable assessment of F for PF-06865571. F will provide information on the amount of PF-06865571 reaching the systemic circulation. Determination of the Fa (obtained from Periods 1 and 2) will provide information on the fraction of the total PF-06865571 dose absorbed, regardless of the fate of that dose after absorption (ie, metabolism, degradation, etc). Since F is dependent on Fa, Fg and Fh, characterization of

both F and Fa will enable determination of the first pass effect. Therefore, the study will aim to characterize both F and Fa.

In order to achieve sufficient bioanalytical sensitivity for the microtracer dose and differentiate the plasma concentrations resulting from the radiolabeled IV dose and those resulting from the oral dose, an ultra-sensitive AMS method will be used to quantify plasma concentrations of radiolabeled parent drug as well as total ^{14}C derived from the microtracer dose based on measurement of ^{14}C.[8] PF-06865571 will be considered highly permeable if either F or Fa is greater than 0.85 (as per BCS guidance).[9]

CCI [redacted]

The potential risk of exposure to PF-06865571 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[10]

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

4.3. Justification for Dose

- **^{14}C-labeled PF-06865571 and unlabeled Oral PF-06865571:**

A radio-dilute ^{14}C-labeled (300 nCi) 300 mg dose of PF-06865571 for Period 1 and unlabeled 300 mg dose in Period 2 were selected as 300 mg is the highest dose being evaluated in phase 2 clinical program. PF-06865571 was found to be well-tolerated with an acceptable safety profile with single doses up to 1500 mg (C2541001) and repeated doses up to 1800 mg/day (C2541002) in healthy participants. A maximum tolerated dose was not identified. In addition, 300 mg BID dose levels were found to be generally well tolerated with an acceptable safety profile over 6-week treatment in NAFLD patients (C3711001). Based on prior experience in healthy participants and NAFLD patients, a single 300 mg dose is expected to have low risk into healthy adult males (see Section 2.2.2).

Further, single-dose administration is chosen because linear and time-independent PK of PF-06865571 have been demonstrated at single or multiple clinical doses, and thus single-dose PK can predict multiple-dose PK of PF-06865571.

- **^{14}C-labeled PF-06865571 IV microtracer:**

The microtracer selection is based on ICH Guidelines.[11] A microtracer [^{14}C]PF-06865571 is

planned in this study for both oral (Period 1; 0.001 µCi/mg active dose or 300 nCi/300 mg active dose) and IV (Period 2; 3 µCi/mg active dose or 300 nCi/100 µg active dose) administration. The total radioactive dose would be approximately 600 nCi of ^{14}C. The IV dose of 100 µg is 0.033% of the oral unlabeled dose of 300 mg. This dose is sufficient to allow quantification of [^{14}C]PF-06865571 based on the sensitivity of the ultrasensitive AMS analytical methodology.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study, including the last scheduled procedure shown in the Schedule of Activities (ie, follow-up phone call).

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male participants, 18 to 60 years of age, inclusive, at the time of signing the ICD.

    - Refer to Appendix 4 for reproductive criteria for male participants (Section 10.4.1).

Type of Participant and Disease Characteristics:

2. Male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac tests.

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

4. Participants that are nonsmoking for at least 3 months at the time of signing the ICD.

Weight:

5. BMI of 17.5 to 30.4 kg/m^2, inclusive; and a total body weight >50 kg (110 lb) with a single repeat assessment of BMI and/or body weight permitted *on a different day* to assess eligibility, if needed.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. History of irregular bowel movements including irritable bowel syndrome or frequent episodes of diarrhea or constipation, defined by less than 1 bowel movement on average per 2 days, or lactose intolerance.

4. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

5. 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 the COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    - History of SARS-CoV-2 PCR or antibody (eg, IgG, IgM, etc) positive result would necessitate accompanying history of asymptomatic state for at least 6 months prior to screening.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of moderate/potent CYP3A inducers which are

prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational drug within 60 days (or as determined by the local requirement) preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

8. A positive urine drug test.

9. A positive urine cotinine test.

10. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

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

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

    - AST **or** ALT level ≥ 1.5 × ULN;

    - Total bilirubin level ≥ 1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is≤ ULN.

13. A positive COVID-19 (SARS-CoV-2) PCR test.

Other Exclusions:

14. 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

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).

15. Total ^{14}C radioactivity measured in plasma exceeding 11 mBq/mL at screening.

16. From 3 months prior to dosing use of tobacco/nicotine containing products or positive urine cotinine test.

17. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

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

19. Unwilling or unable to comply with the lifestyle considerations outlined in Section 5.3 of this protocol.

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

After confirmation of eligibility, participants must be reminded that they must:

- attempt to abstain from ingestion of indigestible foods (eg, corn, nuts) for 2 days prior to dosing (ie, Day -2 and Day -1);
    - ***In addition,*** while inpatient, the meals consumed will follow this restriction to aid fecal homogenization.
- refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits/fruit juices (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample, in each Period.

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

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
- Water is permitted until dosing on Day 1 and without restriction beginning 1 hour after oral dosing.

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- ***While inpatient***, meals will be standardized as follows –

  - On Day 1 of each study period, following an overnight fast of at least 10 hours, participants will be provided a standard meal approximately 30 minutes prior to oral PF-06865571 administration. The breakfast will be consumed over approximately a 20-minute interval with PF-06865571 administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. The percentage of the meal consumed should be documented.

  - Lunch will be provided approximately 4 hours after dosing of oral PF-06865571.

  - Dinner will be provided approximately 9 to 10 hours after dosing of oral PF-06865571.

  - An evening snack is permitted.

  - Standard meals (and an optional evening snack) will be provided at a similar clock time to the clock time when these meals are offered on Day 1.

  - While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

  - To help assure regularity in bowel movements, nutritional composition should contain at least 15 g of fiber per 1000 kcal

    - This may include consumption of fiber capsules, at a frequency dictated by investigator, starting with the evening meal (ie, ~8H post dose) on Day 1, for duration of inpatient stay to ensure at least one bowel movement per day;

  - If an individual participant has not experienced a bowel movement in the first 24 hours after dosing, fluid intake should be increased and administration of a mild laxative [eg, prune juice or a mild stool softener (eg, docusate)] should be implemented, with the goal to facilitate at least one daily bowel movement;

    - Despite these measures, if bowel movement does not occur, on Day 2 and each subsequent day, consideration should be given to administration of mild laxative (eg, milk of magnesia), at the Investigator's discretion. The use of the stool softener / laxative needs to be recorded.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK blood sample in each Period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK blood sample in each Period. Participants may undergo an alcohol breath test or urine alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products from 3 months prior to dosing and while confined to the CRU in the study. Participants may undergo urine cotinine test at the discretion of the investigator.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to admission and while confined to the CRU in the study. Walking at a normal pace will be permitted;

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

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 to the clinical database.

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

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

Unlabeled (ie, non-radiolabeled) PF-06865571 investigational product for oral administration will be supplied to the CRU by Pfizer as bulk for extemporaneous preparation.

Two (2) batches of GMP [^{14}C]PF-06865571 API were prepared with the oral dose being fully radio-diluted to the overall specific activity requirements for Period 1 oral dosing and the other API lot ready for IV formulation for Period 2 IV dosing.

[^{14}C]PF-06865571 components for the IV and oral microtracer administration will be supplied by Pfizer as bulk API and, where necessary, bulk excipients for the manufacture of the [^{14}C] labeled IV solution and oral suspension formulations. The final product composition and presentation will be detailed in a separate Technical Agreement (TA) for the [^{14}C] labeled IV solution and Extemporaneous Dispensing Records (EDRs) for the [^{14}C] labeled and unlabeled oral suspensions.

6.1.1. Administration

In Period 1, [^{14}C]PF-06865571 will be administered as an oral dose. In Period 2, the oral unlabeled PF-06865571 will be administered 3 hours before the IV [^{14}C]PF-06865571 dose.

^{14}C labeled or unlabeled PF-06865571 (300 mg): A standard meal will be provided approximately 30 minutes prior to oral PF-06865571 administration in each period. The breakfast will be consumed over approximately a 20-minute interval. Participants will be encouraged to complete the entire breakfast. Qualified investigator site personnel will administer labeled or unlabeled PF-06865571 via oral route at approximately 0800 hours (plus or minus 2 hours) within approximately 10 minutes of completion of the meal during the designated period with water to a total volume of 240 mL according to the site administration instructions.

[^{14}C]PF-06865571 (100 µg): Ten mL of the 10 µg/mL manufactured IV solution of [^{14}C]PF-06865571 will be administered intravenously (over 15 minutes as a continuous infusion through an infusion line using a calibrated syringe pump or similar). Preparation and administration of [^{14}C]PF-06865571 will be performed by qualified investigator site personnel (in accordance with local regulations and laws). Further details on administration are outlined in the site administration instructions.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

6. See the EDR for storage conditions of the study intervention once reconstituted and/or diluted.

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

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

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

6.2.1. Preparation and Dispensing

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

^{14}C labeled and unlabeled PF-06865571 oral dosing suspensions will be prepared extemporaneously at the CRU by 2 trained personnel, at least 1 of whom is a pharmacist. Details of dose preparations will be given in separate EDRs. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

[^{14}C]PF-06865571 solution for the IV administration will be manufactured at the clinical study site by 2 trained personnel and quality assurance (QA) released prior to administration. Details of the dose preparation will be provided in a separate TA. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements. Leftover containers following both oral and IV administration, including tubing used for infusion, should be shipped to laboratory for assessment of radioactivity, if needed.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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. Separately, prior to dosing on Day 1, each participant will be assigned a 2-digit number to permit analysis of all PK samples.

6.4. 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.

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

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of moderate/potent CYP3A inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall

results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day. If an individual participant has not experienced a bowel movement within 24 hours after dosing of oral (Period 1) or IV (Period 2) [^{14}C]PF-06865571, administration of a mild laxative [eg, prune juice or a mild stool softener (eg, docusate)] should be implemented, with the goal to facilitate at least one daily bowel movement. Despite these measures, if bowel movement does not occur, on Day 2 and each subsequent day, consideration should be given to administration of mild laxative (eg, milk of magnesia), at the Investigator's discretion. The use of the stool softener / laxative should be recorded.

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06865571; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: intolerance of the study drug, SAE, clinically relevant laboratory, vital signs or ECG changes.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the Schedule of Activities for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

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

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

7.2.1. Withdrawal of Consent

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

available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

Adherence to the study design requirements, including those specified in the Schedule of Activities, 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 42 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 42 days as a result of unexpected delays (eg, delayed drug

shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 415 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

There are no efficacy assessments included in this protocol.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. BP should not be taken from the arm with a catheter in place for intravenous infusion. Participants should be instructed not to speak during measurements.

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

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the Schedule of Activities section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended 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 10 minutes in a supine position.

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

values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring.

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

Additional collection times, or changes to collection times, of ECG will be permitted, as necessary, to ensure appropriate collection of safety data.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the Schedule of Activities 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 Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within ***28 calendar days after the last dose of study intervention*** should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

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

8.2.5. COVID-19 Specific Assessments

Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and subsequent COVID-19 tests will be performed twice weekly while confined to the CRU. Additional testing may be required by local regulations or by the Principal Investigator.

In addition, as per local practices, site-generated COVID-19 Questionnaire will be expected to be completed by the participants each time upon arrival to the clinic – refer to Schedule of Activities.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

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

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 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 it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, 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.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of

possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact while preparing or administering the study drug.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until ***28 calendar 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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not Applicable.

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

Not Applicable.

8.3.8. Adverse Events of Special Interest

Not Applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not Applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06865571 greater than 1800 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06865571 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis ***as soon as possible*** upon identification of overdose.

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

8.5. Pharmacokinetics

The samples collected for PK (PF-06865571 concentration), radioactivity (total ^{14}C) and/or metabolite profiling assessment must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the 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.

Samples collected for PK, radioactivity and/or metabolite profiling/ID 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 samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

8.5.1. Period 1 Plasma for Analysis of Total ^{14}C and Metabolite Profiling/ID

During **Period 1**, blood samples of approximately 4 mL for total ^{14}C and 10 mL for metabolite profiling/ID, to provide approximately 1.6 mL and 4 mL of plasma, respectively, will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities. 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. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

8.5.2. Period 2 Plasma for Analysis of [^{14}C]PF-06865571 (After IV Administration)

During **Period 2**, blood samples of approximately 4 mL, to provide approximately 1.6 mL of plasma, for PK analysis of radiolabeled [^{14}C]PF-06865571 will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities. 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. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Windows defined for times relative to oral dosing are intended to ensure accurate sample collection as required for the analysis of both oral and IV data.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

Samples collected for measurement of plasma radiolabeled [^{14}C]PF-06865571 concentrations will be analyzed using a validated quantitative AMS method after chromatographic separation of the parent compound in compliance with applicable SOPs.

8.5.3. Plasma for Analysis of Unlabeled PF-06865571 (Periods 1 and 2)

During **Periods 1 and 2**, blood samples of approximately 3 mL to provide approximately 1.2 mL of plasma for PK analysis of unlabeled PF-06865571 will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities. 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. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

Samples collected for measurement of plasma concentrations of PF-06865571 will be analyzed using a validated analytical method in compliance with applicable SOPs.

8.5.4. Urine for Analysis of Total ^{14}C (Oral and IV) and Metabolite Profiling/ID

Urine will be collected for determination of total ^{14}C measurement and metabolite profiling/ID following oral administration of [^{14}C]PF-06865571 (**Period 1** only) and for determination of total ^{14}C measurement following IV administration of [^{14}C]PF-06865571 (**Period 2** only), at predose and at post dose intervals as specified in the Schedule of Activities.

Each participant will empty his bladder just prior to dosing on Day 1 and an aliquot from this collection will be used as "urine blank". During the entire collection period, the urine collection container should be refrigerated. At the end of each urine collection period, the total volume will be measured and recorded. All urine aliquots should be collected using a new pipette tube for each participant at each time interval. All urine samples within each collection interval will be mixed thoroughly before aliquoting.

Details regarding the collection volume, processing, storage and shipping of the urine samples will be provided in the lab manual.

8.5.5. Feces for Analysis of Total ^{14}C (Oral and IV) and Metabolite Profiling/ID

Feces will be collected for determination of total ^{14}C measurement and metabolite profiling/ID following oral administration of [^{14}C]PF-06865571 in **Period 1** at times specified in the Schedule of Activities. Feces will be collected following IV administration of [^{14}C]PF-06865571 in **Period 2** at times specified in the Schedule of Activities, and may be analyzed for total ^{14}C and/or [^{14}C]PF-06865571 determination and/or metabolic profiling/ID if the fraction of dose excreted as parent in feces of Period 1 is 0.25 greater than unabsorbed drug (1-Fa), indicating biliary and/or GI excretion may be a major pathway for parent drug clearance (e.g. greater than 25% of total clearance).

Fecal voids will be collected at the clinic and immediately frozen. The sample will be labeled and frozen at approximately -20°C.

Total fecal mass is to be recorded for each 24-hour period. Each bowel movement must be collected. Time and date must be recorded.

In the event of diarrhea during the study, all diarrhea, including any swabbing and contaminated linen, should be collected, labeled, and stored in appropriate containers at -20°C for possible analysis of radioactivity. Following completion of radioanalysis and subsample collections for metabolite profiling/ID, the remaining bulk fecal homogenate will be discarded upon approval from the sponsor.

Details regarding the collection, processing, storage and shipping of the feces samples will be provided in the lab manual.

All feces samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

8.5.6. Emesis

If emesis occurs within 24 hours after oral administration of [^{14}C]PF-06865571 (**Period 1** only), then the vomitus must be collected and stored for a radioactivity assessment. All emesis including any swabbing, contaminated linens and facial tissues used to collect bodily discharge; eg, nose bleeding clean-up tissue and any emesis related clean-up is to be collected and stored at -20°C for possible analysis of radioactivity.

Details regarding the collection, processing, storage and shipping of the samples will be provided in the lab manual.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study. Any genetic analysis, if conducted, will not be part of this study report.

8.7.2. Banked Biospecimens for Genetics

A 2 mL blood sample optimized for DNA isolation Prep D1.5 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and/or NAFLD/NASH. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.8. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following sample for biomarker research are required and will be collected from all participants in this study as specified in the Schedule of Activities:

- Whole blood (Prep B1) Banked Biospecimen optimized for plasma

8.8.1. Specified Gene Expression (RNA) Research

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

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are:

- 10 mL whole blood Prep B1 optimized for plasma

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and NAFLD/NASH. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No statistical hypothesis is tested in this study.

9.2. Sample Size Determination

A sample size of 6 male participants has been chosen based on the industry standard sample size for ADME Mass Balance studies and radiolabeled tracer studies. This sample size was not chosen based on any empirical data or hypothesis testing criteria.

Participants who withdraw from the study, for non-safety reasons, may be replaced if the number of participants with evaluable data is less than 4.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Evaluable	All participants assigned to study intervention and who take at least 1 dose of study intervention.

Participant Analysis Set	Description
Extent of Excretion	Extent of excretion population is defined as all participants who have received 1 dose of [^{14}C]PF-06865571 and who have evaluable total radioactivity concentration (urinary and fecal) data and who had no protocol deviations or AEs (such as vomiting of the dose, diarrhoea or severe constipation) that may have affected the extent of excretion analysis.
PK Concentration	The PK concentration population for PF-06895571 is defined as all participants who receive at least 1 dose of PF-06895571 and who have at least 1 measurable concentration of PF-06895571. The PK concentration population for ^{14}C is defined as all participants dosed with [^{14}C]PF-06895571, who have at least one ^{14}C measurement.
PK Parameter	The PK parameter analysis population for PF-06895571 is defined as all participants treated who have at least 1 of the PF-06895571 PK parameters of interest. The PK parameter analysis population for ^{14}C analysis is defined as all participants treated who have at least one of the ^{14}C parameters of interest. The PK concentration and PK parameter analysis sets may differ.
Safety	All participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

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

9.4.1. Primary Endpoint(s)

9.4.1.1. Extent of Excretion (Period 1)

Radioactivity excreted in urine and/or feces will be reported as the percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine and/or feces.

Percent recovery and cumulative recovery of total radioactivity in urine, feces and emesis (if any) will be determined based on total administered dose.

Note: While the total percentage of dose excreted is the primary endpoint, the percentage of the administered radioactivity excreted at each time interval and cumulatively through that interval are tertiary endpoints.

Individual participant and median data profiles will be graphically presented for the cumulative recovery of radioactivity in urine, feces and their combination. The total recovery of radioactivity in urine, feces and their combination will be listed and summarized using descriptive statistics. Where possible, the rate of excretion of radioactivity will be estimated.

9.4.1.2. Metabolic Profiling/Identification (Period 1)

Plasma, urine and fecal samples will be analyzed for metabolites of PF-06865571. Major metabolites of PF-06865571 in plasma, urine, and feces following oral dose of [^{14}C]PF-06865571 will be identified if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

9.4.2. Secondary Endpoint(s)

9.4.2.1. Pharmacokinetic Parameters

9.4.2.1.1. Plasma

The PF-06865571 PK parameters following a single dose administration of unlabeled PF-06865571 (oral) and microtracer dose of [^{14}C]PF-06865571 (oral and IV) will be derived, where appropriate, from the concentration-time profiles as outlined below:

- Parameters for total ^{14}C (^{14}C oral microtracer) will be derived for Period 1 only;
- Parameters for PF-06865571 after oral doses of ^{14}C oral microtracer and unlabeled PF-06865571 for Periods 1 and 2, respectively and for [^{14}C]PF-06865571 after ^{14}C IV microtracer for Period 2 will be derived.

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal rule
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{inf}(dn)[a]	Dose normalized area under the plasma concentration-time profile from time zero extrapolated to infinite time	AUC_{inf}/Dose

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
C_{max}(dn)	Dose normalized maximum plasma concentration.	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression
CL/F[a] (oral)	Apparent clearance following oral administration	Dose/AUC_{inf}
CL[a] (IV)	Systemic clearance	Dose/AUC_{inf}
V_z/F[a] (oral)	Apparent volume of distribution following oral administration	Dose/(AUC_{inf}*k_{el})
V_{ss}[a] (IV)	Steady-state volume of distribution following IV infusion	V_{ss}=CL × [MRT-(infusion time/2)] where MRT is the Mean Residence Time and is calculated as $AUMC_{inf}/AUC_{inf}$

a. If data permit.

Actual PK sampling times will be used in the derivation of PK parameters, defined relative to the oral dose for the oral parameters and relative to the start of the 15-minute IV infusion for the IV parameters. Actual administered ^{14}C doses will be used for the total ^{14}C and [^{14}C]PF-06865571 PK parameter calculations.

Plasma PK parameters above will be listed and summarized descriptively by analyte (total ^{14}C, unlabeled PF-06865571, and [^{14}C]PF-06865571) and treatment, as applicable. The descriptive summary, concentration and PK parameters will be presented in appropriate tables and figures.

9.4.2.1.2. Absolute Oral Bioavailability (F)

F will be estimated as the ratio of adjusted geometric means of dose-normalized AUC_{inf} (if data permit, otherwise AUC_{last}) for oral unlabeled PF-06865571 and IV labeled ^{14}C-PF-06865571 in plasma (from Period 2 only) which is equivalent to the following equation:

$$F = [\text{PF-06865571\_}AUC_{po}/[^{14}C]\text{PF-06865571\_}AUC_{iv}]\times[\ [^{14}C]\text{PF-06865571\_Dose}_{iv}/\text{PF-06865571\_Dose}_{po}]$$

- Geometric Mean Ratio and 90% confidence interval: Natural log transformed AUC_{inf}(dn) (if data permit) and AUC_{last}(dn) from Period 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% CI will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratio. IV [^{14}C]PF-06865571 is the Reference formulation and unlabeled oral PF-06865571 is the Test formulation.

9.4.2.1.3. Fraction Absorbed (Fa)

9.4.2.1.3.1. Urine Parameters

Following urine parameters will be calculated following single dose administration of a microtracer dose of [^{14}C]PF-06865571 (oral and IV administration). Residual ^{14}C levels from Period 1 will be accounted for using an appropriate method, based on AMS principles and methodology.

Parameter	Definition	Method of Determination
Total ^{14}C_Urine_PO	Total radioactivity excreted into the urine postdose following oral administration of [^{14}C]PF-06865571 microtracer dose	Sum of [^{14}C urine concentration × sample volume] for each collection interval
Total ^{14}C_Urine_IV	Total radioactivity excreted into the urine following IV administration of [^{14}C]PF-06865571 microtracer dose	Sum of [^{14}C urine concentration × sample volume] for each collection interval
%^{14}C_Urine_PO	Percent of the radioactive dose administered that is excreted in the urine following oral administration	Total ^{14}C_Urine_PO/^{14}C $Dose_{po}$ × 100 Where ^{14}C $Dose_{po}$ is the dose of ^{14}C following oral administration of [^{14}C]PF-06865571
%^{14}C_Urine_IV	Percent of the radioactive dose administered that is excreted in the urine following IV administration	Total ^{14}C _Urine_IV/^{14}C $Dose_{iv}$ × 100 Where ^{14}C $Dose_{iv}$ is the dose of ^{14}C following IV administration of [^{14}C]PF-06865571

Total urine ^{14}C amounts, percent ^{14}C dose will be listed by treatment (oral in Period 1 and IV in Period 2) and summarized using descriptive statistics.

9.4.2.1.3.2. Calculation of Fa

Fa will be estimated as the ratio of the adjusted geometric means of % of administered radioactive dose excreted into the urine following oral and IV administration of [^{14}C]PF-06865571 microtracer dose over the same collection time (up to 48 hours post dose) in Periods 1 and 2, respectively:

Fa = [% ^{14}C_Urine_PO/% ^{14}C_Urine_IV];

- Geometric Mean Ratio and 90% confidence interval: Natural log transformed % Total ^{14}C in Urine from Period 1 and Period 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% CI will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratio. Total ^{14}C_Urine_IV is the Reference formulation and Total ^{14}C_Urine_PO is the Test formulation.

Theoretically Fa would be expected to be greater than F. In the event that F is estimated to be greater than Fa, the greater of the 2 values will be used to represent the fraction of PF-06865571 absorbed. PF-06865571 will be considered highly permeable if either F or Fa is greater than 0.85 (as per BCS guidance).[9]

9.4.3. Tertiary/Exploratory Endpoint(s)

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9.4.3.2. Cumulative Rate of Excretion (Period 1)

See Section 9.4.1.1.

9.4.3.3. Pharmacokinetics Parameters (Unlabeled PF-06865571 - Period 2)

See Section 9.4.2.1.1.

9.4.4. Other 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.

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

data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.5. Other Analyse(s)

Pharmacogenomic or biomarker data from Banked Biospecimens 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.

9.5. Interim Analyses

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

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant 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, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in Study Monitoring Plan.

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities 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. Participants may undergo random urine drug and cotinine testing at the discretion of the investigator

Table 1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
• Hemoglobin • Hematocrit • RBC count • MCV • MCH • MCHC • Platelet count • WBC count • Total neutrophils (Abs) • Eosinophils (Abs) • Monocytes (Abs) • Basophils (Abs) • Lymphocytes (Abs)	• BUN • Serum creatinine • Serum glucose (fasting) • Calcium • Sodium • Potassium • Chloride • Total CO_2 (bicarbonate) • AST, ALT • Total bilirubin • Direct (conjugated) bilirubin[a] • Indirect (unconjugated) bilirubin[a] • Alkaline phosphatase • Uric acid • Albumin • Total protein	• pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urobilinogen • Urine bilirubin • Microscopy[b]	At screening only unless otherwise stated: • Urine drug screening, Period 1, Day -1[c] • Urine cotinine screening, Period 1, Day -1 • HBsAg • HCVAb • HIV • COVID-19 testing[d]

a. To be assessed as reflex tests when total bilirubin is > ULN.

b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

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

d. Testing for COVID-19 pathogen (SARS-CoV-2) by PCR will be performed at each visit to the CRU (Screening and Admission). For participants admitted for residence in the CRU, a subsequent COVID-19 test will be performed 2x/week at a minimum.

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. 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 either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.5. 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 multistudy 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:

    - Samples for banking 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 Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
Abs	absolute
ACCi	acetyl-CoA carboxylase inhibitor
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
Ae_{tau}	cumulative amount of drug recovered unchanged in the urine during a dosing interval
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval τ
$AUMC_{inf}$	area under the first moment curve from time 0 to infinity
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BID	twice a day
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
CL/F	apparent clearance following oral administration
CL_r	renal clearance
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration

Abbreviation	Term
C_{max}(dn)	dose normalized C_{max}
COVID-19	coronavirus disease 2019
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CYP	cytochrome P450
DAG	diacylglycerol
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	absolute oral bioavailability
Fa	fraction absorbed
Fg	fraction escaping gut metabolism
Fh	fraction escaping hepatic first-pass elimination
F/U	follow up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
ID	identification

Abbreviation	Term
Ig	immunoglobulin
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LBBB	left bundle branch block
LC/MS	liquid chromatography tandem mass spectrometry
LFT	liver function test
Log_e	natural logarithm
MATE	multidrug and toxic compound extrusion transporter
mBCRP	mouse breast cancer resistance protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance protein
mrem	millirem
MRT	mean residence time
msec	millisecond
N/A	not applicable
Nab	neutralizing antibodies
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
nCi	nanocurie
NOAEL	no-observed-adverse-effect level
OCT	organic cation transporter
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
PT	prothrombin time
PVC	premature ventricular contraction/complex
P1	Period 1
P2	Period 2
QA	quality assurance
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
Q8H	every 8 hours

Abbreviation	Term
qual	qualitative
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject identifier
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TA	technical agreement
TEAE	treatment-emergent adverse event
TBili	total bilirubin
TG	triglyceride
THC	tetrahydrocannabinol
T_{max}	time to reach maximum observed concentration
UGT	uridine diphosphate-glucuronyltransferase
ULN	upper limit of normal
US	United States
V_{ss}	steady-state volume of distribution following IV infusion
V_z/F	apparent volume of distribution following oral administration
VLDL	very low density lipoprotein
WBC	white blood cell

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