Title Page

A PHASE 1, OPEN-LABEL, SINGLE-PERIOD, NON-RANDOMIZED STUDY TO EVALUATE THE PHARMACOKINETICS, EXCRETION, MASS BALANCE AND METABOLISM OF [^{14}C]PF-07265803 ADMINISTERED ORALLY TO HEALTHY ADULT MALE PARTICIPANTS

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Brief Title: A Phase 1 Radiolabel Pharmacokinetics, Excretion, Mass Balance and Metabolism Study of [^{14}C]PF-07265803.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title

A Phase 1 Radiolabel Pharmacokinetics, Excretion, Mass Balance and Metabolism Study of [^{14}C]PF-07265803.

Rationale

The purpose of this Phase 1 study is to assess the pharmacokinetics, excretion, mass balance and metabolism of PF-07265803 (formerly known as known as ARRY-371797) in healthy adult male participants. Only males will be included in this study given the use of radiolabeled substance and the desire to enroll a homogeneous population given the small sample size of this study.

Administration of the investigational product, [^{14}C]PF-07265803 in this study will be via the oral route to reflect the intended route of administration in the treatment of lamin A/C gene mutation (*LMNA)*-related DCM. PF-07265803 will be administered as an extemporaneously prepared liquid formulation in this study. In order to limit the confounding of absorption, [^{14}C]PF-07265803 will be administered following an overnight fast of at least 10 hours.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
To characterize rate and extent of excretion of total radioactivity in urine and feces, following a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.	Mass Balance: cumulative recovery of urinary, fecal, and total excretion of radioactivity over time expressed as percentage of total radioactive dose administered.
To characterize metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.	Metabolic profiling/identification and determination of relative abundance of PF-07265803 and the metabolites of PF-07265803 in plasma, urine, and feces.
Secondary:	**Secondary:**
To quantify plasma concentrations and pharmacokinetic parameters of PF-07265803, its known circulating metabolites (PF-07327859, PF-07327860, PF-07327890) and total radioactivity in plasma following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.	Pharmacokinetics parameter AUC_{last}, AUC_{inf}, CL/F, V_z/F, C_{max}, T_{max}, and $t_{½}$ to describe single dose PK of: PF-07265803 and where appropriate PF-07327859, PF-07327860, PF-07327890. Total radioactivity in plasma; PF-07265803, PF-07327859, PF-07327860 and PF-07327890 concentrations in plasma.
To evaluate safety and tolerability of a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.	Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs and ECG.

Overall Design

This is a Phase 1, open-label, single-period, single-center, non-randomized study in healthy adult male participants.

Brief Summary

In this study, mass balance and metabolism of 400 mg PF-07265803 containing 100 µCi [^{14}C]PF-07265803 will be assessed. Healthy participants will be screened up to 28 days prior to dosing to determine eligibility.

Number of Participants

Approximately 6 participants will be enrolled to study intervention.

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

Intervention Groups and Duration

The duration of this non-randomized Phase 1, open-label, single-center, single-dose study is approximately 7 days, with a 30-day safety follow up. The maximum period of confinement is expected to be 14 days. The minimum period of confinement is expected to be 3 days.

Data Monitoring Committee or Other Independent Oversight Committee: No

This study will not use a DMC or IOC.

Statistical Methods

There will be no formal hypothesis testing in this study. The sample size of 6 participants, for this study, was not based on empirical data or hypothesis testing criteria. The sample size has been selected to ensure that at least 4 participants provide evaluable data; with intent not to replace participants who prematurely withdraw (or offer non-evaluable or partially evaluable data).

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 Abbreviations used in this table may be found in 10.9.	**Screening**	**Period 1**							**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6-14**	**28-35 Days[b]**	
Informed consent	X									
CRU confinement[a]		X	X	X	X	X	X	X[a]		
Inclusion/exclusion criteria	X	X								
Medical/medication history	X	X								
Physical exam[b]		X						X[c]		X
Safety laboratory[i]	X	X						X[c]		X
Demography	X									
Height and Weight	X									
Urine drug/alcohol/cotinine testing[k]	X	X								
12-Lead ECG	X		X[g,j]					X[c]		X
Blood pressure and pulse rate	X		X[h,j]					X[c]		X
Contraception check									X	
HIV, HBsAg, HCVAb	X									
COVID-19 CRU Internal Procedure[d]	X	X	X	X	X	X	X	X[c]		X
Study intervention administration			X							
Standard Meals[e]		X	X	X	X	X	X	X		
Spot Collection for Urinalysis (and Microscopy, if needed)	X	X						X[c]		X
Retained Research Sample for Genetics (Prep D1)[f]			X							
CRU discharge								X[a]		
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X

Visit Identifier Abbreviations used in this table may be found in 10.9.	**Screening**	**Period 1**							**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6-14**	**28-35 Days[b]**	

a. Inpatient stay must be extended until >90% radioactive dose administered has been recovered or <1% is excreted in total (urine and feces) in any 24H period for two consecutive days. Maximum confinement will be 14 days.
b. Complete 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. Follow-up over the phone may be conducted if no new/open AE's at Investigators discretion.
c. Procedures to be completed at time of discharge (approximately 144 hours post dose) only, with clinical laboratory tests conducted only after criteria for discharge (footnote "a") are satisfied
d. Assessments for COVID-19 infection will be done per CRU standards for testing and those described in Section 8.2.5
e. Starting at enrollment, meals to be served, at clock times matching approximately 0H, 4H, and 9H relative to dosing on Day 1. No meal administered on Day 1 0 h in accordance with the fasted window. To help assure regularity in bowel movements, nutritional composition should contain at least 15 g of fiber per 1000 kcal or fiber capsules containing the equivalent amount of fiber may be administered daily (beginning at least 8 hr after dosing).
f. Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. Sample should be collected prior to dose.
g. ECG assessment will occur prior to dosing (approximately 1 hour).
h. Pre-dose vital sign measurements. Predose (approximately 1 hour) vital sign measurements on Day 1.
i. Safety laboratories consistent with those described in Section 10.2
j. ECG and vital signs assessment for eligibility may be considered at both screening and Day 1 visit (predose).
k. Urine drug screen and cotinine conducted at screening and check-in, and urine alcohol conducted at check-in only.

Visit Identifier	**Period 1**															
Study Day	**1**									**2**		**3**	**4**	**5**	**6**	**Early Termination/ Discontinuation**
Hours Before/After Dose	**0[a]**	**0.5**	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	
Study intervention administration	X															
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Radioactivity and metabolite ID in blood	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval collection for radioactivity and metabolite ID in urine[b]	X	→	→	→	→	→	X	→	X	X	→	X	X	X	X	
Interval collection for radioactivity and metabolite ID in feces[c]	X	→	→	→	→	→	→	→	X	X	→	X	X	X	X	
Emesis Collection for Radioactivity Measurement, if Occurs	X	→	→	→	→	→	→	→	→	X						

a. Predose sample collection
b. "Blank" spot urine sample to be collected anytime predose (Day 1) *and* postdose in intervals of 0-6H, 6-12H, 12-24H, 24-48H, 48-72H, 72-96H, and each subsequent 24H interval up to discharge.
c. "Blank" fecal sample to be collected prior to dosing *but* post admission to CRU *and* in intervals of each 24H period post dose up to discharge

2. INTRODUCTION

PF-07265803 (formerly known as known as ARRY-371797) is a potent and selective, oral small molecule inhibitor of the α isoform of p38 MAPK. Mutations in the *LMNA* gene encoding nuclear lamina components cause nuclear envelope dysfunction leading to altered nuclear activity, impaired structural dynamics and aberrant cell signaling including activation of p38α MAPK signaling pathways. Structural alterations in the nuclear envelope and connected cytoskeleton resulting from *LMNA* mutations make cardiomyocytes highly susceptible to damage even by physiological mechanical stress, leading to a disease specific maladaptive activation of the p38α MAPK. Up-regulation of p38 MAPK has been observed in the hearts of animal models and adult patients with *LMNA*-related DCM compared to wild-type/healthy individuals. Inhibition of p38 MAPK in this disease setting may halt aberrant apoptosis and cardiac remodeling resulting in improved cardiac function.

2.1. Study Rationale

The purpose of this Phase 1 study is to assess the pharmacokinetics, excretion, mass balance and metabolism of PF-07265803 (formerly known as ARRY-37197) in healthy adult male participants. Only males will be included in this study given the use of radiolabeled substance and the desire to enroll a homogeneous population given the small sample size of this study.

Administration of the investigational product, [^{14}C]PF-07265803 in this study will be via the oral route to reflect the intended route of administration in the treatment of lamin A/C gene mutation (*LMNA)*-related DCM. PF-07265803 will be administered as an extemporaneously prepared liquid formulation in this study. In order to limit the confounding of absorption, [^{14}C]PF-07265803 will be administered following an overnight fast of at least 10 hours.

2.2. Background

In the completed Phase 2 study ARRAY-797-231, treatment with PF-07265803 resulted in rapid (<4 weeks), sustained increases in functional capacity in participants with *LMNA*-related DCM. Improvements on the 6MWT compared to baseline, the primary endpoint, were mirrored by favorable changes in NT-proBNP levels, LVEF, and RV fractional area. PF-07265803 was generally well tolerated. The AEs for most participants were mild to moderate, and only 1 participant discontinued the study because of a treatment-related AE. Based on these clinical data, inhibition of p38 MAPK with the selective p38 inhibitor PF-07265803 may provide a novel therapeutic approach and has the potential to fill an unmet medical need for the treatment of symptomatic *LMNA*-related DCM and is being evaluated in the Phase 3 study, C4411002.

2.2.1. Nonclinical Studies with PF-07265803

Detailed information regarding nonclinical studies of PF-07265803 is presented in the IB.

2.2.2. Nonclinical Pharmacology

Numerous in vitro and in vivo studies were performed to evaluate and confirm the ability of PF-07265803 to interact with its intended target, p38 MAPK. In enzyme studies, PF-07265803 inhibits p38a with a half-maximal inhibitory concentration (IC_{50}) of 8.2 nM. In cellular studies, PF-07265803 is a potent inhibitor of p38-mediated downstream phosphorylation of HSP27 in HeLa cells with an IC_{50} of 17 nM. This compound has demonstrated little to no activity against over 201 enzymes, receptors, channels, and transporters.

Two in vivo murine models of *LMNA*-related DCM have allowed exploration of pathophysiologic mechanisms of disease progression and novel therapies for these conditions. In vivo studies have demonstrated that p38 MAPK is activated in murine models of *LMNA*-related DCM and that this activation of p38 MAPK precedes the development of cardiac dysfunction. PF-07265803 has been tested in the homozygous *LMNA* H222P model of EDMD with cardiomyopathy (EDMD2, MIM:181350) and in the homozygous LMNA N195K model of *LMNA*-related DCM, one of the original *LMNA* mutations linked to familial DCM with conduction defects[1]. These 2 nonclinical models bracket the spectrum of phenotypes (EDMD2: cardiac and skeletal muscle disease and DCM: cardiac disease only). Results from these studies confirm that treatment with PF-07265803 improves cardiac structure and function and reduces myocardial apoptosis.

2.2.3. Nonclinical Pharmacokinetics and Metabolism

Multiple Phase 1 enzymes (CYPs, FMOs, amidases, and esterases) are involved in the metabolism of PF-07265803.

In vitro experiments indicated that PF-07265803 has moderate membrane permeability and may be a substrate for active efflux. PF-07265803 was moderately, but reversibly, bound to plasma proteins in vitro across mouse, monkey, and human plasma, as was AR00420643, the principal metabolite in vivo. PF-07265803 was predicted to have moderate-to-good stability in humans with respect to hepatic metabolism. The principal metabolite in vivo, AR00420643, is formed in in vitro incubations with liver microsomes, hepatocytes, plasma, or blood.

CYP-mediated metabolism was primarily by CYP3A4 and CYP2D6; however, these enzymes do not generate the principal metabolite in vivo. In vivo, other Phase 1 enzymes (FMOs, amidases, and esterases) are involved in the metabolism of PF-07265803, with the major mechanism of clearance thought to be through an unidentified hydrolase enzyme. PF-07265803 and its metabolites were weak inhibitors of 5 major CYP isoforms in vitro (CYP2C19, CYP2C9, CYP1A2, CYP2D6, CYP3A4. PF-07265803 is a weak time-dependent inhibitor of CYP3A4. In in vitro studies in human hepatocytes, PF-07265803 and its metabolites are inducers of CYP3A, while only metabolites AR00420643 and AR00428028 induce CYP2B6. Based on potential for mixed induction/inhibition of CYP3A4, the net effect of PF-07265803 interaction with drugs that are identified as CYP3A4 cannot be predicted. PF-07265803 has the potential to inhibit P-gp, but overall data suggest that PF-07265803 is not a very potent P-gp inhibitor.

PF-07265803 is not a substrate or inhibitor of recombinant MAO-A or MAO-B. AR00420643 is a principal metabolite from in vitro incubations with liver microsomes, hepatocytes, plasma, or blood. Other, less abundant, metabolites that are found in vitro or in vivo are a result of oxidative metabolism. No glucuronide conjugates were detected in hepatocyte incubations

2.2.4. Nonclinical Safety

Preclinical toxicological studies have indicated that PF-07265803 was well-tolerated at multiple doses of up to 100 mg/kg BID in rats and monkeys, with GI side effects and minimal clinical pathology changes. Associated histopathology changes were reversible in monkeys treated with doses of up to 100 mg/kg BID for 28 days. Histopathology findings in rats receiving PF-07265803 for 28 days were partially reversible with respect to severity and incidence at the 100 mg/kg BID (200 mg/kg/day) dose level. In the chronic dosing studies for up to 6 months in the rat and 9 months in the monkey at doses up to 30 mg/kg BID, there were no significant adverse histopathology findings. In general, administration of PF-07265803 at doses of up to 30 mg/kg BID was tolerated in-life in rats and monkeys in chronic safety studies. Administration of PF-07265803 to rats for up to 3 months was associated with microscopic findings of skeletal muscle fiber changes, with no effects on clinical chemistry. These skeletal muscle changes were reversible after dosing cessation and with continued dosing for up to 6 months. Evidence of gastric irritation and increased gastric fluid secretion was observed in rats after a single oral dose of 100 mg/kg of PF-07265803. After treatment with PF-07265803 for multiple days, evidence of changes in stool consistency, ranging from loose stools to diarrhea was observed in monkeys. The GI disturbances were mild to moderate in the lower dose groups. In most dose groups, these GI effects resolved within 28 days after discontinuation of treatment with PF-07265803.

2.2.5. Clinical Overview

PF-07265803 is currently undergoing investigation in a Phase 3, multinational, randomized, placebo controlled study in which patients with symptomatic *LMNA*-related DCM (planned N=160) are randomized 1:1 to receive PF-07265803 400 mg BID or placebo.

PF-07265803 has been investigated in 12 completed clinical studies including a Phase 2 study in patients with *LMNA*-related DCM and long-term rollover extension to the Phase 2. In addition, 5 studies (one Phase 1b and four Phase 2) in patients with painful inflammatory conditions have been completed as well as five Phase 1 studies in healthy subjects.

In 5 clinical studies in healthy subjects, PF-07265803 demonstrated an acceptable safety profile when administered at single doses up to 900 mg QD, up to 400 mg/day for 14 days and up to 2000 mg/day for 7 days. In these studies, the most commonly reported AEs in subjects receiving PF-07265803 were dizziness, headache, diarrhea, nausea and acne; the incidence of these AEs was not clearly related to the PF-07265803 dose or to the duration of exposure.

Detailed information regarding clinical studies of PF-07265803 is presented in the IB.

2.3. Benefit/Risk Assessment

PF-07265803 as a single dose is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07265803 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-07265803		
An identified risk associated with this study intervention is stomatitis. It is a common (≥1/100 to <1/10) event in the protocol population.	The potential risks are based on adverse events reported in early studies of PF-07265803 (ARRY-371797).	AEs will be monitored on an ongoing basis. Instructions for managing potential cases of stomatitis can be discussed with the sponsor.
First time clinical administration of [^{14}C]PF-07265803	• Single *oral* doses up to 900 mg of PF-07265803 observed to be well tolerated; single, oral dose of PF-07265803 in this study (400 mg) represents is >2-fold lower • The maximum whole-body exposure of humans to radioactivity from a 100 μCi (3.7 MBq) PO dose of [^{14}C] PF-07265803PF-07265803, which was predicted using this rodent tissue distribution data was 0.39 mrem. This was approximately 0.013% of the 3 to 5 rem limit specified for whole-body exposure by the Code of Federal Regulations. The predicted exposure of the blood-forming organs, gonads and 29 other tissues to radioactivity from an PO dose of 100 μCi of [^{14}C]PF-07265803 to humans were each less than 1.0% of the 3 to 5 rem limits specified by the Code of Federal Regulations.	• Administration of PF-07265803 will occur in an inpatient setting under close supervision • Clear communication via ICD of negligible risk with the [^{14}C]PF-07265803 doses administered relative to previously administered oral doses.

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. Physical examination, 12-lead ECGs, vital signs) which will occur as outlined in this protocol.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07265803 are justified by the anticipated benefits that may be afforded to participants with *LMNA*-related DCM.The overall benefit:risk profile for PF-07265803 supports continued clinical development and the conduct of this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
To characterize rate and extent of excretion of total radioactivity in urine and feces, following a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.	Mass Balance: cumulative recovery of urinary, fecal, and total excretion of radioactivity over time expressed as percentage of total radioactive dose administered.
To characterize metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.	Metabolic profiling/identification and determination of relative abundance of PF-07265803 and the metabolites of PF-07265803 in plasma, urine, and feces.
Secondary:	**Secondary:**
To quantify plasma concentrations and pharmacokinetic parameters of PF-07265803, its known circulating metabolites (PF-07327859, PF-07327860, PF-07327890) and total radioactivity in plasma following administration of a single oral dose of [^{14}C]PF-07265803 to healthy adult male participants.	Pharmacokinetic parameters AUC_{last}, AUC_{inf}, CL/F, V_z/F, C_{max}, T_{max}, and $t_{½}$ to describe single dose PK of: PF-07265803 and where appropriate PF-07327859, PF-07327860, PF-07327890. Total radioactivity in plasma; PF-07265803, PF-07327859, PF-07327860 and PF-07327890 concentrations in plasma.
To evaluate safety and tolerability of a single oral dose of [^{14}C]PF-07265803 administered to healthy adult male participants.	Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs and ECG.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, single-period, single-center, non-randomized single oral dose study administering a liquid formulation with 400 mg of PF-07265803 containing 100 µCi of [^{14}C]PF-07265803 to healthy male participants. Participants will be screened for participation in this study within 28 days before dosing on Day 1 to confirm that they meet the inclusion/exclusion criteria specified in Section 5.1.

The duration of this non-randomized Phase 1, open-label, single-center, single-dose study is approximately 7 days, with a 30-day safety follow up. The maximum period of confinement is expected to be 14 days. The minimum period of confinement is expected to be 3 days. Inpatient stay must be extended until >90% radioactive dose administered has been recovered or <1% is excreted in total (urine and feces) in any 24H period for two consecutive days. Maximum confinement will be 14 days

The expected duration of participation from Screening to the follow-up telephone contact will be approximately 5 weeks (minimum) to 8 weeks (maximum). Approximately 6 participants will be enrolled to study intervention.

On Day-1, participants will be admitted in order to ensure that a group of 6 participants are dosed on Day 1. The study will dose 6 adult male participants in order to ensure that at least 4 participants provide evaluable data. There are no plans to replace participants who are prematurely withdrawn.

4.2. Scientific Rationale for Study Design

This study will investigate the ADME of [^{14}C]PF-07265803 and characterize plasma, fecal and urinary radioactivity and identify any metabolites of [^{14}C]PF-07265803 in male participants. Only nonsmokers will be enrolled to minimize any potential effect on metabolism by smoking. Oral dosing will be administered in the absence of food, as food has been shown to potentially decrease exposures of PF-07265803 and mimics how PF-07265803 is being administered in the clinical program. Female subjects will be excluded to align with regulatory guidance. The ‘as low as (is) reasonably achievable’ (ALARA) principle prescribed by the FDA recommends that radiation exposure to subjects should be kept ALARA; therefore, if no specific reason exists to include females (ie, no available data suggest metabolism of the PF-07265803 is different in females versus males), then the radiation exposure to female subjects should ideally be kept at zero by not including females in this radioactivity study and only enrolling and dosing male subjects.

The potential risk of exposure to PF-07265803 in a sexual partner of a male participant in this study via ejaculate is possible, and therefore contraception (condom) use in male participants is warranted. The embryo-fetal developmental toxicity studies support the exclusion of pregnant women from clinical studies of PF-07265803 and the continued consideration that partners of study participants who are WOCBP use appropriate contraception in addition to condom use.

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

4.2.1. Choice of Contraception/Barrier Requirements

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for PF-07265803. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

In more than 100 healthy participants and relatively healthy participants, 400 mg BID PF-07265803 has proven to be a well-tolerated dose. In Study ARRAY-797-223, 41 participants with OA of the knee received 400 mg BID for 28 days, and this dosing regimen was well tolerated. In PD studies using clinical samples, 400 mg QD doses of PF-07265803 provided inhibition of PD markers p38 pathway inhibition (cytokines, CRP) of greater than 80% (Study ARRAY-797-101). In a clinical study of pain relief (Study ARRAY 797-221), 400 mg QD of PF-07265803 provided maximal effect (associated with p38 MAPK inhibition), with 200 mg PF-07265803 providing significantly less benefit.

Doses utilized in the nonclinical studies of *LMNA*-related DCM, where positive effects on cardiovascular function and survival were demonstrated, provided exposure consistent with clinical exposure observed with 200 to 400 mg BID of PF-07265803. Study ARRAY-797-231 was a Phase 2, two-arm study designed to investigate the efficacy and safety of 48 weeks of treatment with PF-07265803 in 12 stable participants with DCM secondary to *LMNA* mutations. In this study, participants were alternately assigned to receive PF-07265803) at 100 mg BID or 400 mg BID resulting in n = 6 per dose group. Participants in the 100 mg BID dose group were allowed to dose escalate to 400 mg BID after 24 weeks of treatment. Three participants dose escalated to 400 mg BID after their Week 24 visits and all 3 remained at the 400 mg BID dose through Week 48. In this study PF-07265803 was generally well tolerated; most AEs were mild and only 1 participant discontinued due to a study intervention-related AE. There was also an apparent trend towards a dose response with greater efficacy observed with the 400 mg BID dose. Finally, the 400 mg BID dose of ARRY-371797 (PF-07265803) appeared to be associated with larger favorable changes in NT-proBNP concentration than the 100 mg BID dose in an analysis of aggregated mean change from baseline at all time points.

4.3.1. Dosimetry Calculations

Dosimetry calculations for this proposed [^{14}C]PF-07265803 ADME study in healthy, male subjects are based on a tissue distribution study conducted with Sprague Dawley and Long Evans male rats receiving an oral dose of PF-07265803. Pharmacokinetic parameters and dosimetry projections were calculated for blood and tissues, including (but not limited to) International Commission on Radiological Protection (ICRP) 30 critical tissues of bones, bone marrow, lungs, testes (gonads), and thyroid and the four tissues with highest concentrations of radioactivity in tissues including the gastrointestinal tract, liver, renal cortex, and renal medulla.

The maximum whole-body exposure of humans to radioactivity from a 100 µCi PO dose of [^{14}C]PF-07265803, which was predicted using this rodent tissue distribution data, was 0.00039 rem. This was approximately 0.013% of the 3 to 5 rem limit specified for whole-body exposure by the Code of Federal Regulations. The predicted exposure of the blood-

forming organs, gonads and 29 other tissues to radioactivity from an PO dose of 100 µCi of [^{14}C]PF-07265803 to humans were each less than 1.0% of the 3 to 5 rem limits specified by the Code of Federal Regulations.

The planned radioactive dose in the current study is 100 µCi of [^{14}C]PF-07265803; based on ICRP 30 weighting factors, this would result in an effective dose to the whole body of 0.39 mrem. The planned radioactive dose of approximately 100 µCi of [^{14}C]PF-07265803 is expected to provide a sufficient radioactive signal to achieve the study objectives with minimal radiation risk to subjects.

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 SoA (ie, follow-up phone call).

The end of the study is defined as the date of the last scheduled procedure shown in SoA 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. Participants must be male and ≥18 years of age at the time of signing the ICD.

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

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 ECG monitoring.

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

Weight:

4. BMI of 18.0 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, 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, gastric bypass, duodenotomy, colectomy, history of inflammatory bowel disease).

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

4. Participants with a history of irregular bowel movements; e.g., less than 1 bowel movement per day, regular episodes of diarrhea or constipation, irritable bowel syndrome (IBS) or lactose intolerance.

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 COVID-19 pandemic (eg. Contact with positive case)] that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

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 6.8 Concomitant Therapy for additional details).

7. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

8. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

9. A positive urine drug test.

10. Screening and baseline 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. Screening and baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, atrial fibrillation, 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 the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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.

Other Exclusions:

13. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) 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).

14. Positive urine drug screen or cotinine at screening or check-in, and positive urine alcohol at check-in.

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

16. History of sensitivity to heparin or heparin-induced thrombocytopenia.

17. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

18. 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.

19. Subjects with exposure to significant diagnostic or therapeutic radiation (eg, serial x-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to check-in.

20. Subjects who have participated in more than 3 radiolabeled drug studies in the last 12 months (previous study to be at least 4 months prior to check-in to the study site where exposures are known to the investigator, or 6 months prior to check-in to the study site for a radiolabeled drug study where exposures are not known to the investigator). The total 12-month exposure from this study and a maximum of 2 other previous radiolabeled studies within 4 to 12 months prior to this study will be within the Code of Federal Regulations (CFR) recommended levels considered safe, per United States (US) Title 21 CFR 361.1.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 8 hours prior to the collection of the predose PK sample.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- 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 or fiber capsules containing the equivalent amount of fiber may be administered daily (beginning at least 8 hr after dosing).

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 sample.

- 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 sample. Participants may undergo urine alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 3 months prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. 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;

5.3.4. Contraception

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

the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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, study intervention refers to PF-07265803.

6.1. Study Intervention(s) Administered

One batch of GMP [^{14}C]PF-07265803 API will be prepared with the oral dose being fully radio-diluted (100 μCi / 400 mg (~0.25 μCi/mg)) to the overall specific activity requirements for oral dosing. A bulk bottle of this will be shipped to the CRU from the radiochemical vendor.

[^{14}C]PF-07265803 components for oral administration will be supplied by Pfizer as bulk API and, where necessary, bulk excipients for the manufacture of the oral formulation. The final product composition and presentation will be detailed in a separate Extemporaneous Dispensing Record (EDR) for the [^{14}C] labeled oral formulation.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention according to the EDR.

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

6.2. Preparation, Handling, Storage, and 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 Responsibilities 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 and the IP manual 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 as detailed in the IP manual.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP Manual. 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 as detailed in the IP manual.

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

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 and the IP Manual. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-07265803 oral dosing formulation will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a separate EDR located in the IP Manual. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is an open-label study.

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.

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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Not applicable.

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

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

6.7. Treatment of Overdose

For this study, any dose of PF-07265803 greater than 400 mg (+/- 10% based on the preparation of the final oral dosing formulation) within a 24-hour time period [±2 hours] will be considered an overdose.

There is no specific treatment for an overdose.

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

1. Contact the 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-07265803 (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 Pfizer Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within as soon as possible from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

6.8. 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 (e.g. to treat an AE) following approval by the sponsor.

If an individual participant has not experienced a bowel movement within a 36 – 48 hour window following dose administration, fluid intake should be increased and administration of a mild laxative (e.g., prune juice, milk of magnesia or a mild stool softener) should be implemented, with the goal to facilitate at least one daily bowel movement. A mild laxative may also be used prior to dosing to assist with collection of a pre-dose fecal sample, irrespective of the time of last bowel movement. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Treatments taken within 28 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.

6.8.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07265803; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.1.1. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period are noted to have 2 consecutive SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

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 study procedures;
- 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 SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/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 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.

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. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing

address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, 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 SoA. 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 SoA, is essential and required for study conduct.

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

Healthy participants will be screened up to 28 days prior to dosing to determine eligibility. If the time between screening and dosing exceeds 28 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.

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 312 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 500 mL during any period of 56 consecutive days.

Table 1. Blood Sampling Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Clinical Laboratory Tests	16	1		16
Clinical Laboratory Tests	8		2	16
PK of PF-07265803	4		15	60
Total radioactivity (post-dose)	4		14	56
Total radioactivity (pre-dose)	10		1	10
Metabolite ID	10		15	150
Banked Biospecimen for DNA – Prep D1	4		1	4
TOTAL				**312**

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

8.1. Efficacy Assessments

There are no efficacy assessments included in this protocol.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety 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 SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

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

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

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

8.2.3. Electrocardiograms

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

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 msec from the baseline (predose) **and** is >450 msec; or b) an absolute QT 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 QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT 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 (e.g. holter monitor) and consultation with a cardiologist. A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.2.4. Clinical Safety Laboratory Assessments

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

The investigator must review the laboratory report, document this review, and record any clinically 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 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 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-COVID-19 infection by PCR at screening and at the time of being admitted to the clinic for confinement. Additional testing may be required by local regulations or by the Principal Investigator.

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

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

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

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

During the active collection period as described in Section 8.3.1, 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, except as indicated below, 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.

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and 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.

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

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

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

Further information on follow-up procedures is 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

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

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

Any such exposure to the study intervention under study 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 EDP:

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

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 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 ingestion, 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

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

8.3.6. 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.

8.3.9.1. 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. Pharmacokinetics

The samples collected for PK (non-radiolabeled PF-07265803 concentrations), 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 analysis will not be performed on these samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

8.4.1. Plasma Analysis of Non-Radiolabeled PF-07265803

Blood samples of approximately 4 mL, will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA of the protocol to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of PF-07265803 and metabolites as specified in the Bioanalytical Plan. 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 concetrations of “cold” PF-07265803 will be measured by a validated LCMS method.

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.

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

8.4.2. Metabolite Profiling/ID

8.4.2.1. Plasma for Metabolite Profiling/ID

Blood samples (10 mL) to provide plasma, will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA section of the protocol. Handling of plasma samples, including procedures to stabilize metabolites will be addressed in the Laboratory Manual.

8.4.2.2. Urine for Metabolite Profiling/ID

Urine will be collected over intervals described in the SoA section of the protocol. Handling of urine samples, including procedures to stabilize metabolites will be addressed in the Laboratory Manual.

- ***Prior to dosing on Day 1 at any time***, each subject must empty his urinary bladder, and an aliquot from this urine will serve as the "urine blank". Approximately 10 mL of urine will be collected predose for analysis.

- ***Following dosing on Day 1***, each void post dose will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval. An aliquot of approximately 100 mL from ***each collection interval*** will be withdrawn for measurement of metabolite concentrations/profiling.

- At the end of the collection interval, subjects will attempt to empty bladder prior to the start of the next interval with this void included as part of the interval collection;

    - **If** end of urine collection interval coincides with a meal, subjects will attempt to void *prior to initiation of the meal*; in such cases, so long as the actual time of forced void is recorded, ***for practical reasons***, the fact that this collection may be more than 30-minutes (and up to 45-minutes) ***prior*** to end of collection interval is acceptable and will not be considered as protocol deviation.

- The urine container will be mixed thoroughly and total weight of the urine collected during the interval recorded

8.4.2.3. Feces for Metabolite Profiling/ID

- All feces will be collected over intervals described in the SoA section of the protocol. A pre-dose sample will also be collected. When feces are being collected, all toilet paper that come in contact with the subject's feces will also be collected for possible analysis in appropriately labelled containers stored at approximately -20°C. 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 approximately -20°C for possible analysis of radioactivity. ***Prior to dosing on Day 1 at any time***, each subject must complete a fecal void. A mild laxative may be used to promote a bowel movement and complete fecal void to improve radiolabel material recovery. Approximately 15 g of feces will be collected predose for analysis.***For***

each collection interval, an aliquot of 40 g will be withdrawn for metabolic identification and profiling. A mild laxative may be used to promote a bowel movement in concordance with the guidance in Section 6.8. Detailed sample handling instructions will be provided separately to the site before the start of the study.

8.4.3. Radioactivity

8.4.3.1. Sample Collection

It is extremely important to quantitatively collect all scheduled blood, urine, feces and emesis samples. The separate collection of urine and feces is critical to the success of this study. If urine and feces becomes mixed at any collection, note the weight and add the feces-contaminated urine to the feces collection. Samples missed or lost for any reason should be documented on the case report forms (CRFs).

8.4.3.2. Plasma/Blood Sample Collection for Total Radioactivity

Blood samples (4 mL) to provide plasma (10 mL predose), will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA section of the protocol and submitted for analysis of total radioactivity. Detailed sample handling instructions will be provided separately to the site before the start of the study and described in the Laboratory Manual.

8.4.3.3. Urine Sample Collection for Total Radioactivity

Urine will be collected over intervals described in the SoA. A predose aliquot of 10 mL will be collected. Following dosing, a 25 mL aliquot from ***each post dose collection interval*** will be withdrawn for total radioactivity analysis. Detailed sample handling instructions will be provided separately to the site before the start of the study and described in the Laboratory Manual.

8.4.3.4. Fecal Sample Collection for Total Radioactivity

Feces will be collected over intervals described in the SoA. A predose aliquot of 15 g will be collected. ***For each post dose collection interval***, an aliquot of 100 g will be withdrawn for total radioactivity measurements. Detailed sample handling instructions will be provided separately to the site before the start of the study and described in the Laboratory Manual.

8.4.3.5. Emesis Sample Collection for Total Radioactivity

If emesis occurs within the first 24 hours post dosing, vomitus will be collected for potential analysis of radioactivity. Approximately 4 mL should be collected if emesis occurs. All emesis discharge 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) should be collected and stored in a labeled emesis bag at minimally -20°C for possible analysis of radioactivity. Detailed sample handling instructions will be provided separately to the site before the start of the study.

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). 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 Laboratory Manual.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Specified Gene Expression (RNA) Research

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

8.6.2. Specified Protein Research

Specified protein research is not included in this study.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Analysis Sets

For purposes of analysis, the following analysis sets are defined in the table below:

Table 2. Analysis Sets

Participant Analysis Set	Description
Enrolled	"Enrolled" means all participants who complete the informed consent process.
Safety Analysis Set	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.
PK Concentration	The PK concentration population for PF-07265803 is defined as all participants who receive at least 1 dose of PF-07265803 and who have at least 1 measurable concentration of PF-07265803. The PK concentration population for ^{14}C is defined as all participants dosed with [^{14}C]PF-07265803, who have at least one ^{14}C measurement.
Extent of Excretion	Extent of excretion population is defined as all participants who have received 1 dose of [^{14}C]PF-07265803 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 Parameter	The PK parameter analysis population for PF-07265803 is defined as all participants treated who have at least 1 of the PF-07265803 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.

9.3. Statistical Analyses

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

9.3.1. General Considerations

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious

data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.2. Primary Endpoint(s)

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.

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.

9.3.2.1. Metabolic Profiling/Identification

Plasma, urine and fecal samples will be analyzed for metabolites and/or chiral inversion of PF-07265803. Major metabolites and/or stereoisomers of PF-07265803 in plasma, urine, and feces following oral dose of [^{14}C] PF-07265803 will be identified.

Contributions of each major metabolite to total radioactivity recovered and to circulating radioactivity in plasma will be approximated. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

9.3.3. Secondary Endpoint(s)

9.3.3.1. Pharmacokinetic Parameters

9.3.3.1.1. Plasma

The PK parameters for PF-07265803 and for known circulating metabolites PF-07327859, PF-07327860, PF-07327890 and total radioactivity will be derived following a single dose administration of [^{14}C] PF-07265803, where appropriate, from the concentration-time profiles as outlined below. Additional PK parameters may be included at the discretion of the sponsor and described in the Statistical Analysis Plan.

The PF-07265803 (including circulating metabolites PF-07327859, PF-07327860, PF-07327890) and total radioactivity (plasma) concentrations and parameters (below) will be listed and summarized using descriptive statistics. Individual subject and median concentration-time profiles will be graphically presented.

Table 3. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration	Linear/Log trapezoidal rule
AUC_{inf}[a]	Area under the concentration-time curve from time zero to infinity	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time of maximum observed concentration	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 of drug from e.g.,plasma, for extravascular routes of administration	$Dose/AUC_{inf}$
V_Z/F[a] (oral)	Apparent volume of distribution, estimated from terminal phase, for extravascular dosing	$Dose/(AUC_{inf}*k_{el})$

a. Where appropriate

9.3.4. 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.

9.3.4.1. Electrocardiogram Analyses

Absolute value and changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be listed by treatment and time.

9.3.4.2. Other Analyses

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

9.4. Interim Analyses

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

9.5. 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[2]. This sample size was not chosen based on any empirical data or hypothesis testing criteria. The sample size has been selected to ensure that at least 4 participants provide evaluable data; with intent not to replace participants who prematurely withdraw (or offer non-evaluable or partially evaluable data).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines 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, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

The investigator must ensure that each 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 on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

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

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

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 ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC or IOC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, 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 data from these trials available 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.

10.1.7. Data Quality Assurance

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

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

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate

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

10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in Study Monitoring Plan, which is maintained by the sponsor.

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

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

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

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

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

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

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

If the sponsor decides to terminate the study for a reason unrelated to the safety of PF-07265803, participants may continue to receive PF-07265803 per the investigator's judgement and protocol-specified safety assessments will continue to be performed for these participants until the end of study as defined in Section 4.4. The following non-safety-related study procedures and assessments may be stopped upon written notification from the sponsor:

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

10.1.10. Publication Policy

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.

10.1.11. Sponsor's Qualified Medical Personnel

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

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

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, 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 SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 4. 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 and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin[c] Alkaline phosphatase Uric acid Albumin Total protein	Local Dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and Culture[a]	COVID-19 testing At screening only: • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus At screening and admission (check-in) only: • Urine cotinine • Urine drug screening[b] At admission (check-in) only: • Urine alcohol

a. Microscopy will be conducted if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase. Culture only conducted if bacteriuria present upon microscopy.

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

c. Direct and indirect bilirubin will be measured if total bilirubin is elevated

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

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

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is 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 an SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's

medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

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

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

administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours

of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic 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) 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
    - Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.

10.4.2. Female Participant Reproductive Inclusion Criteria

Females are not eligible to enroll in this study

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

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

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

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

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

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

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;
    - Intravaginal;
    - Transdermal;

7. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;
    - Injectable.

8. Sexual abstinence.

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

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

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

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

Potential Cases of Drug-Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and 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: Prohibited Concomitant Medications That May Result in DDI

Concomitant medications are not allowed in this study

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
6MWT	six minute walk time distance
Abs	absolute
ADE	adverse device effect
ADL	activities of daily living
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
ALARA	as low as reasonably achievable
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration -time curve from zero to time of last measurable concentration
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
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
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{last}	last observable concentration
CL/F	Apparent clearance of drug from e.g.,plasma, for extravascular routes of administration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CRP	c-reactive protein
CRU	clinical research unit
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial; computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDMD	Emery-Dreifuss Muscular Dystrophy
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FMO	flavin monooxygenase
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HSP28	heat shock protein 28
IB	Investigator's Brochure
IBS	irritable bowel syndrome
IC_{50}	concentration corresponding to 50% inhibition
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements

Abbreviation	Term
	for Pharmaceuticals for Human Use
ID	identification
ICRP	International Commision on Radiological Protection
IND	Investigational New Drug
INR	international normalized ratio
IOC	independent oversight committee
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous
K_{el}	Rate constant for terminal phase
LBBB	left bundle branch block
LFT	liver function test
Log_e	natural logarithm
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
msec	millisecond
N/A	not applicable
NT-proBNP	N-terminal pro b-type natriuretic peptide
p38α MAPK	p38-alpha mitogen activated protein kinase
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	oral
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
qual	qualitative
RNA	ribonucleic acid
RV	right ventricular
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Term
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
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
THC	tetrahydrocannabinol
T_{max}	time of maximum observed concentration
$t_{1/2}$	terminal elimination half-life
TOC	table of contents
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
$V_{z/F}$	Apparent volume of distribution, estimated from terminal phase, for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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