A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE DOSE ESCALATION STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-07059013 AND OPEN-LABEL ASSESSMENT OF FOOD AND FORMULATION ON PHARMACOKINETICS OF PF-07059013 IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07059013
Study Intervention Name:	N/A
US IND Number:	N/A
EudraCT Number:	2019-004918-34
Protocol Number:	C4061001
Phase:	1
Short Title: A Phase 1 Study of Single and Multiple Ascending Doses of PF-07059013 in Healthy Adult Participants	

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	24 July 2020	Section 1.3. (Schedule of Activities), and 4.2 (Scientific Rationale for Study Design) have been revised to include sample for reticulocyte on Day 7 of Part 2 of the study. Rationale: Alignment with pre-IND meeting feedback from FDA Section 1.3. (Schedule of Activities), Section 3 (Objectives and Endpoints) and CCI [redacted] CCI [redacted] Section 5.3.1 (Meals and Dietary Restrictions) clarifies that water is permitted during the breakfast of fed treatment period in Part 3. Section 5.1 (Inclusion Criteria) was updated to clarify cardiac monitoring in Part 1 only. Section 6.1 (Study Intervention) was updated with tablet dose strength. Section 1.3. (Schedule of Activities), Section 5.3.2 and Section 10.4.4 have been updated to incorporate Protocol

		AdministrativeClarification Letters (dated 20 February 2020 and 04 June 2020).
Original protocol	12 February 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study of Single and Multiple Ascending Doses of PF-07059013 in Healthy Adults

Rationale

PF-07059013 is a novel small molecule allosteric modulator of hemoglobin that is currently being developed for the treatment of Sickle Cell Disease. The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) of single and multiple ascending oral doses of PF-07059013 in healthy adult participants. Additionally, effects of different formulations and food on parameters, including PK may be explored. This study is the first time that PF-07059013 will be administered to humans, and the results obtained from this study will inform future clinical development of PF-07059013. Based on modulation of the PD parameters (p20 and p50), results from Part 2 of this study may provide a demonstration of pharmacology for modulation of hemoglobin oxygen affinity.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• Part 1 and 2 • To evaluate safety and tolerability of single and multiple escalating oral doses of PF-07059013 suspension administered in healthy adult participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including blood pressure, pulse rate, respiratory rate and oral temperature) and cardiac conduction intervals and heart rate as assessed via 12-lead electrocardiogram (ECG).
Secondary:	**Secondary:**
• Part 1 and 2 • To characterize the blood and plasma exposures of PF-07059013 following administration of single and multiple oral suspension doses in healthy adult participants.	• PF-07059013 blood and plasma exposure parameters, as data permit: • Part 1 • C_{max}, T_{max}, and AUC_{last}. • Part 2 • C_{max}, T_{max}, AUC_{τ}, on Days 1, 7 and 14.
• Part 1 and 2 • To evaluate the PD profile of PF-07059013 following administration of single and multiple oral doses of suspension in healthy adult participants.	• p20 and p50 change from baseline.

Overall Design

This study consists of 3 parts, with ongoing review of safety, tolerability, PK and PD data planned. Part 1 comprises of 4 periods with 2 interleaving cohorts of healthy adult participants. Part 1 Period 1 to 3 is investigator- and participant-blinded, sponsor-open, randomized, single ascending dose, with 3-period placebo substitution crossover, and Period 4 will be open-label.

Part 2 of this study will be investigator- and participant-blinded, sponsor-open, randomized, placebo-controlled, sequential, multiple ascending dose, with 3 planned cohorts of healthy adult participants. Two additional cohorts of healthy adult participants may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study.

Part 3 of this study will be an open-label, randomized, 4-period crossover, single dose assessment of formulation and/or food effects in healthy adult participants.

Number of Participants

A total of approximately 50 (2 planned cohorts with approximately 9 in each cohort for Part 1 and 4 planned cohorts with approximately 8 in each cohort for Part 2 and 3) or up to approximately 70 (including optional Cohorts 6 and 7 and possible expansion to Part 3) healthy adult participants will be randomized.

Intervention Groups and Duration

For all parts of the study, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 and may be discharged at investigator discretion following completion of assessments per SoA.

Part 1 – Single Ascending Dose

Each participant may receive up to 3 single oral doses of PF-07059013 suspension and up to 1 placebo dose. For Period 1 to 3, at each period, approximately 6 participants will receive a single dose of PF-07059013 suspension formulated with polymer, and approximately 3 participants will receive placebo. In Period 4, a single dose of PF-07059013 suspension, formulated without polymer, will be administered at a dose level that has been previously administered in the same cohort. Between each dose administration to a given participant there will be a washout interval of at least 14 days. The washout interval may be adjusted based on data emerging from previous cohorts/periods. An on-site visit is scheduled for Day 8 (±1 day) of Period 3 and 4, and telephone follow-up contact will occur 28 to 35 days after the last dose of investigational product in the final period. The total planned duration of participation, from the Screening visit to the Follow-up phone call, is approximately 15 weeks.

Part 2 – Multiple Ascending Dose

Each participant may receive multiple oral doses of PF-07059013 suspension (either with or without polymer, depending on results from Part 1) or placebo, over a duration of 14 days, depending on randomization. Participants will be required to stay at the CRU for the duration of the treatment phase. An on-site follow-up visit and a telephone follow-up contact will take place at Day 21 (±1 day) and between Day 42-49, respectively. The total planned duration of participation, from the Screening visit to the Follow-up phone call, is approximately 10 weeks.

Part 3 – Formulation and Food Effects

Each participant may receive single oral dose of suspension with different formulations, or tablet, either under fasted condition or following a high-fat/high-caloric meal. Between each dose administration to a given participant there will be a washout interval of at least 14 days. The washout interval may be adjusted based on data emerging from previous cohorts/periods. A telephone follow-up contact will occur 28 to 35 days after the last dose of investigational product in the final period. The total planned duration of participation, from the Screening visit to the Follow-up phone call, is approximately 15 weeks.

Data Monitoring Committee or Other Independent Oversight Committee: No

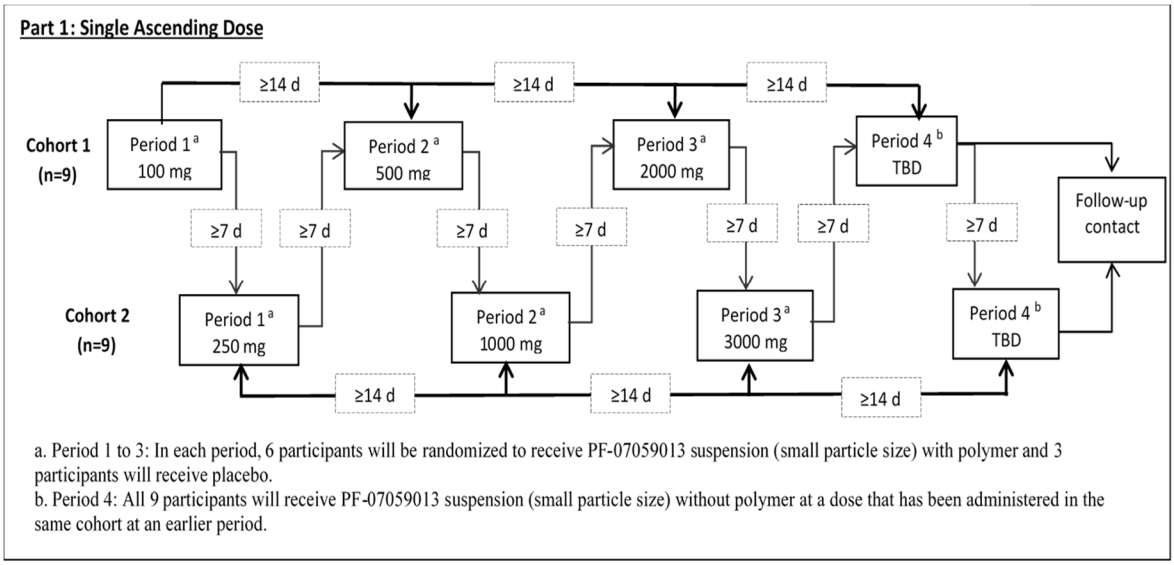
Statistical Methods

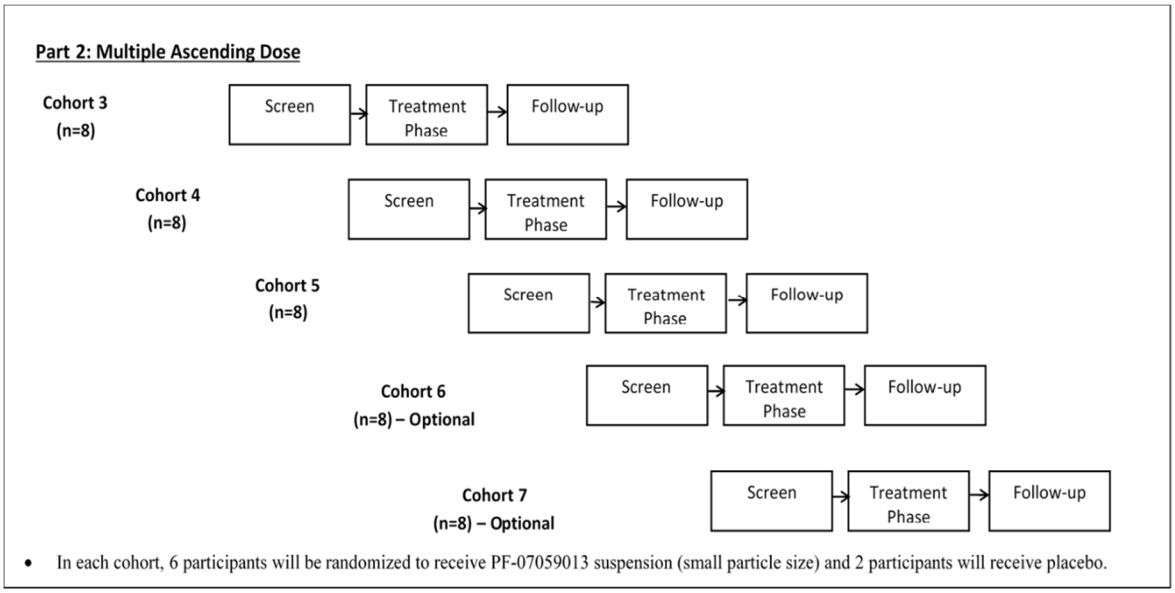
Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor.

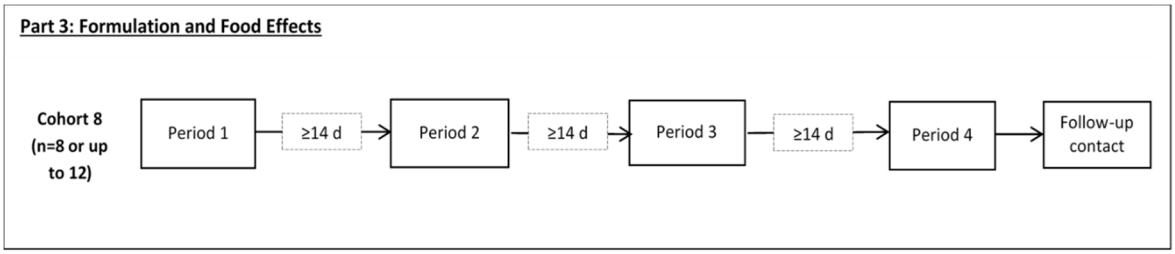
No formal sample size calculation or statistical hypothesis testing will be performed in this study. Cohort size has been chosen to ensure appropriate sample size to provide adequate safety, toleration and PK information at each dose level and to provide a placebo comparison group, while minimizing exposure to humans of a new biologic entity. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. PK and PD data will be listed and descriptively summarized as required.

1.2. Schema

Sample study design schematics of Study Part 1, 2 and 3 are provided below. Doses are provided for illustrative purpose only.







Sample Dosing Scheme (Part 3 – Formulation and Food Effect)

Cohort		Period 1	Period 2	Period 3	Period 4
8	N=2	A	B	C	D
	N=2	D	A	B	C
	N=2	C	D	A	B
	N=2	B	C	D	A

Treatment A: PF-07059013 oral suspension (Small particle size), fasted.
Treatment B: PF-07059013 oral suspension (Small particle size), fed.
Treatment C: PF-07059013 oral suspension (Moderate particle size), fasted.
Treatment D: PF-07059013 oral tablet, fasted.

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.

A. Part 1 SoA – Single Ascending Dose

Visit Identifier[a]	**Screening**	**Period 1 to Period 4**[b]													**F/U Contact**[c]	**E/T**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**							**Day 2**		**Day 3**	**Day 4**	**Day 5**	**Visit**[d] **Day 8±1**	**28-35 Days**	
Hours Post dose			0[e]	0.5	1	2	5	8	12	24	36	48	72	96	168		
Informed consent	X																
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	X			
Inclusion/exclusion criteria	X	X[o]															
Medical/medication history	X																
Demography	X																
Physical exam (height and weight at Screening, only)[f]	X	X															X
12-Lead ECG[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Supine blood pressure[h] and pulse rate	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Orthostatic blood pressure, respiratory rate and oral temperature			X			X		X		X							
Continuous cardiac telemetry monitoring		X[i]	X	→	→	→	→	→	X								
Contraception check	X	X												X	X	X	X
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Study intervention administration[j]			X														

A. Part 1 SoA – Single Ascending Dose

Visit Identifier[a]	Screening	Period 1 to Period 4[b]													F/U Contact[c]	E/T
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**							**Day 2**		**Day 3**	**Day 4**	**Day 5**	**Visit[d] Day 8±1**	**28-35 Days**	
Hours Post dose			0[e]	0.5	1	2	5	8	12	24	36	48	72	96	168		
Blood sampling:																	
HIV, HBsAg, HBsAb, HBcAb, HCVAb, PT/INR, aPTT and serum FSH (postmenopausal females only)	X																
Safety laboratory[k]	X	X						X		X				X	X		X
Lactate[l]	X	X						X		X				X			X
Ferritin and C reactive protein	X	X												X			X
Pharmacokinetic			X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X		X
p20 and p50			X					X									X
CCI [redacted]			[redacted]														
Urine sampling:																	
Urine drug and cotinine testing	X	X															
Urinalysis (and microscopy, if needed)	X	X								X				X	X		X

Abbreviations: → = ongoing/continuous event; aPTT = activated partial thromboplastin time; E/T = early termination; F/U = follow-up; HBcAb = hepatitis B core antibody; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; H= hour; p20 = oxygen pressure at which 20% of the hemoglobin in a given blood sample is oxygenated; p50 = oxygen pressure at which 50% of the hemoglobin in a given blood sample is oxygenated; PT/INR = prothrombin time/internationalized normalized ratio.

A. Part 1 SoA – Single Ascending Dose

Visit Identifier[a]	Screening	Period 1 to Period 4[b]													F/U Contact[c]	E/T
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1							Day 2		Day 3	Day 4	Day 5	Visit[d] Day 8±1	28-35 Days	
Hours Post dose			0[e]	0.5	1	2	5	8	12	24	36	48	72	96	168		

a. **Visit Identifier**: Day relative to start of study treatment (Day 1).
b. **Period 1 to Period 4:** Washout duration of at least 14 days between periods. May be adjusted based on emerging data.
c. **F/U Contact:** Follow-up phone call may occur via telephone and must occur 28 to 35 days after the last dose of investigational product in the final period.
d. **Visit Day 8:** Only applicable for Period 3 and 4.
e. **Day 1 0 H:** Predose sample collection/procedure, except for study treatment administration.
f. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1) in Period 1. Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.
g. **12-lead ECG:** Single at Screening, and triplicate at all other timepoints.
h. **Supine blood pressure:** Where orthostatic blood pressure assessment will be conducted, supine blood pressure does not need to be repeated separately.
i. **Continuous cardiac telemetry monitoring:** Baseline telemetry to be recorded for at least 2 hours between admission and prior to dosing in Period 1 only while awake. Post dose telemetry will continue for 12 hours after dosing for each period.
j. **Study Treatment Administration:** Participants should fast for at least 10 hours prior to dosing. Refer to Section 6.1.1 and Section 5.3.1.
k. **Safety laboratory**: Participants should fast for at least 4 hours prior to sample collection, except Day 1 eight hours postdose sample. Only chemistry panel is required for Day 1 eight hours postdose.
l. **Lactate:** Unless needed for screening, review of data is not required prior to dosing but data up to at least 8 hours post dose will be reviewed prior to dose escalation.
CCI [redacted]
n. **Pharmacokinetic samples at 72 and 96 hours:** Only applicable for Period 2 to 4.
o. **Inclusion/exclusion criteria Day -1:** Period 1 only.

B. Part 2 SoA – Multiple Ascending Dose

Visit Identifier[a]	Screening	Treatment Phase (all activities at 0H (predose) unless otherwise specified)																		Follow-up[b]		E/T
Days Relative to Day 1	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7[j]**	**8**	**9**	**10**	**11**	**12**	**13**	**14[j]**	**15**	**16**	**17**	**18**	**Visit: 21±1**	**Contact: 42-49**	
Informed consent	X																						
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
Inclusion/exclusion criteria	X	X																					
Medical/medication history	X																						
Demography	X																						
Physical exam (height and weight at Screening, only)[c]	X	X																					X
12-Lead ECG[d]	X		X	X		X[k]			X			X[k]				X	X			X	X		X
Supine blood pressure and pulse rate[e]	X		X	X		X[k]			X			X[k]				X	X			X	X		X
Orthostatic blood pressure, respiratory rate and oral temperature			X						X							X				X			
Contraception check	X	X																		X	X	X	X
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Study intervention administration[f]			X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Blood Sampling:																							
HIV, HBsAg, HBsAb, HBcAb, HCVAb, PT/INR, aPTT and serum FSH (postmenopausal females only)	X																						
Safety laboratory[g]	X	X	X	X		X			X			X				X				X	X		X
Lactate[h]	X	X	X	X		X			X			X				X				X	X		X
EPO[h]		X							X							X				X	X		X
Reticulocytes[h]	X	X							X							X				X	X		X
Ferritin & C reactive protein	X	X														X				X	X		X
Pharmacokinetic[i]			X	X		X[k]			X	X		X[k]				X	X	X	X	X	X		X
CCI [redacted]			[redacted]													[redacted]	[redacted]						
[redacted]			[redacted]													[redacted]							
p20 and p50			X	X					X							X	X			X			X
[redacted] C			[redacted]																				
Urine Sampling:																							
Urine drug and cotinine testing	X	X																					
Urinalysis (and microscopy, if needed)	X	X		X		X			X			X				X				X	X		X

B. Part 2 SoA – Multiple Ascending Dose

Visit Identifier[a]	Screening	Treatment Phase (all activities at 0H (predose) unless otherwise specified)																			Follow-up[b]		E/T
Days Relative to Day 1	-28 to -2	-1	1[j]	2	3	4	5	6	7[j]	8	9	10	11	12	13	14[j]	15	16	17	18	Visit: 21±1	Contact: 42-49	
CCI [redacted]																							
[redacted]																							

a. **Visit Identifier**: Day relative to start of study treatment (Day 1).
b. **Follow-up:** Onsite follow-up visit to occur between Day 20 to Day 22. Follow-up contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of investigational product (ie, Day 42 to Day 49).
c. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1). Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.
d. **12-lead ECG:** Single at Screening, and triplicate at all other timepoints.
e. **Supine blood pressure:** Where orthostatic blood pressure assessment will be conducted, supine blood pressure does not need to be repeated separately.
f. **Study Treatment Administration:** Refer to Section 6.1.1 and Section 5.3.1.
g. **Safety laboratory**: Participants should fast for at least 4 hours prior to sample collection, except 8 hours postdose sample. Only chemistry panel is required for 8 hours postdose.
h. **Lactate, EPO, Reticulocytes:** Unless needed for screening, review of data is not required prior to dosing but lactate and EPO data up to at least Day 7, and reticulocyte data up to at least Day 14 will be reviewed prior to dose escalation. Refer to Section 6.6.1 for details.
i. **Pharmacokinetics:**
For dosing days - Samples will be collected predose, *where applicable*. For Day 1, 7 and 14, refer to C List of Procedures for Part 2 Study Day 1, 7 and 14.
For post last dose - Day 15 samples will be collected 24H and 36H post last dose, Day 16 to 18 samples will be collected 48H, 72H and 96H post last dose respectively.
j. **Day 1, 7 and 14:** Refer to C List of Procedures for Part 2 Study Day 1, 7 and 14 for details.
k. **Day 4 and 10:** PK samples, 12-lead ECG, supine blood pressure and pulse rate will be taken at predose and 8 hours postdose.
C [redacted]
C [redacted]

C. List of Procedures for Part 2 Study Day 1, 7 and 14

Hours Post dose	0[a]	0.5	1	2	4	6	8	12	24
Continued CRU confinement	→	→	→	→	→	→	→	→	→
12-Lead ECG[b]	X	X	X	X	X	X	X	X	
Supine blood pressure[c] and pulse rate	X	X	X	X	X	X	X	X	
Orthostatic blood pressure, respiratory rate and oral temperature	X				X		X		
Serious and nonserious adverse event monitoring	→	→	→	→	→	→	→	→	→
Study intervention administration[d]	X								
Safety laboratory[e]	X[g]						X		
Lactate[f]	X[g]						X		
EPO (Day 7 and 14 only)[f]	X								
Reticulocytes (Day 7 and 14 only)[f]	X								
Ferritin & C reactive protein (Day 14 only)	X								
Pharmacokinetic	X	X	X	X	X	X	X	X	
CCI									
p20 and p50	X						X		
Urinalysis (and microscopy, if needed)	X[g]								
Urine blank (Day 1 only)	X								
CCI									

a. **0 H:** Predose sample collection.
b. **12-lead ECG:** Triplicate supine measurements.
c. **Supine blood pressure:** Where orthostatic blood pressure assessment will be conducted, supine blood pressure does not need to be repeated separately.
d. **Study Treatment Administration:** Refer to Section 5.3.1 and Section 6.1.1.
e. **Safety laboratory**: Participants should fast for at least 4 hours prior to sample collection, except 8 hours postdose samples. Only chemistry panel is required for 8 hours postdose samples.
f. **Lactate**, **EPO, Reticulocytes:** Unless needed for screening, review of data is not required prior to dosing but lactate and EPO data up to at least Day 7, and reticulocyte data up to at least Day 14 will be reviewed prior to dose escalation, and cumulative results will be reviewed as they become available. Refer to Section 6.6.1.
g. **Safety laboratory and lactate 0 H:** For Day 7 and 14 only.
C

D. Part 3 SoA

Visit Identifier[a]	Screening	Period 1 to Period 4[b]												F/U Contact[c]	E/T
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**							**Day 2**		**Day 3**	**Day 4**	**Day 5**	**28-35 Days**	
Hours After Dose			0[d]	0.5	1	2	5	8	12	24	36	48	72	96		
Informed consent	X															
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X[k]														
Medical/medication history	X															
Demography	X															
Physical exam (height and weight at Screening, only)[e]	X	X														X
12-Lead ECG[f]	X		X			X	X	X	X	X		X		X		X
Supine blood pressure and pulse rate	X		X			X	X	X	X	X		X		X		X
Respiratory rate and oral temperature			X							X				X		
Contraception check	X	X												X	X	X
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
High-fat/High-caloric meal			X[g]													
Study intervention administration			X[g]													
Blood sampling:																
HIV, HBsAg, HBsAb, HBcAb, HCVAb, PT/INR, aPTT and serum FSH (postmenopausal females only)	X															
Safety laboratory[h]	X	X								X				X		X
Lactate[i]	X	X								X				X		X
Ferritin and C reactive protein	X	X												X		X
Pharmacokinetic			X	X	X	X	X	X	X	X	X	X	X	X		X
CCI [redacted]			[redacted]													
Urine sampling:																
Urine drug testing	X	X														
Urinalysis (and microscopy, if needed)	X	X								X				X		X

D. Part 3 SoA

Visit Identifier[a]	Screening	Period 1 to Period 4[b]												F/U Contact[c]	E/T
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1							Day 2		Day 3	Day 4	Day 5	28-35 Days	
Hours After Dose			0[d]	0.5	1	2	5	8	12	24	36	48	72	96		

a. **Visit Identifier**: Day relative to start of study treatment (Day 1).
b. **Period 1 to Period 4:** Washout duration of at least 14 days between periods. May be adjusted based on emerging data.
c. **F/U Contact:** Follow-up contact may occur via telephone and must occur 28 to 35 days after the last dose of investigational product in the final period.
d. **Day 1 0 H**: Predose sample collection/procedure, except for study treatment administration.
e. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1) in Period 1. Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.
f. **12-lead ECG:** Single at Screening, and triplicate at all other timepoints.
g. **Study Treatment Administration & Meal:** As determined by randomization scheme, dosing to occur with either high-fat/high-caloric meal (ie, provided approximately 30 mins prior to dosing at 0H and expected to be completed approximately 10 minutes prior to dosing) ***or*** following an overnight fast of at least 10-hours, without breakfast. Refer to Section 5.3.1 and Section 6.1.1.
h. **Safety laboratory**: Participants should fast for at least 4 hours prior to sample collection.
i. **Lactate:** Unless needed for screening, review of data is not required prior to dosing; accumulative results will be reviewed as they become available.
C [redacted]
C
k. **Inclusion/exclusion criteria Day -1:** Period 1 only.

2. INTRODUCTION

PF-07059013 is a novel small molecule allosteric modulator of hemoglobin that is currently being developed for the treatment of Sickle Cell Disease.

2.1. Study Rationale

The purpose of Part 1 of the study is to evaluate the safety, tolerability, PK and PD of single ascending oral doses of PF-07059013 in healthy adult participants. Part 2 of this study will evaluate safety, tolerability, PK and PD following repeated oral doses of PF-07059013 in healthy adult participants at multiple ascending dose levels and in Part 3, effects of different formulations and food on parameters, including PK, after single oral dose, may be explored. This study is the first time that PF-07059013 will be administered to humans, and the results obtained from this study will inform future clinical development of PF-07059013. Based on modulation of the PD parameters (p20 and p50), results from Part 2 of this study may provide a demonstration of pharmacology for modulation of hemoglobin oxygen affinity.

2.2. Background

Sickle cell disease (SCD) is a multisystem disorder associated with episodes of acute illness and progressive organ damage and is one of the most common genetic disorders worldwide.[1] SCD is caused by a single point mutation on the β-chain of adult hemoglobin A (HbA), β6 glutamic acid (Glu) to valine (Val) hemoglobin S (HbS). This mutation results in a gain of function; Hb S polymerizes in the deoxygenated state, leading to red blood cell (RBC) sickling, precipitating downstream consequences including vaso-occlusion (pain crisis), hemolytic anemia, stroke and related pathophysiology.[1-3] Over time, these features cause significant organ damage and eventual organ failure, dramatically impacting both quality of life and expected lifespan.

HbS polymerization is highly concentration dependent and requires concentration levels found in RBCs (upwards of 5 mM). The exponential dependence of polymerization on HbS concentration indicates that relatively small changes in deoxy HbS concentration will have significant impact on time to polymerization and ultimately the clinical course of the disease.[4-6] Further, the cyclical nature of oxygen delivery by hemoglobin means that the polymerization reaction is initiated and terminated with every passage of RBCs through the circulatory system, with most of the HbS fibers dissociating upon reoxygenation. This "resetting" predicts that a delay in polymerization long enough for the RBC's to return to the lungs is sufficient to ameliorate RBC sickling. Thus delaying polymerization by stabilizing the oxygenates state of HbS is likely to have a significant impact on sickling. Stabilizing the oxygenated state of HbS by small molecule covalent modification is a clinically validated approach.[7,8] Stabilization of the oxygenated state has been clinically demonstrated to inhibit HbS polymerization, reduce RBC sickling, reduce the frequency of VOC and resolve hemolytic anemia by reducing hemolysis.[7,9] Further, SCD patients with co-inheritance of hereditary persistence of fetal hemoglobin (fetal hemoglobin does not participate in the polymerization process), have a mild course of SCD.[10,11] Each of these conditions effectively reduces the concentration of deoxy-HbS available to polymerize, thereby inhibiting the degree of cell sickling and impacting the course of the disease.

2.2.1. Nonclinical Pharmacology

PF-07059013 is a selective allosteric modulator of hemoglobin that is being developed as a prophylactic therapy that reduces the severity of anemia and reduces the frequency of vaso-occlusive crisis (VOC) in patients with SCD. The binding kinetics of PF-07059013 to purified human HbS were analyzed using Surface Plasmon Resonance (SPR) and the binding affinity found to be in the double digit nanomolar range. Co-crystallization of purified human HbA with PF-07059013 and subsequent X-ray crystallographic analysis indicate that PF-07059013 stabilizes the oxy-state conformation of HbA with 2 molecules of PF-07059013 bound at the interface of 2 α-subunits of the HbA tetramer. A series of in vitro functional assays demonstrated that PF-07059013 can maintain purified human HbS in an oxygenated state under deoxygenating conditions and inhibit HbS polymerization in a dose dependent manner based on the extent of hemoglobin binding. In in vitro cell based assays PF-07059013 induced modulation of oxygen affinity in whole blood measured using a Hemox Analyzer to determine shifts in the partial pressure of oxygen. P50 is the partial pressure at which the hemoglobin in the sample is 50% O_2 saturated, and the p20 is the partial pressure at which the hemoglobin in the sample is 20% O_2 saturated, and both measurements report on the oxygen affinity of the sample. In these studies, the p20 and p50 of whole blood from human, dog, and mouse incubated with 1 mM PF-07059013 was shifted to a similar magnitude suggesting that the PF-07059013 is similarly active in relevant toxicology species.

The Townes SCD mouse model has a knock-in mutation for human α-globin and human β sickle globin,[12,13] recapitulates the main features of the disease and was used to test PF-07059013 PD effects in vivo. In a series of single dose studies in Townes SCD mice, PF-07059013 treatment reduced RBC sickling in a dose-dependent fashion. In a 15-day multiple-dose study in Townes SCD mice, PF-07059013 (200 mg/kg, BID), significantly improved markers of hemolytic anemia including increasing both hemoglobin and hematocrit and reducing reticulocytes in peripheral blood. Further, SCD mice treated with PF-07059013 showed reduced levels of the inflammatory marker sVCAM-1 relative to control animals in the 2-week study.

Details of the nonclinical pharmacology are included in the Investigator's Brochure (IB).

2.2.2. Nonclinical Pharmacokinetics and Metabolism

The PK of PF-07059013 are driven by the ditopic nature of binding to Hb across species. PF-07059013 is moderately bound in plasma (fu_p ranging from 0.088 in mouse to 0.162 in human), but significantly more highly bound in blood. The blood binding is concentration dependent, with fu_b ranging from 0.00661 to 0.000559 in human blood between 1 and 3000 µM. This indicates that PF-07059013 partitions extensively into RBCs due to concentration dependent binding to hemoglobin. This concentration dependence leads to dose dependent PK based on blood concentrations. Such dose dependent blood PK make interpretation of each PK study relevant only to the doses used in that study.

Single dose PK studies with PF-07059013 were conducted following intravenous (1 mg/kg) and oral (10 mg/kg) administration to dogs. PF-07059013 was rapidly absorbed following oral administration with an oral bioavailability of greater than 100%, which likely reflects the dose dependency. Blood clearance following intravenous administration was 2 mL/min/kg and volume of distribution at steady state was 0.3 L/kg.

In toxicology studies, higher oral doses of PF-07059013 (80 to 1000 mg/kg/day) were administered to mice and dogs once or twice daily for up to 29 days. At these doses, the blood concentrations generally increased with increase with dose.

The high dose PK in preclinical species indicate that oral absorption of PF-07059013 is likely extensive, despite limited aqueous solubility at pH 6.5 and the P-glycoprotein substrate potential of the molecule.

Based on the preliminary biotransformation studies, glucuronidation was the primary metabolic pathway of PF-07059013. The major human clearance pathway for PF-07059013 is expected to be UGT-mediated metabolism by UGT1A9 (predicted $f_m = 0.6$) with minor contributions from other UGT (predicted $f_m = 0.36$) and CYP (predicted $f_m = 0.04$) enzymes. No human unique metabolites were observed from in vitro human hepatocytes compared to metabolic profiles in mouse and dog blood. Renal excretion of PF-07059013 was limited in dog.

At the predicted clinically efficacious dose, following existing regulatory guidance, there is a low potential risk of a clinical interaction due to PF-07059013 time dependent inhibition (TDI) of CYP3A4, induction of CYP3A4 and CYP2B6, and inhibition of UGT1A9 and UGT1A1. Additionally, in vitro PF-07059013 is a weak inhibitor of P-glycoprotein, BCRP, OATP1B1 and OCT1.

Further details may be found in the IB.

2.2.3. Nonclinical Safety

PF-07059013 was evaluated in pivotal 1-month toxicity studies (with 1-month recovery) in mice (80, 250, 1000 mg/kg/day) and dogs (100 [50 BID], 300 [150 BID], 1000 [500] mg/kg/day). Safety pharmacology studies included a 1-day dog cardiovascular (CV; 80 [40 BID], 240 [120 BID], 540 [270 BID] mg/kg/day) and a single-dose mouse neuro-pulmonary (80, 250, 1000 mg/kg/day) assessment. While the whole blood concentrations correlate with the pharmacological responses of PF-07059013, exposure margins are calculated based on unbound plasma concentrations because, at steady state, they are the concentrations that tissues (outside of the red blood cells) are exposed to. Safety margins are presented as multiples of unbound plasma C_{max} (0.18 µg/mL) and $AUC_{(0-24)}$ (3.9 µg•h/mL) for the human projected C_{eff}. Further information for whole blood is provided in the IB.

Consistent with its pharmacology, the blood and hematopoietic organs are the primary target of PF-07059013, leading to increased erythropoiesis in the bone marrow, spleen, and/or liver and associated hematology changes (mainly RBC mass parameters and reticulocytes increases) in both species. The increase in reticulocytes (up to 4.0 to 5.5-fold control or baseline in mouse and dog, respectively) was only noted at the high dose of 1000 mg/kg.

Other effects such as heart rate (HR) increase (up to +53 bpm, baseline to Day 1 postdose) and marginal blood pressure (BP) changes in dogs, decreases in body temperature and locomotor activity (up to -95% of control), lower respiratory rates (up to -50% of control) and minute volume in mice, and iron deposition in the liver and/or kidney in mice and/or dogs (minimal to mild severity) are mostly considered secondary to the pharmacology of increased oxygen affinity to hemoglobin leading to transient tissue hypoxia.

None of the nonclinical findings were adverse in the context of the studies; therefore, the NOAEL was the highest dose tested in both mouse and dog pivotal toxicity studies, 1000 mg/kg/day, which was associated with exposure (C_{max}/AUC_{24}) margins of 24.6×/7.9× in mice and 8.6×/5.8× in dogs of the projected unbound plasma C_{max}/AUC_{24} at the projected efficacious dose. The NOAEL in dog was associated with unbound plasma C_{max} of 1.5 µg/mL and $AUC_{(0-24)}$ of 22.5 µg·h/mL.

PF-07059013 was weakly aneugenic at 1000 mg/kg with a NOEL of 250 mg/kg/day in mice (10.7× projected unbound plasma C_{max} at the projected efficacious dose). The follow-on chromosome aberration assessment at 1000 mg/kg was confirmed negative for clastogenicity. PF-07059013 absorbs ultraviolet/visible light and its risk for phototoxicity will be further assessed prior to large enrollment clinical trials.

Details of the nonclinical safety are provided in the IB.

2.2.4. Biopharmaceutics

PF-07059013 is a basic compound. cLogP and permeability, as measured in cell lines, indicate that the molecule should rapidly permeate the intestinal membrane. The solubility will be high in gastric fluid and moderate in intestinal pH. Based on preclinical exposure data and/or modelling, PF-07059013 is expected to be moderately to well absorbed at the predicted dosing range in the First in Human (FIH) study (100 – 3000 mg) using a suspension formulation. Based on physical chemical properties and in silico prediction, food is expected to have an ambiguous impact on PF-07059013 exposure.

A formulation with a small particle size and a formulation with a moderate particle size may be studied to determine the effect of particle size on bioperformance. This data will be utilized to identify a preferred particle size range for optimal performance of the drug product. The impact of the presence of a polymer on the pharmacokinetics of the formulation may be evaluated and compared to the formulation without polymer. This data will be utilized to select the preferred formulation composition for the drug product.

Further details are included in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-07059013 may be found in the IB, which is the single reference safety document (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-07059013		
Tissue hypoxia	Data from hemoglobin variants with excessively high oxygen affinity demonstrate homeostatic responses reflective of tissue hypoxia.	Treatment dose is modeled to target exposure levels that will not provide a level of hemoglobin coverage that would be anticipated to compromise oxygen delivery to tissues. Monitor for evidence of impaired oxygen delivery based on endpoints of lactate and erythropoietin level. Monitor for excessive pharmacology that could result in impaired oxygen deliver to tissues based on endpoint of p50 with associated laboratory correlates of erythropoietin level, lactate, and absolute reticulocyte count, with stopping rule on dose escalation based on the above.
Tachycardia	In single dose cardiovascular and 1-month repeat dose GLP study in dogs, exposure above the NOEL was associated with dose responsive increases in heart rate.	Monitor based on heart rate. Can be pharmacologically treated. Reversible.
Hypertension/Hypotension	Marginal changes in blood pressure were noted in both the single dose cardiovascular and 1-month repeat dose GLP studies in dogs at the highest dose level tested in those studies. These changes included increases in systolic and diastolic blood pressure, as well as a biphasic decrease in systolic blood pressure.	Monitor based on blood pressure. Can be treated pharmacologically. Reversible.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Iron accumulation	In the 1-month GLP toxicology studies at the intermediate and high dose levels in mouse and dog there was evidence of pigment (iron deposition) in the kidney, as well as in the liver at the high dose in the dog.	Monitor based on serum ferritin. Can be treated with iron chelator drugs or with phlebotomy.
Aneugenic genetic toxicity	Micronucleus induction was noted in the mouse blood and bone marrow at 1000 mg/kg with a NOEL at 250 mg/kg.	Maintain sufficient safety margin based on micronucleus NOEL.
Phototoxicity	UV absorption was noted in UV spectral analysis.	Light restriction on storage, preparation and administration. Participants will be advised to avoid direct sunlight exposure or high intensity UV exposure and instructed to apply sunscreen. Further risk assessment will be conducted prior to large enrollment clinical trials.

2.3.2. Benefit Assessment

Study C4061001 is the first time that PF-07059013 will be administered to humans. For healthy participants participating in this study, no clinical benefit is expected. The purpose of the study is to generate safety, tolerability, PK and PD data to provide the basis for further clinical development of PF-07059013 as a potential new, pharmacological agent for the treatment of individuals with SCD. This is an area of unmet need. As of issuance of this protocol, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.3. The clinical impact of these potential risks will be minimized through the proposed cautious dose escalation process where in higher doses of PF-07059013 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile, use of stopping rules for dose escalation, as well as by specific safety monitoring measures that have been incorporated into this study including erythropoietin, reticulocyte, lactate and ferritin levels, where appropriate. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of oral doses of the investigational product.

2.3.3. Overall Benefit/Risk Conclusion

PF-07059013 is not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with PF-07059013 are justified by the anticipated benefit, in terms of contribution to the process of developing new therapy in an area of unmet medical need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• Part 1 and 2 • To evaluate safety and tolerability of single and multiple escalating oral doses of PF-07059013 suspension administered in healthy adult participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including blood pressure, pulse rate, respiratory rate and oral temperature) and cardiac conduction intervals and heart rate as assessed via 12-lead electrocardiogram (ECG).
Secondary:	**Secondary:**
• Part 1 and 2 • To characterize the blood and plasma exposures of PF-07059013 following administration of single and multiple oral suspension doses in healthy adult participants.	• PF-07059013 blood and plasma exposure parameters, as data permit: • Part 1 • C_{max}, T_{max}, and AUC_{last}. • Part 2 • C_{max}, T_{max}, AUC_{τ}, on Days 1, 7 and 14.
• Part 1 and 2 • To evaluate the PD profile of PF-07059013 following administration of single and multiple oral doses of suspension in healthy adult participants.	• p20 and p50 change from baseline.

Objectives	Endpoints
CCI	

4. STUDY DESIGN

4.1. Overall Design

This study consists of 3 parts, with ongoing review of safety, tolerability, PK and PD data planned.

Part 1 – Single Ascending Dose

The design for Period 1 to 3 for Part 1 of this study is investigator- and participant-blinded, sponsor-open, randomized, single ascending dose, with 3-period placebo substitution crossover, while Period 4 will be open-label. There will be 2 interleaving cohorts of healthy adult participants, with a total of approximately 18 participants planned (approximately 9 participants in each cohort). Each participant may receive up to 3 single oral doses of PF-07059013 and up to 1 placebo dose. For Period 1 to 3, at each period, approximately 6 participants will receive a single dose of PF-07059013 oral suspension formulated with polymer, and approximately 3 participants will receive placebo. In Period 4, a single dose of PF-07059013 oral suspension, formulated without polymer, will be administered at a dose level that has been previously administered in the same cohort.

Part 2 – Multiple Ascending Dose

Part 2 of this study will be investigator- and participant-blinded, sponsor-open, randomized, placebo-controlled, sequential, multiple ascending dose. A total of approximately 24 healthy adult participants will be randomized for Cohort 3 to 5. In each cohort, approximately 6 participants will receive PF-07059013 oral suspension (either with or without polymer, depending on results from Part 1) and approximately 2 participants will receive placebo, over a duration of 14 days, depending on randomization. Two additional cohorts (optional Cohort 6 and 7) with approximately 8 participants each, with the same randomization ratio may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study.

The first dose level in Part 2 will only initiate after review of safety and PK data from both cohorts in Part 1 Period 4. Refer to Section 4.3.3 for additional details regarding determination of initial dose in Part 2 relative to dose(s) evaluated in Part 1.

Part 3 – Formulation and Food Effects

Part 3 of this study is designed to allow exploration of potential effects of food, particle size and tablet versus suspension formulation, on the PK of a single oral dose of PF-07059013. This part will be an open-label, randomized, 4-period crossover design. Approximately 8 healthy adult participants will be randomized in Cohort 8.

Depending on emerging data from Part 1 (dosing of suspension-small particle size under fasted condition), assessment of the effects of 1) high-fat/high-caloric meal versus a fasted state, 2) moderate particle size versus small particle size, and 3) tablet formulation versus

suspension-small particle size, on the pharmacokinetics of PF-07059013 may be undertaken in Part 3. The reference treatment and dose for Part 3 will be based on Part 1 (refer to Section 4.3.3.3). Part 3 will occur only after completion of Part 1, though it may occur in parallel to Part 2. The number of participants in Part 3 may be altered to randomize up to 12 healthy adult participants, depending on emerging PK data from Part 1 of this study.

For Part 1 and 3, between each dose administration to a given participant there will be a washout interval of at least 14 days. Participants may stay at the clinical research unit (CRU) for the duration of the washout period at the discretion of the investigator, this may be for safety or for logistic reasons. The washout interval may be adjusted based on data emerging from previous cohorts/periods. An on-site visit is scheduled for Day 8 (±1 day) of Part 1 Period 3 and 4 only, and a telephone follow-up contact will occur 28 to 35 days after the last dose of investigational product in the final period. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from the Screening visit to the Follow-up phone call, is approximately 15 weeks.

For Part 2, participants will be required to stay at the CRU for the duration of the treatment phase. An on-site follow-up visit will take place at Day 21 (±1 day) and a telephone follow-up contact between Day 42 to 49. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from the Screening visit to the Follow-up phone call, is approximately 10 weeks.

For all parts of the study, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 and may be discharged at investigator discretion following completion of assessments per SoA. If a participant has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

Participants who discontinue for non-safety related reasons prior to completion of the study may be replaced, at the discretion of the principal investigator (PI) and sponsor. The replacement participant(s) may or may not be required to complete all Periods of the cohort in which they are participating at the discretion of the PI and sponsor.

Sample design overview of the study is shown in Section 1.2. Treatment sequences, actual doses and dose increments may be adjusted and intermediate or alternative dose levels may be substituted during the study based on emerging safety, tolerability and PK data.

4.2. Scientific Rationale for Study Design

The population planned for this study will be healthy male and female participants. Female participants will be confirmed to be of non-childbearing potential, since at the present time embryo-fetal developmental toxicity studies with PF-07059013 have not been conducted. In male participants, appropriate measures should be expected to be followed to minimize potential transfer of PF-07059013 via semen to partners (see Appendix 4: Contraceptive Guidance).

Part 1

Given the current study is the first to dose PF-07059013 to humans, an escalating single oral dose design with careful assessment and ongoing review of safety and PK data of PF-07059013 is planned. The crossover design will permit both a within and between participant assessment of safety, tolerability and PK. Furthermore, 2 interleaving cohorts will permit assessment of safety and PK over a wider dose range within a given participant compared to a sequential cohort design.

To guide formulation development, PF-07059013 suspension formulated with and without polymer will be assessed in Period 1 to 3 and Period 4, respectively. As the purpose for inclusion of the polymer is to explore potential enhancement of absorption, conduct of the dose escalation through Period 1 to 3, with the suspension formulated with the polymer allows assessment of safety at potentially higher PF-07059013 exposures, prior to the open-label assessment of the suspension formulation without polymer in Period 4, at dose level(s) previously evaluated in Period 1 to 3 of the same cohort.

To permit an unbiased assessment of safety, the administration of active versus placebo in Period 1 to 3 will be double blinded to site staff (except those involved in preparation of doses) as well as the study participants. To permit real-time review of the safety, PK data (as well as PD data, when available), a limited number of sponsor study team members will be unblinded (see Section 9.5).

In addition, dosing in the initial part of the study (Part 1) will be conducted in the fasting state (at least 10 hours) to facilitate management of any AEs which may occur shortly after dosing. For a given participant, dosing will be separated by ≥14 days. This planned dosing interval is deemed sufficient to permit washout of previous treatment based on the projected PF-07059013 effective half-life (see Section 4.3.1). Given that shorter effective half-life are anticipated at lower doses in Period 1 to 2 and to minimize burden on participants, additional visit on Day 8 is only planned for Period 3 and 4.

Part 2

Part 2 of this study is designed to assess the safety, tolerability, and PK, as well as potential PD of escalating doses of PF-07059013 administered for 14 days as a once-daily (QD) regimen. In addition, based on in vitro data (Section 2.2.2), potential of PF-07059013 to cause P450 CYP3A4 induction will also be explored. The proposed duration of dosing (14 days) is of shorter duration than the 30 days of non-clinical toxicology data currently available. This duration is also deemed to be sufficient to assess steady-state safety, PK, and PD given the projected effective half-life of PF-07059013 (see Section 4.3.1). The planned

doses in the escalation sequence (refer to Section 6.6.1) may be modified or repeated, as guided by emerging safety and PK data (as well as PD data, when available) but will follow the dose escalation rules defined in Section 6.6.1.

To permit an unbiased assessment of safety, the administration of active versus placebo in each period will be double blinded to site staff (except those involved in preparation of doses) as well as the study participants. To permit real-time review of the safety, PK data (as well as PD data), a limited number of sponsor study team members will be unblinded (see Section 9.5).**Part 3**

Based on the biopharmaceutical profile of PF-07059013 (see Section 2.2.4) and preliminary in silico predictions, there is uncertainty in the potential impact of food on the rate and extent of absorption, hence preliminary evaluation of the effect of food on the PK of PF-07059013 is planned, to help guide the dose and dosing condition (fed versus fasting state) for future clinical studies with PF-07059013.

To better understand and guide formulation development for future clinical studies, preliminary assessment of a tablet formulation and examination of different particle size is also planned.

Since the dose in this Part (refer to Section 4.3.3.3) will be selected based on observed safety and tolerability of single doses in Part 1 and the dose selected will be lower than the highest dose tested in Part 1, standard safety monitoring will be used in this part of the study, without placebo control, and without on-site visit following discharge.

For all parts of the study

Considering the nonclinical safety studies with PF-07059013 in mice and dogs (see Section 2.2.3), the standard safety assessments used by the sponsor in trials administering investigational product for the first time to humans are deemed suitable (see Appendix 2: Clinical Laboratory Tests). In addition to the standard safety assessments, levels of lactate (Part 1 to 3), EPO and reticulocyte count (Part 2 only) will also be monitored to evaluate the potential risk of reduction in tissue oxygen delivery per unit volume of blood, for this class of mechanism. Due to the long half-life of RBC and lag for EPO stimulation, any potential effects on reticulocyte count and EPO will likely only manifest after a sustained period, hence assessments are planned for Part 2, from Day 7 onwards for EPO and reticulocyte count. Ferritin levels and respiratory rate will be also assessed based on non-adverse findings in the nonclinical studies with PF-07059013 (see Section 2.2.3), with ferritin assessment planned on/after Day 5 due to physiologic rationale that this is likely the earliest point at which modulation of ferritin could be detected.

To ensure that participants with undiagnosed hematological conditions and elevated baseline lactate are not enrolled, hemoglobin, reticulocyte count (Part 2 only), lactate, PT/INR and aPTT levels will also be assessed at screening.

To further permit assessment of modulation of oxygen affinity and possibly limit excessive pharmacological effect, measures of hemoglobin oxygen affinity (p20 and p50) will be

assessed at multiple timepoints in Part 1 and 2, including at the projected blood T_{max}. Stopping criterion for dose escalation in Part 1 and 2, based on excessive modulation of p50, in association with physiologic correlates such as EPO, reticulocyte, and lactate level, where applicable, is detailed in Section 6.6.1. Given the potential effect of smoking on p50 levels, participants who smoke or use nicotine containing products are excluded from Part 1 and 2 of the study.

CCI [redacted]

4.3. Justification for Dose

Doses and dosing scheme presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Prediction of Human Pharmacokinetics

PF-07059013 binds ditopically and cooperatively to Hb (2 drug molecules/Hb tetramer) as evidenced by a concentration dependent decrease in blood fraction unbound in vitro and in vivo. A 2-step binding Hb model was developed and applied to PF-07059013 blood binding data in multiple species which accounted for this concentration dependency.

Human PK was predicted using a minimal physiologically-based pharmacokinetic (PBPK) model that utilizes in vitro data and SimCYP predictions, and incorporates the binding to Hb. As a result of concentration dependent Hb binding properties of PF-07059013, non-linear concentration dependent PK profile is projected. Dose-dependent decrease in apparent blood clearance (CL) and V_{ss} is projected. Effective half-life predicted from the model ranges from 7 hours at 100 mg to 41 hours at 3000 mg for healthy participants.

4.3.2. Prediction of Efficacious Dose/Concentration

Efficacious concentration is defined as average concentration at the dose resulting in approximately 25% Hb coverage in sickle cell patients at steady state – a coverage level expected to significantly reduce RBC sickling and improve Hb levels in SCD patients.[14,15] Using the minimal PBPK model and ditopic Hb binding affinities for PF-07059013, the steady state average concentration meeting this objective is predicted to be 0.16 µg/mL unbound plasma and 260 µg/mL blood total drug achieved at 1500 mg QD oral dose. The associated unbound plasma C_{max} and unbound plasma AUC_{24} are projected to be 0.18 µg/mL and 3.9 µg•hr/mL respectively.

4.3.3. Dose Selection

Projections of human PK exposure for PF-07059013, along with the toxicity study data, and a minimal anticipated biological effect level (MABEL) approach, based on projected Hb coverage, are used to establish the nominal dose range to be studied in Part 1 (single escalating doses) and Part 2 (repeated escalating doses), with the aim to bracket the expected clinically efficacious dose range in humans and provide safety coverage for a wide range of predicted levels of Hb coverage. Approximately 40% Hb coverage has been previously

studied in healthy adult participants, for compounds with the same pharmacological mechanism, with no safety concerns detected.[16,17]

4.3.3.1. Rationale for Dose Selection in Part 1

Based on PK and Hb coverage predictions from the minimal PBPK model, 100 mg is proposed as the starting dose in Part 1. A single oral dose of 100 mg is predicted to provide maximum Hb coverage of less than 0.5%, and >66-fold safety margin relative the PK stopping limits (refer to Table 1). To account for uncertainty in the prediction of unbound intrinsic clearance using human hepatocytes, sensitivity analysis was performed assuming 30% lower unbound intrinsic clearance. Projected maximum Hb coverage based on this assumption is less than 0.7%. Considering the precedence of the pharmacological mechanism, along with the projected safety margins and Hb coverage, the starting dose of 100 mg is anticipated to be safe and have minimal pharmacological effect.

The planned dose escalation procedure will be dictated by the rules summarized in Section 6.6.1 and is aimed to occur in increments of ≤½-log (ie, 3.3-fold) based on predicted unbound exposure, with smaller increments envisioned at higher doses, and will not exceed unbound exposures defined in the PK stopping limits (See Section 6.6.1), or the highest practical dose of 4000 mg, whichever is the most conservative.

At the current proposed maximum single dose of 3000 mg, projected Hb coverage is 23%, and >5-fold safety margin relative to the PK stopping limits is predicted. Projected exposure of PF-07059013 at each planned dose level, as well as corresponding safety margins relative to exposures at the NOAEL in dog are summarized in Table 1. The PK stopping limits were chosen based on unbound PF-07059013 exposure achieved at the NOAEL dose (1000 mg/kg/day) in the 30-day toxicity study in dog, which provides more conservative margins than mouse NOAEL dose– refer to Section 2.2.3.

Table 1. Predicted Human Exposure and Safety Margins Following Administration of Single Oral Doses of PF-07059013, in Part 1

Dose[a] (mg)	Predicted Human Exposure of blood and plasma PF-07059013[b]						Predicted Safety Margin based on ***unbound*** PF-07059013[c]		Max Hb coverage (%)
	Blood C_{max} (µg/mL)	***Plasma*** C_{max} (µg/mL)	***Unbound*** C_{max}[d] (µg/mL)	***Blood*** AUC_{24} (µg•hr/mL)	***Plasma*** AUC_{24} (µg•hr/mL)	***Unbound*** AUC_{24}[d] (µg•hr/mL)	C_{max}	AUC_{24}	
100	6.8	0.14	0.0227	81	2	0.324	66.1	69.4	0.47
250	21	0.26	0.0421	310	4.4	0.713	35.6	31.6	1.4
500	48	0.39	0.0632	820	7.5	1.22	23.7	18.5	3.2
1000	110	0.59	0.0956	2000	12	1.94	15.7	11.6	6.9
2000	230	0.91	0.147	4600	19	3.08	10.2	7.31	15
3000	370	1.2	0.194	7300	26	4.21	7.72	5.34	23

Table 1. Predicted Human Exposure and Safety Margins Following Administration of Single Oral Doses of PF-07059013, in Part 1

Dose[a] (mg)	Predicted Human Exposure of blood and plasma PF-07059013[b]						Predicted Safety Margin based on ***unbound*** PF-07059013[c]		Max Hb coverage (%)
	Blood C_{max} (µg/mL)	***Plasma*** C_{max} (µg/mL)	***Unbound*** C_{max}[d] (µg/mL)	***Blood*** AUC_{24} (µg•hr/mL)	***Plasma*** AUC_{24} (µg•hr/mL)	***Unbound*** AUC_{24}[d] (µg•hr/mL)	C_{max}	AUC_{24}	

a. Depending on the available safety and PK data, dose escalation may be adjusted to doses other than those outlined above with intermediate doses evaluated instead of or in addition to the planned dose levels with increments being ≤½-log (ie, 3.3-fold) while following dose escalation and stopping rules outlined in Section 6.6.1.
b. Human exposure was predicted based on a minimal PBPK model using in vitro data and SimCYP predictions.
c. Derived using exposure of PF-07059013 at NOAEL (1000 mg/kg/day) from 1 month dog toxicity study of unbound C_{max} = 1.5 µg/mL and AUC_{24} = 22.5 µg•hr/mL.
d. Unbound values calculated taking into account plasma protein binding in humans(fu_p=0.162).

4.3.3.2. Rationale for Dose Selection in Part 2

Initiation of dosing in Part 2 will occur following review of safety and PK data from both cohorts in Part 1 Period 4 (see Section 4.1). At the starting dose level for Part 2, projected unbound exposures (C_{max} and AUC) at steady-state will be covered (approximately 2-fold lower) by exposures observed to have an acceptable safety profile in Part 1 of this study. Projected Hb coverage will not exceed that from Part 1, and will not be higher than 15%.

The proposed starting dose in Part 2 is 600 mg QD. At this planned initial dose level, projected maximum Hb coverage is 7.4%, and predicted steady-state unbound exposures are C_{max} of 0.0972 µg/mL and AUC_{24} of 1.94 µg•h/mL (>11-fold exposure multiples relative to the PK stopping limits). Planned dose escalation procedure will be dictated by the rules summarized in Section 6.6.1 and is aimed to occur in increments of ≤½-log (ie, 3.3-fold) based on predicted unbound exposures, with smaller increments envisioned once the projected clinically efficacious dose is exceeded, and will not exceed the predefined PK stopping limits (Section 6.6.1), or the highest practical dose of 4000 mg, whichever is the most conservative. The proposed nominal doses, corresponding projected PK exposures based on QD dosing, and safety margins relative to PK stopping limits set based on NOAEL from dog are summarized in Table 2.

Table 2. Predicted Human Exposure and Safety Margins Following Administration of Multiple Oral QD Doses of PF-07059013 for 14 Days, in Part 2

Dose[a] (mg)	Predicted Steady-State Human Exposure of Blood and Plasma PF-07059013[b]						Predicted Safety Margin at Steady State based on *unbound* PF-07059013[c]		Max Hb coverage (%)
	Blood C_{max} (µg/mL)	*Plasma* C_{max} (µg/mL)	*Unbound* C_{max}[d] (µg/mL)	*Blood* AUC_{24} (µg•hr/mL)	*Plasma* AUC_{24} (µg•hr/mL)	*Unbound* AUC_{24}[d] (µg•hr/mL)	C_{max}	AUC_{24}	
600	110	0.6	0.0972	2100	12	1.94	15.4	11.6	7.4
1200	350	1.1	0.150	7100	25	3.10	10.0	7.26	22
2000	700	1.9	0.308	15000	41	6.64	4.87	3.39	45

a. Depending on the available safety and PK data, dose escalation may be adjusted to doses other than those outlined above with intermediate doses evaluated instead of or in addition to the planned dose levels with increments being ≤½-log (ie, 3.3-fold) while following dose escalation and stopping rules outlined in Section 6.6.1.
b. Human exposure was predicted based on a minimal PBPK model using in vitro data and SimCYP predictions.
c. Derived using exposure of PF-07059013 at NOAEL (1000 mg/kg/day) from 1 month dog toxicity study of unbound C_{max} = 1.5 µg/mL and AUC_{24} = 22.5 µg•hr/mL.
d. Unbound values calculated taking into account plasma protein binding in humans(f_{up}=0.162).

4.3.3.3. Rationale for Dose Selection in Part 3

Depending on emerging data from Part 1 (and if available, data from Part 2), if Part 3 is conducted, a single dose level of PF-07059013 will be studied, and the dose selected will be lower than the highest dose found to be safe and well tolerated in Part 1. Furthermore, the dose selected will be in the range of likely pharmacologically active doses.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the Schedule of Activities and any requested unplanned visits.

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female (of non-child bearing potential) participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.

    - Refer to Appendix 4: Contraceptive Guidance for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, including blood pressure, pulse rate, respiratory rate and temperature measurement, standard 12-lead ECG, laboratory tests, and cardiac monitoring (in Part 1 only).

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 17.5 to 30.5 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).

3. History of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C; positive testing at screening for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCVAb). As an exception a positive HBsAb test due to hepatitis B vaccination is permissible.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Use of 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. (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

6. 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:

7. A positive urine drug test at screening or admission.

8. A positive urine cotinine test at screening or admission in Part 1 and 2.

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

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

11. 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;
    - PT/INR >1.2 × ULN;
    - aPTT ≥1.5 × ULN;
    - Hemoglobin <11.0 g/dL;
    - Lactate >1 x ULN.

12. For Part 2 only, participants with absolute reticulocyte count >150,000/uL at screening, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary.

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) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

14. Use of tobacco/nicotine containing products for Part 1 or 2, and use of more than 5 cigarettes/day for Part 3.

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

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations, except for 8 hour post dose samples.

- For Part 1 and Part 3, water is permitted until 1 hour prior to dosing and during breakfast when dosing under fed **(high-fat/high-caloric)** condition. Water may be consumed without restriction beginning 1 hour after dosing.

- For Part 2, there are no water restriction prior to or after dosing.

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

  Part 1 and when dosing under fasted condition in Part 3:

  On Day 1 of each period, with dosing under fasted condition (overnight fast of at least 10 hours):

  - Breakfast will not be provided.

  - 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.

Part 2:

On all dosing days,

- A standard breakfast will be provided approximately 30 minutes prior to administration of the investigational product and is expected to be completed approximately 10 minutes prior to dosing. Participants will be encouraged to consume the entire meal. If participants are unable to complete the meals, the portion consumed in 25% increments will be documented and potential impact on results assessed by the Sponsor study team on a case-by-case basis.

- 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.

When dosing under fed (high-fat/high-caloric) condition in Part 3:

- Following an overnight fast of at least 10 hours, participants will receive high-fat (approximately 50% of the total caloric content of the meal)/high-caloric (approximately 800 to 1000 calories) breakfast approximately 30 minutes prior to administration of the investigational product on Day 1.

- The breakfast will be consumed over approximately a 20-minute period and the investigational product administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to consume the entire meal. If participants are unable to complete the meals, the portion consumed in 25% increments will be documented and potential impact on results assessed by the sponsor study team on a case-by-case basis.

- 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, fruit juices) from 7 days prior to the first dose of investigational product 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 (except when investigational product is administered with high-fat/high-calorie breakfast). The daily caloric intake per participant should not exceed approximately 3200 kcal.

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 of each study period in Part 1 and 3 and final PK sample of Part 2.

- 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 of each study period in Part 1 and 3 and final PK sample of Part 2. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- For Part 3, participants will abstain from the use of tobacco- or nicotine -containing products for 24 hours 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, respiratory rate, oral temperature and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing;

- For Part 1 only, participants will be confined to the procedure room/participant room, as appropriate, for the first 4 hours after dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the continuous cardiac monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

- Participants will be advised to avoid direct sunlight exposure or any high intensity ultraviolet light exposure, from the first day of dosing with investigational product and until 14 days after the last dose of investigational product. In addition, participants will be instructed to apply sun cream/lotion with a high sun protection factor, as appropriate.

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 partner(s) from the permitted list of contraception methods (see Appendix 4: Contraceptive Guidance, 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 Schedule

of Activities, 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). 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 randomly assigned to study intervention/enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-07059013 and placebo.

6.1. Study Intervention(s) Administered

For this study, the investigational product(s) is PF-07059013 and placebo.

PF-07059013 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

PF-07059013 and placebo will be presented to the participants in individual dosing containers.

PF-07059013 will be supplied by Pfizer as 200-mg tablets.

Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Administration of the investigational product will occur with and without meals, as outlined below. Further details on meals and dietary requirements are provided in Section 5.3.1.

For tablet formulation, participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing. Investigator site personnel will administer study intervention during each period with ambient temperature water or polymer solution (if required, this will be provided and investigator site personnel will be

notified prior to start of dosing in Part 3) to a total volume of approximately 240 mL. If needed, an additional volume of water up to 150 mL may be provided for tablet dosing. This will be documented by the site.

For suspensions, 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, respiratory rate, oral temperature and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

For Part 1:

Following an overnight fast of at least 10 hours, participants will receive investigational product at approximately 0800 hours (plus or minus 2 hours) without breakfast.

For Part 2:

On each dosing day, participants will receive a standard breakfast approximately 30 minutes prior to dosing which is to be completed within approximately 20 minutes as outlined in Section 5.3.1. The participants will then receive investigational product at approximately 0800 hours (plus or minus 2 hours).

For Part 3:

As determined by randomization scheme, dosing will occur either with or without breakfast.

For fed assignment, following an overnight fast of at least 10 hours, participants will receive high fat/high caloric breakfast approximately 30 minutes prior to dosing which is to be completed within approximately 20 minutes as outlined in Section 5.3.1. The participants will then receive investigational product at approximately 0800 hours (plus or minus 2 hours).

For fasted assignment, following an overnight fast of at least 10 hours, participants will receive investigational product at approximately 0800 hours (plus or minus 2 hours) without breakfast.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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. 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.

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

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

6.2.1. Preparation and Dispensing

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

PF-07059013 and placebo oral dosing suspensions 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. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

See the EDR for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

PF-07059013 and placebo will be prepared by qualified unblinded site personnel according to the EDR. Blinded study intervention will be administered in a blinded fashion to the participant.

Tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements. Polymer solution, if needed for the tablets administration, will be prepared by qualified site personnel according to the EDR.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

Participants will be randomly assigned to receive study intervention from a central randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all study intervention according to the randomization schedule and assigned treatment for the individual participant.

Blinding procedures do not apply to Part 1 Period 4 and Part 3 of this study because it will be conducted as open-label. Where the design is open-label, 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.

6.3.2. Breaking the Blind (Part 1 Period 1 to 3 and Part 2 only)

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a

secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

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 electronic CRF. The study treatment assignment 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. 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. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

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

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07059013; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

The decision to proceed to the next dose level of PF-07059013 (either an increase, decrease or repeat of previous dose level) will be made by the study team and the investigator based on safety, tolerability, and preliminary PK data obtained in at least 6 participants (at least 5 out of 6 actively treated participants and at least 1 placebo-treated participant) dosed at the prior dose level.

The dosing schedule may also be adjusted to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities (as described in Appendix 8: Criteria for Vital Signs Abnormality), in the same organ class, indicating dose-limiting intolerance.

- If post-treatment p50 values in 2 or more of the participants receiving active drug at a given dose level (but not participants receiving placebo), drops below 20 mmHg, in association with one or more of the following, in any of the respective participants:
  - Treatment emergent increase in EPO above the upper limit of reference range (Part 2 only).
  - Treatment emergent increase from baseline in absolute reticulocyte count, with magnitude of increase ≥250,000 /uL (Part 2 only).
  - Treatment emergent increase in lactate to above upper limit of normal.
- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.
- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.
- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.
- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits: unbound plasma C_{max} = 1.5 µg/mL or unbound plasma AUC_{24} = 22.5 µg•hr/mL.
- If, based on the observed data, the group mean of unbound plasma C_{max} or AUC of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

For Part 1, each dose escalation will be based on review of lactate and p50 data up to at least 8 hour post dose and all other safety data up to a minimum of 72-hours post dose plus PK assessments up to 24-hours post dose, in at least 5 out of 6 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level.

For Part 2, each dose escalation will be based on review of EPO and lactate data up to at least Day 7, reticulocyte and p50 data up to at least Day 14, and all other safety data up to Day 15 plus PK assessments up to Day 8, in at least 5 out of 6 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: withdrawal of consent by the participant, SAE or clinically significant finding that impacts safety of participant per PI judgement, death, protocol deviation impacting study data or integrity, study terminated by study sponsor.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated at the early termination/discontinuation visit. See the Schedule of Activities for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

ECG Changes

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

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/treatment arm 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 follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the 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.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the 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.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants 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, CCI [redacted] 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 529 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

Not applicable.

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. May be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.

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.

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.

The procedure for collecting postural or orthostatic data will be:

- Assess BP after the participant is in the supine position for a minimum of 5 minutes;
- Have the participant stand up for 2 minutes;
- Assess BP after the participant is in the standing position for approximately 2 minutes.

Orthostatic hypotension is defined as a decrease of ≥20 mm Hg for systolic BP or ≥10 mm Hg for diastolic BP 2 minutes after standing from a supine position. Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of orthostatic hypotension are those that develop upon assuming the erect posture from a supine position and may include: lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and/or neck ache.

If a participant has symptoms suggestive of orthostasis, but not documented orthostatic hypotension, repeated measurements of supine/standing BP should be obtained. Lesser degrees of BP reduction may still be considered clinically significant if the participant becomes symptomatic upon standing, especially in the presence of a significant increase in pulse rate (≥30 beats per minute [bpm]).

8.2.2.1. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying

by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

8.2.2.2. Temperature

Temperature will be measured orally. No eating, drinking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Standard 12-Lead ECGs 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. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period will serve as each participant's baseline QTc value.

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) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criterion 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 QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7: ECG Findings of Potential Clinical Concern.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically

significant event will be recorded in the CRF/DCT. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

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 7 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.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact. Specific for the study intervention in this study, skin contact is not applicable and exposure by inhalation refers to inhalation of the bulk powder.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception. Specific for the study intervention in this study, skin contact is not applicable and exposure by inhalation refers to inhalation of the bulk powder.

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 participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact. Specific for the study intervention in this study, skin contact is not applicable and exposure by inhalation refers to inhalation of the bulk powder.

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-07059013 greater than 4200 mg within a 24-hour time period will be considered an overdose. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07059013 (whichever is longer)
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 9 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

8.5. Pharmacokinetics

8.5.1. Blood and Plasma for Analysis of PF-07059013

Blood samples of approximately 2 mL will be collected for measurement of whole blood concentrations of PF-07059013 as specified in the SoA. 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.

Blood samples of approximately 4 mL, to provide an approximate of 1.5 mL of plasma, will be collected for measurement of plasma concentrations of PF-07059013 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT). 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 will be used to evaluate the PK of PF-07059013. Samples collected for analyses of PF-07059013 plasma and blood concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, CCI evaluation of the bioanalytical method, CCI [redacted] Details for collection and handling of the samples for this cohort will be provided in the laboratory manual or by the sponsor, and the CRU will be informed prior to dosing.

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

Samples collected for measurement of plasma and whole blood concentrations of PF-07059013 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

CCI [redacted]

CCI [redacted]

8.5.3. Urine for Analysis of PF-07059013 – Part 2, Only

Urine will be collected at times defined in the Schedule of Activities Table C (Part 2).

- ***Prior to dosing on Day 1***, each participant must complete a forced void with an **aliquot** from this urine ("urine blank") labeled and stored frozen for measurement of drug concentrations, per detailed instructions offered in a laboratory manual prior to the start of the study.

- ***Prior to dosing on Day 14***, each participant must complete a forced void with an **aliquot** used to conduct urinalysis and microscopy, if needed; with remaining urine discarded.

- ***Following dosing on Day 14***, each void post dose will be collected, saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval

(ie, 24 H). At the end of the dosing interval (ie, Day 15, 0 H [hour]), participants must complete a forced void with this complete void included as part of the interval collection.

The total volume will be measured and recorded. CCI [redacted] Details regarding the collection, processing, storage and shipping of the urine samples will be provided in the lab manual, prior to the start of the study.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. CCI [redacted]

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

As part of understanding the PK of the investigational product, urine samples may be used for evaluation of the bioanalytical method, CCI [redacted] for drug transporters and/or drug metabolizing enzymes. CCI [redacted]

8.6. Pharmacodynamics

Blood samples of approximately 3 mL, will be collected for measurement of p20 and p50 at times specified in the Schedule of Activities.

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 data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT).

CCI [redacted]
These data will not be included in the clinical study report (CSR).

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

8.7. Genetics

8.7.1. Specified Genetics

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

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

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 formal statistical hypothesis testing will be performed in this study.

9.2. Sample Size Determination

No formal sample size calculation was performed. Cohort size has been chosen to ensure appropriate sample size to provide adequate safety, toleration and PK information at each dose level and to provide a placebo comparison group, while minimizing exposure to humans of a new biologic entity. Participants who discontinue during the trial may be replaced at the discretion of the sponsor and investigator.

- **Part 1 and 2:** A sample size of up to approximately 42 participants (58 including optional cohorts) was chosen based on the need to minimize exposure of humans to PF-07059013 and the requirement to provide adequate safety, tolerability, and PK information at each dose level.

- **Part 3:** A sample size of up to approximately 8 participants was selected for the exploration of PK differences of different formulations and food effect. The sample size for Part 3 may be altered (up to 12 participants) depending on PK variability data from Part 1 of this study.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. 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. All enrolled participants randomly assigned to investigational product regardless of whether or not the investigational product was administered.

Participant Analysis Set	Description
PK Population	The PK concentration population will be defined as all randomized participants who received at least 1 dose of PF-07059103 and in whom at least 1 plasma and blood concentration value is reported. The PK parameter analysis population will be defined as all randomized participants who received at least 1 dose of PF-07059103 and who have at least 1 of the PK parameters of interest calculated.
PD Population	The PD analysis population is defined as all randomized participants who received at least one dose and have at least one PD assessment in at least one cohort.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

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

9.4.1. Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.4.1.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time. Baseline will be average of triplicate measurement at pre-dose on Day 1.

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

Safety QTcF Assessment

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

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship may be examined.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Derivation of Pharmacokinetic Parameters

PK parameters to be derived (if data permit) from the concentration-time data using standard noncompartmental methods following single and multiple dose administrations are defined in Table 3 and Table 4, respectively. CCI [redacted]

Table 3. Plasma and Blood PK Parameters Definitions for Part 1 (Single Ascending Dose) and Part 3

Parameter	Definition	Method of Determination
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
C_{max}	Maximum plasma concentration.	Observed directly from data
T_{max}	Time for $C_{max.}$	Observed directly from data as time of first occurrence.
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
C	[redacted]	[redacted]
C	[redacted]	[redacted]

Table 4. Plasma and Blood PK Parameters for Part 2 (Multiple Ascending Doses)

Parameter	Day	Definition	Method of Determination
AUC_{τ}	1, 7, 14	Area under the plasma concentration-time profile from time zero to time τ (tau), the dosing interval.	Linear/Log trapezoidal method.
C_{max}	1, 7, 14	Maximum plasma concentration during the dosing interval.	Observed directly from data.
T_{max}	1, 7, 14	Time for $C_{max.}$	Observed directly from data as time of first occurrence.
CCI			
CCI			
CCI			
CCI			
CCI			
CCI			
CCI			
CCI			

Actual PK sampling times will be used in derivation of PK parameters.

CCI			
CCI			
CCI			
CCI			

9.4.2.2. Statistical Methods for PK Data

No formal inferential statistics will be applied to the PK data from Part 1 and 2.

Part 1 and Part 2

The PK parameters listed in Table 3 and Table 4 will be summarized descriptively by dose, treatment group (where applicable) and day (for Part 2). The blood and plasma concentration of PF-07059013 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual participant, as well as mean and median profiles of the blood and plasma concentration-time data will be plotted by treatment group using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and log scales.

Dose normalized (to 1 mg) AUC and C_{max} of PF-07059013 will be plotted against dose (using a logarithmic scale) for single- and multiple dose phases, and will include individual participant values as well as the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

Urine amounts of PF-07059013 CCI will be listed and summarized descriptively, if data permits.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

Food Effect and Formulation Evaluation

The pharmacokinetic parameters CCI C_{max}, and T_{max} for PF-07059013 will be summarized descriptively by treatment group. For CCI C_{max}, individual participant parameters will be plotted by treatment group. Blood and plasma concentrations will be summarized descriptively by treatment group, fed versus fasted condition, and PK sampling time. Individual participant, as well as mean and median profiles of concentration-time data will be plotted by treatment group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and log scales.

The statistical comparison of PF-07059013 PK parameters following high-fat/high-caloric meal (Test) versus overnight fast (Reference), moderate particle size (Test) versus small particle size (Reference) suspension administered under fasted condition, and tablet formulation (Test) versus small particle size suspension formulation (Reference) administered under fasted condition will be detailed in the SAP. The analyses will include reporting the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios for C_{max}, CCI as data permit.

9.4.3. Pharmacodynamic Analyses

Absolute and change from baseline measurements of the PD endpoints (p20 and p50) will be listed and summarized descriptively by study part, dose, treatment group (where applicable) and sampling time. Further details will be provided in the SAP.

CCI [redacted]

CCI [redacted]

9.5. Interim Analyses

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

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

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

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

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

signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in source document locator.

Description of the use of computerized system is documented in source document locator.

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication

pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[c]	Lactate Ferritin C reactive protein Urine drug screening[a] Urine cotinine test (Part 1 and 2 only) EPO (Part 2 only) Reticulocytes (Abs and %) (Part 2 only) At screening only: • Serum FSH[b] • Hepatitis B surface antigen • Hepatitis B suface antibody • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus • PT/INR • aPTT

Abbreviations: Abs = absolute; aPTT = activated partial thromboplastin time; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide (bicarbonate); EPO = erythropoietin; FSH = follicle-stimulating hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT/INR = prothrombin time/international normalized ratio; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. At Screening and Admission (Day -1) for each inpatient stay, the minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

b. For confirmation of postmenopausal status only.

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

d. Unless needed for screening, review is not required prior to dosing; accumulative data will be reviewed as they become available. Refer to Section 6.6.1 for data needed for review prior to dose escalation, where applicable.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

Any remaining serum 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. CCI [redacted] These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

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

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

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

10.3.2. Definition of SAE

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

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

Assessment of Intensity

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

GRADE	Clinical Description of Severity
1	MILD adverse event

2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

- Common Terminology Criteria for Adverse Events (CTCAE) Version v5 will be utilized for grading, and Grade 1 will be recorded as mild, Grade 2 as moderate, and Grade 3 and above as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.4.3).

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to 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.

2. Postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - 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.
5. Vasectomized partner.
   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation.
    - Oral;
    - Injectable.
3. 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).

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- CCI [redacted]
- [redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events
• 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 May Qualify as Serious Adverse Events

• 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 Serious Adverse Events

- 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: Criteria for Vital Signs Abnormality

Pulse Rate	Supine: <40 or >120 bpm Standing: <40 or >140 bpm
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture
	Systolic <90 mm Hg
	Diastolic ≥20 mm Hg change from baseline in same posture
	Diastolic <50 mm Hg

Assessment should be based on at least 2 consecutive measurements. Repeat measurements should be taken within 15 minutes if values fall outside the normal range.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
→	ongoing/continuous event
Abs	absolute
ADE	adverse device effect
AE	adverse event
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
AESI	adverse events of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from time zero to 24 hours
AUC_{τ}	area under the plasma concentration-time profile from time zero to time τ (tau), the dosing interval
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
C_{last}	last quantifiable concentration
CCI [redacted]	[redacted]

Abbreviation	Term
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CT SAE	clinical trial serious adverse event
CV	cardiovascular
CYP	Cytochrome P450
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EMA	European Medicines Agency
EPO	erythropoietin
E/T	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FIH	First in Human
FSH	follicle-stimulating hormone
F/U	follow-up
fu_p	fraction unbound in plasma
f_m	fraction metabolized
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Glu	glutamic acid
Hb	hemoglobin
HbA	hemoglobin A
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HbS	hemoglobin S

Abbreviation	Term
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous
IWR	interactive Web-based response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LFT	liver function test
MABEL	minimal anticipated biological effect level
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
msec	millisecond
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NOAEL	no-observed-adverse-effect level
NOEL	no observed effect level
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
p20	oxygen pressure at which 20% of the hemoglobin in a given blood sample is oxygenated
p50	oxygen pressure at which 50% of the hemoglobin in a given blood sample is oxygenated
PBMC1	peripheral blood mononuclear cells
PBPK	physiologically-based pharmacokinetic
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)

Abbreviation	Term
PGx	pharmacogenomic(s)
PI	principal investigator
PIB	powder in bottle
PK	pharmacokinetic(s)
PT	prothrombin time
PT/INR	prothrombin time/internationalized normalized ratio
CCI	[redacted]
PVC	premature ventricular contraction/complex
QD	once daily
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QT	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
CCI	[redacted]
RBC	red blood cell
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SPR	Surface Plasmon Resonance
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
sVCAM	soluble Vascular Cell Adhesion Molecule
CCI	[redacted]
TBili	total bilirubin
TDI	time dependent inhibition
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
UGT	uridine diphosphate glycosyltransferase
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
Val	valine
VOC	vaso-occlusive crisis
V_{ss}	volume of distribution

Abbreviation	Term
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. The Lancet. 2010 Dec 11; 376(9757): 2018-31.

2. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 2007; 21(1): 37-47.

3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med 2017; 376(16):1561-73.

4. Hofrichter J, Ross PD, Eaton WA. Kinetics and mechanism of deoxyhemoglobin S gelation: a new approach to understanding sickle cell disease. Proceedings of the National Academy of Sciences. 1974 Dec 1;71(12):4864-8.

5. Sunshine HR, Hofrichter J, Eaton WA. Requirement for therapeutic inhibition of sickle haemoglobin gelation. Nature 1978; 275:238-40.

6. Ferrone FA, Hofrichter J, Eaton WA. Kinetics of sickle hemoglobin polymerization. II. A double nucleation mechanism. J Mol Biol 1985; 183(4):611-31.

7. Arya R, Rolan PE, Wootton R, et al. Tucaresol increases oxygen affinity and reduces haemolysis in subjects with sickle cell anaemia. Br J Haematol 1996; 93(4):817-21.

8. Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood 2019; 133(17):1865-75.

9. Deiderich DA, Trueworthy RC, Gill P, Cader AM, Larsen WE. Hematologic and clinical responses in patients with sickle cell anemia after chronic extracorporeal red cell carbamylation. The Journal of clinical investigation. 1976 Sep 1;58(3):642-53.

10. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. Am J Hematol 2012; 87(8):795-803.

11. Antwi-Boasiako C, Frimpong E, Ababio GK, et al. Sickle cell disease: reappraisal of the role of foetal haemoglobin levels in the frequency of vaso-occlusive crisis. Ghana Med J 2015; 49(2):102-6.

12. Paszty C, Brion CM, Manci E, Witkowska HE, Stevens ME, Mohandas N, Rubin EM. Transgenic knockout mice with exclusively human sickle hemoglobin and sickle cell disease. Science. 1997 Oct 31;278(5339):876-8.

13. Ryan TM, Ciavatta DJ, Townes TM. Knockout-transgenic mouse model of sickle cell disease. Science. 1997 Oct 31;278(5339):873-6.

14. Estepp, J.H., et al., A clinically meaningful fetal hemoglobin threshold for children with sickle cell anemia during hydroxyurea therapy. Am J Hematol, 2017. 92(12): p. 1333-1339.

15. Vichinsky, E., et al., A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med, 2019. 381(6): p. 509-519.

16. Hutchaleelaha A, Patel M, Washington C, Siu V, Allen E, Oksenberg D, Gretler DD, Mant T, Lehrer-Graiwer J. Pharmacokinetics and pharmacodynamics of voxelotor (GBT440) in healthy adults and patients with sickle cell disease. Br J Clin Pharmacol. 2019 Jun; 85(6): 1290-1302.

17. Rolan PE, Mercer AJ, Wootton R, Posner J. Pharmacokinetics and pharmacodynamics of tucaresol, an antisickling agent, in healthy volunteers. British journal of clinical pharmacology, 1995 Apr; 39(4): 375-380.