Title Page

A PHASE 1 / 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ESCALATING DOSES OF PF-07868489 IN HEALTHY ADULT PARTICIPANTS AND, ADDITIONALLY, CLINICAL ACTIVITY OF REPEAT DOSES IN PARTICIPANTS WITH PULMONARY ARTERIAL HYPERTENSION

Study Intervention Number:	PF-07868489
Study Intervention Name:	NA
US IND Number:	164291
EudraCT/EU CT Number:	2024-514064-17-00
ClinicalTrials.gov ID:	NCT06137742
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5001001
Phase:	1/2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Learn How the Study Medicine Called PF-07868489 is Tolerated and Acts in Healthy Adult People and People With Pulmonary Arterial Hypertension

Document History

Document	Version Date
Amendment 1	23 September 2024
Original protocol	06 October 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (23 September 2024)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate country-specific language, update the dose for Part B, update eligibility criteria, update endpoints, incorporate PACL updates and other clarifications.

Description of Change	Brief Rationale.	Section # and Name
Substantial Modification(s)		
Update protocol title and phase	Updated to align with study design of Part B	Title page, 1.1 Synopsis, 2.1. Study Rationale, 4.1 Overall Design
Updates to Part B Inclusion criterion 7,8 & 9; Exclusion criterion 18 (previously 19) and Concomitant medications	Updated to refine the patient population and align the allowable background therapies with current SOC	1.1.3 Synopsis, 1.1.4 Synopsis, 5.3 Study Population, 5.4 Study Population, 6.9.3. Prohibited During the Study – Part B, 6.9.4. Prohibited Prior Treatments-Part B, 6.9.5. Permitted PAH Therapies During the Study-Part B, 6.9.6 Other Permitted Therapies During the Study-Part B
Updates to Part B Inclusion criteria 4, 5; Exclusion criteria 1,2,5,15 (previously 16), 19 (previously 20) & 22	Clarification	1.1.3 Synopsis, 1.1.4 Synopsis, 5.3 Study Population, 5.4 Study Population
Removed Part B Exclusion criterion 14	Removed since was not applicable for Part B.	1.1.4 Synopsis, 5.4 Study Population

Description of Change	Brief Rationale.	Section # and Name
Added Part B Exclusion criterion 21	Added to ensure participants were not taking substances that could potentially have an impact on efficacy and safety.	1.1.4 Synopsis, 5.4 Study Population
Updated Objectives, Endpoints and Estimands: • NT-proBNP endpoint updated from Secondary to Primary • All efficacy estimands changed from Principal Strata to Hypothetical • Separated Part A and Part B Objectives • Updates to Ethical Considerations	• Updated to align with the expectations of a phase 2 study with a PD endpoint as primary. • Updated to incorporate a change in how missing data will be handled. • Clarification • Clarification	1.1 Synopsis, 3. Objectives, Endpoints and Estimands, 9.1.3. Estimands, 9.1.3.1. Primary Estimand/Coprimary Estimands, 9.1.3.2. Secondary Estimands, 9.3.2.2. Change in NT-proBNP, 9.3.2.2.1. Main Analysis, 9.3.3.1. Change in PVR, 9.3.3.1.1. Main Analysis
Addition of number of participants that may be replaced in Part B	Update based upon consideration of participant withdraw	1.1 Synopsis, 4.1.2. Part B: Participants with PAH
Update Part B study treatment dose	Update based upon evaluation of Part A PK data.	1.2 Schema, 4.2.2. Part B: Participants with PAH, 4.3.2. Dose Justification for Parts A and B
Addition of dose modification for Part B	Update based upon consideration of volume of injections.	6.6. Dose Modification
Update Part B Follow-up Timeframe	Update based upon evaluation of follow-up period timeframe being 5 half-lives post last dose.	1.4.1.2. Table 4: Schedule of Activities Part B Participants with PAH-Follow-up
Addition of Borg CR10 scale®	Incorporate measurement of dyspnea and fatigue	1.4.1.1. Table 3: Schedule of Activities Part B Participants with PAH Treatment period,

Description of Change	Brief Rationale.	Section # and Name
	before and after the 6MWT	1.4.1.2. Table 4: Schedule of Activities Part B Participants with PAH-Follow-up, 8.2.2. 6-Minute Walk Test, 8.2.4.6 Borg CR10 scale®
Added use of oxygen at additional time points	Alignment with 6MWT	1.4.1. Schedule of Activities Part B Participants with PAH
Updated PRO descriptions and timepoints	Alignment and clarification across assessments and endpoints	1.4.1.1. Table 3: Schedule of Activities Part B Participants with PAH Treatment period, 1.4.1.2. Table 4: Schedule of Activities Part B Participants with PAH-Follow-up, Section 8.2.4.3 PAH-SYMPACT, 8.2.4.5. PGI-C
Added Country-specific appendices	Incorporate country-specific language based upon country footprint	10.9 Appendix 9 Country-Specific Requirements
Non-Substantial Modification(s)		
Added US IND number, EudraCT number and ClinicalTrials.gov ID	Information available for amendment	Title page and 1.1 Synopsis
Updated synopsis to make more concise	Alignment with EU CTR requirement.	1.1 Synopsis
Updated schema	Clarification and consistency in participant numbers.	1.2 Schema
Removed description of the type of blood samples collected for biomarkers	Alignment with the sample collection matrix.	1.4.1. Schedule of Activities Part B Participants with PAH, 8.7. Biomarkers
Separated descriptions of study arms, administration, preparation and dispensing, blinding and continued access for Part A and Part B	Modification	1.1 Synopsis, 6.1 Study Intervention(s) Administered, 6.1.1. Administration, 6.2.1. Preparation and Dispensing, 6.4. Blinding, 6.4.2. Blinding of Site Personnel, 6.4.3. Blinding of the Sponsor, 6.7. Continued Access to Study Intervention After the End of the Study

Description of Change	Brief Rationale.	Section # and Name
Removed telephone contact	Modification	1.4.1.1. Table 3: Schedule of Activities Part B Participants with PAH Treatment period
Updated Synopsis to include language describing emerging Part A data to inform Part B	Alignment of language across sections.	1.1 Synopsis, 4.1.2. Part B: Participants with PAH
Updated Nonclinical and Clinical information	Alignment with nonclinical toxicology studies and ongoing Part A clinical data.	2.2.2. Nonclinical Pharmacokinetics and Metabolism, 2.2.3. Nonclinical Safety, 2.2.4. Clinical Overview, 2.3. Benefit/Risk Assessment
Updated risk assessment text	Modification	2.3.1. Risk Assessment
Removed paragraph related to initiation of optional Japanese and Chinese cohorts	Removed since Part A dose escalation is complete.	4.1.1. Part A: Single ascending doses in healthy participants
Updated blood volume	Alignment with lab manual.	8.1 Administrative and Baseline Procedures
Added Spirometry Section	Alignment with SoA and clarification of procedure	8.1.1. Spirometry
Potential addition of central read of available RHC data	To help improve accuracy and consistency of pulmonary hemodynamic data.	8.2.1. Pulmonary Vascular Resistance by Right Heart Catheterization
Updated WHO Functional Class Assessments text into a table format	Modification	8.2.3. WHO Functional Class Assessments
Potential addition of Steering Committee	To provide external scientific oversight and assistance with logistics.	10.1.5.2. Steering Committee
Added EU CTR protocol requirements	Alignment with EU CTR requirements.	10.1.6 Dissemination of Clinical Study Data, 10.9.1 European Union

Description of Change	Brief Rationale.	Section # and Name
Editorial clarifications	Protocol Administrative Change Letter dated 11 Dec 2023	1.1 Synopsis Exclusion Criteria Part A, # 10 and Section 5.2 Exclusion Criteria Part A, #9, 1.1 Synopsis Exclusion Criteria Part A, # 11 and 5.2 Exclusion Criteria Part A, # 10, 10.2 Appendix 2 Clinical Laboratory Tests, footnote c, 5.5.3 Caffeine, Alcohol and Tobacco (Part A only) and 8.3.2 Vital Signs
Modified contact details for a medically qualified individual and removed as an abbreviation.	Protocol Administrative Change Letter dated 01 Feb 2024	10.1.12 Sponsor's Medically Qualified Individual and 10.10 Appendix 10: Abbreviations
Text updates and clarifications	Minor clarifications and editorial/typographical changes provided to correct typos and improve readability.	4.3.2. Dose Justification for Parts A and B, 5.6. Screen Failures, 6.4.4 Sensitive Clinical Data, 6.4.5. Breaking the Blind, 7.1. Discontinuation of Study Intervention, 9.2 Analysis Sets, 9.3.1.1. Analyses for Longitudinal Continuous Endpoints, 9.5 Sample Size Determination, 10.10. Appendix 10: Abbreviations, and 11. REFERENCES

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1/2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Escalating Doses of PF-07868489 in Healthy Adult Participants And, Additionally, Clinical Activity of Repeat Doses in Participants With Pulmonary Arterial Hypertension

Brief Title: A Study to Learn How the Study Medicine Called PF-07868489 is Tolerated and Acts in Healthy Adult People and People With Pulmonary Arterial Hypertension

Regulatory Agency Identification Number(s):

US IND Number:	164291
EudraCT/EU CT Number:	2024-514064-17-00
ClinicalTrials.gov ID:	NCT06137742
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5001001
Phase:	1/2

Rationale:

This is the first time that PF-07868489 will be given to humans. The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and immunogenicity of single doses of PF-07868489 in healthy adult participants; Part B will evaluate the clinical activity, safety, tolerability, PK, immunogenicity and pharmacodynamics (PD) of repeat doses of PF-07868489 in patients with pulmonary arterial hypertension (PAH).

Objectives, Endpoints, and Estimands:

Part A

Objectives	Endpoints	Estimands
Primary:	**Primary:**	
• To evaluate the safety and tolerability of escalating single SC injections of PF-07868489 in healthy adult participants.	• Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs) • Change from baseline in vital signs. • Change from baseline in clinical laboratory values. • Change from baseline in electrocardiogram (ECG) parameters (heart rate, corrected QT interval (QT), QTc corrected using	• NA

Objectives	Endpoints	Estimands
	Fridericia's formula (QTcF), pulse rate (PR), and QRS intervals).	
Secondary:	**Secondary:**	
• To characterize serum exposure of escalating single SC injections of PF-07868489 in healthy adult participants.	• After single dose: PF-07868489 PK parameters as data permit: (Area under the curve) AUC_{last}, AUC_{inf}, maximum observed concentration (C_{max}), time to reach C_{max} (T_{max}), terminal elimination half-life ($t_{1/2}$)	• NA
• To evaluate the immunogenicity profile of PF-07868489 following single dose administration in healthy adult participants.	• Incidence of the development of antidrug antibodies (ADA) against PF-07868489 following single dose.	• NA

Part B

Objectives	Endpoints	Estimands
Primary:	**Primary:**	
• To evaluate the safety and tolerability of repeat SC doses of PF-07868489 in participants with PAH.	• Incidence and severity of AE and SAEs. • Change from baseline in vital signs. • Change from baseline in clinical laboratory values. • Change from baseline in ECG parameters (heart rate, QT, QTcF, PR, and QRS intervals).	• NA
• To characterize change in blood concentration of NT-proBNP following repeat SC dose administration of PF-07868489 in participants with PAH.	• Change from baseline at Week 24 of NT-proBNP	• E1: The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in NT-proBNP in PAH patients. This analysis will exclude data after use of rescue medications and after study treatment discontinuation.
Secondary:	**Secondary:**	
• To characterize serum exposure following repeat SC doses of PF-07868489 in participants with PAH.	• PF-07868489 PK parameters after repeat doses; as data permit: C_{min}, and $t_{1/2}$	• NA
• To evaluate the immunogenicity profile of PF-07868489 following repeat SC doses in participants with PAH.	• Incidence of the development of ADA against PF-07868489 following repeat doses.	• NA
• To evaluate the effects of repeated PF-07868489 dosing on 6MWD and PVR in participants with PAH	• Change from baseline at 24 Week on (6-minute walk distance) 6MWD • Change from baseline at 24 Week on Pulmonary Vascular Resistance (PVR)	• E2: The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in PVR at Week 24 in PAH patients. This analysis will exclude data after use of rescue medications and after study treatment discontinuation

Overall Design:

This is a Phase 1/ 2, randomized, double-blind, placebo-controlled study conducted in 2 sequential parts. Part A is designed to evaluate the safety, tolerability, PK, and

immunogenicity of single escalating doses of PF-07868489 in healthy adult participants. Part B is designed to evaluate the clinical activity, safety, tolerability, PK, immunogenicity, and PD of repeat doses of PF-07868489 in participants with PAH.

Part A

Part A is an investigator- and participant-blind, sponsor-open, placebo-controlled, single ascending dose study of PF-07868489 administered subcutaneously (SC) in healthy adult participants. There are 8 planned cohorts, including optional cohorts of healthy adult Japanese, and Chinese participants. The inclusion of these optional cohorts is to enable the recruitment of Japanese and Chinese patients into future clinical trials and will depend on the operational feasibility of recruiting the relevant populations. These cohorts, if conducted, will be done at a dose that is determined to be safe and well-tolerated in Western participants. Up to approximately 54 participants will be enrolled into Part A of this study and randomly assigned to receive PF-07868489 or placebo.

Based on emerging data from Part A of the study, the dose, dosing frequency, and the follow-up schedule in Part B may be modified to characterize better the safety, PK, and efficacy profile of the molecule.

Part B

Part B is a 24-week, randomized, double-blind, placebo-controlled study design in participant with PAH.

Approximately 36 participants with PAH who meet all eligibility criteria at Screening and Baseline, will be randomized in a 1:1 ratio to receive study intervention (PF-07868489 or placebo) SC every 4 weeks. Beginning on Day 1, participants will receive of a total of 6 doses administered every 4 weeks (Q4W) SC (through Week 20). Following Day 1, there will be a visit at Week 1 (Day 8) for initial safety monitoring followed by visits at Week 4 and Q4W thereafter. The active treatment period is defined as extending from Day 1 through the Week 24/EOT visit.

Participants who complete the active treatment period of study C5001001 may be offered the opportunity to enroll in an OLE study. All participants in the OLE study will receive active study intervention (details of the OLE study will be provided in a separate protocol).

Participants who discontinue study intervention prematurely will complete the Week 24 / EOT visit 4 weeks after termination of study intervention. Alternatively, in discussion with the PI and with Sponsor agreement, a participant who has completed at least through Week 12, may have the option to enter the OLE.

If participants do not elect to enter the aforementioned optional OLE study, the last dose of study intervention will be at Week 20. Participants who do not elect to enroll in the OLE study will enter a 12-week Follow-Up Period beginning after completion of the Week 24 visit, after which they will be discharged from the study (EOS visit for these participants being Week 36).

Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

If a participant withdraws from the study prior to completion of the Week 24 visit for a reason unrelated to efficacy or due a non-treatment-related AE (as determined by the investigator and sponsor) that meets individual participant study intervention stopping criteria, additional participants may be randomized at the discretion of the sponsor to ensure there are sufficient data for analysis.

An independent oversight committee in the form of an internal review committee (IRC) will monitor unblinded safety and tolerability data of PF-07868489 in the participants in Part B of the study on an ongoing, regularly scheduled basis.

Number of Participants:

In Part A, approximately 54 healthy adult participants will be enrolled in the study, with 4 participants (2 active: 2 placebo) in Cohort 1, 6 participants per cohort (4 active: 2 placebo) for Cohorts 2 and 3 and 8 participants per cohort (6 active: 2 placebo) for Cohorts 4 – 6. 5 participants (4 active: 1 placebo) will be recruited per cohort for Optional Cohorts 7 and 8.

In Part B, approximately 36 adult participants with PAH will be enrolled in the study and randomly assigned to receive PF-07868489 or placebo. Up to approximately 10 % of participants who are discontinued may be replaced.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion / Exclusion Criteria

Participants must meet the following key inclusion criteria and none of the exclusion criteria to be eligible for enrollment into the study:

1.1.1. Inclusion Criteria: Part A-Single Ascending Doses in Healthy Participants

Participants must meet the following key inclusion criteria to be eligible for enrollment into Part A of the study:

1. Male and female participants must be 18 to 65 years of age, inclusive, at the time of screening who are overtly healthy as determined by medical evaluation including medical history, physical examination (PE), vital sign assessments and laboratory tests and 12-lead electrocardiogram or electrocardiography (ECGs).

2. Body mass index (BMI) of 16 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

1.1.2. Exclusion Criteria: Part A-Single Ascending Doses in Healthy Participants

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

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. Evidence of active, latent, or inadequately treated infection with Mycobacterium TB. Participants with any acute or chronic infections or infection history.

3. Have undergone significant trauma or major surgery within 30 days prior to the first dose of study drug.

4. Any 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.

5. Participants who smoke more than 10 cigarettes (or equivalent) per day or have a smoking history ≥10 pack-years.

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

7. Current use of any prohibited concomitant medication(s).

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

9. A positive urine drug test.

10. Screening sitting or semi-recumbent blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of rest.

11. Renal impairment as defined by an estimated glomerular filtration rate (eGFR) in adults with < 75 mL/min/1.73 m^2.

12. Standard 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc corrected using Fridericia's formula [QTcF] >450 ms, complete left bundle branch block [LBBB], signs of an acute or indeterminate age myocardial infarction, STT interval changes suggestive of myocardial ischemia, second or third degree AV block, or serious bradyarrhythmias or tachyarrhythmias).

13. 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

    - ALT or AST level ≥ 1.05 x ULN
    - T bili level ≥ 1.05 x ULN
    - Albuminuria as defined by urine albumin/creatinine ratio (UACR) >30 mg/g

1.1.3. Inclusion Criteria: Part B-Participants with PAH

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

1. Participants aged ≥18 years (or the minimum age of consent in accordance with local regulations) at screening who have signed informed consent.
2. Documented diagnostic RHC prior to Screening confirming diagnosis of PAH (WHO Group 1 PH) including any of the following subtypes:
    - Idiopathic or heritable PAH.
    - Drug- or toxin-induced PAH.
    - PAH associated with connective tissue disease.
    - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair.
3. PAH classified as WHO functional class II or III.
4. Pre-randomization RHC documenting a minimum of PVR ≥ 400 dyn ·sec/cm^5 (5 Wood units); and no contraindication to RHC.
    - RHC performed within 12 weeks of Screening as part of the participants management of PAH can satisfy this criterion, if the requisite hemodynamic data are available. Otherwise, a RHC needs to be performed prior to randomization. In this case, the RHC should only be performed if the potential participant meets <u>all</u> other inclusion / exclusion criteria for eligibility.
5. PFTs (spirometry) performed as part of the diagnostic evaluation of PAH excluding clinically relevant obstructive or restrictive pulmonary physiology (unless the participant is an active smoker of > 10 cigarettes/equivalent per day or a smoking history ≥10 pack-years, in which case, the PFTs should be done within 6 months prior to Screening). A high-resolution chest computed tomography within 1 year of Screening indicating no more than minimum emphysematous or interstitial changes may be used to satisfy this requirement.

6. Documentation in the participant's medical history that CTEPH has been excluded.

7. 6MWD ≥ 150 m and ≤ 500 m repeated at least twice during Screening and top two values within 15% of each other, calculated from the highest value.

8. A stable dose of at least 2 SOC PAH vasodilator class therapies for 60 days prior to Screening.

    a. Titration of IV/SC prostanoids are permitted within 10% of optimal dose in accordance with standard of care.

9. BMI 16 to 35 kg/m^2.

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

1.1.4. Exclusion Criteria: Part B-Participants with PAH

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

1. Any 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.

2. Stopped receiving pulmonary hypertension chronic general supportive therapy (eg, diuretics, oxygen, anticoagulants, digoxin) within 90 days prior to Screening.

3. History of atrial septostomy within 180 days prior to Screening.

4. Pulmonary capillary wedge pressure (PCWP)/Pulmonary Arterial Occlusion Pressure (PAOP) > 15 mmHg on RHC conducted during Screening.

5. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in investigational product.

6. History of clinically significant (as determined by the investigator) non-PAH related cardiac, endocrine, hematologic, hepatic, immune, metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or other disease that may limit participation in the study.

7. Current use of any prohibited concomitant medication(s) or participants unwilling or unable to use a required concomitant medication(s).

8. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer) and not concurrently involved in a clinical trial with another investigational product during the study.

9. Uncontrolled systemic hypertension as evidenced by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg during Screening after a period of rest.

10. Systolic BP < 90 mmHg during Screening or at baseline.

11. ECG with QTcF >490 msec during Screening or Randomization.

12. Any of the following clinical chemistry values during Screening:

    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN (> 5 ULN if solely due to right heart failure) or total bilirubin ≥2 × ULN (For Gilbert's syndrome, direct bilirubin >ULN [or ≥ 2 x ULN if solely due to right heart failure] is exclusionary)

    - eGFR < 30 mL/min/1.73 m^2 within 30 days prior to randomization or required renal replacement therapy within 90 days of randomization.

13. Hematologic abnormalities defined as:

    - Platelets ≤ 50,000/mm^3

14. Participants with a diagnosis of COPD or other clinically significant lung disease.

Study Arms and Duration:

PF-07868489 and placebo sterile vials will be centrally sourced by Pfizer. Each vial will be labeled as required per country requirement.

Study Intervention(s)		
Intervention Name	PF-07868489	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	PF-07868489 (anti-BMP9) Solution for Injection, 100 mg/mL (Single Use Vial)	Placebo Solution for Injection (Single Use Only)
Unit Dose Strength(s)	100 mg/vial	Placebo
Route of Administration	SC	SC
Sourcing	Provided Centrally by the Sponsor. Refer to the IPM for more information.	Provided Centrally by the Sponsor. Refer to the IPM for more information.

Study Intervention(s)		
Packaging and Labeling	Study intervention will be provided in 6-ml vials with 1.4 ml fill volume. Each vial will be labeled as required per country requirement.	Study intervention will be provided in 6-ml vials with a 1.4 ml fill volume. Each vial will be labeled as required per country requirement.
SRSD	IB	NA
Current/Former Name(s) or Alias(es)	NA	NA

For Part A, the decision to proceed to the next dose level of PF-07868489 (either an increase or a decrease) will be made by the study team and the investigators based on safety, tolerability, and preliminary PK data obtained at the prior dose level. Provided no safety concerns or AEs suggesting limits of tolerability have been reached in the current or preceding cohorts, dose escalation may proceed if at least 14 days of safety and 7 days of PK data are available. 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.

Current doses are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

Statistical Methods:

Part A

No formal sample size calculations were performed for part A. Cohort size of approximately 4 to 8 participants have been chosen to ensure appropriate sample size to provide adequate safety, tolerability and PK information at each dose level and to provide a placebo comparison group, while minimizing exposure to humans of a new biologic entity.

Part B

Sample size determination for part B is based on the change in N-terminal-pro hormone-B-type natriuretic peptide (NT-proBNP), of PF-07868489 vs. placebo which will be evaluated. An IA may be performed to assess efficacy. IA results may be used for internal business decisions regarding future study planning, stopping for futility, conducting a sample size re-estimation, or to guide decisions regarding the possible crossover of PAH patients from placebo to active treatment.

Details of the objectives, decision criteria, dissemination plan, timing of any IA and method of maintaining the study blind pertaining to the IA (if applicable) as per Pfizer's standard operating procedures (SOPs) will be documented and approved in an IRC charter or separate IA plan.

All analyses will be provided for public disclosure in the European Union (EU) within 1 year after the end of study. All interim analysis results are to be provided for public disclosure in the EU within 1 year of the interim analysis date.

Ethical Considerations:

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

For Part B, given the stage of development of PF-07868489, there are no data attesting to its beneficial effect in patients with PAH. While no clinical benefit from administration of PF-07868489 to participants with PAH in Part B of Study C5001001 can therefore be assumed, inhibition of BMP9 signaling by PF-07868489 may demonstrate clinical activity in this patient population.

Based on the totality of available nonclinical data and taking into account the measures to minimizing risk to study participants, the overall benefit/risk profile supports clinical testing of PF-07868489 in this study as part of the clinical development for PAH.

The use of a placebo-controlled study design is ethically justified given the stage of the development and a need to define the clinical efficacy and safety of PF-07868489. Moreover, study intervention is being administered in addition to current standard of care treatment for PAH.

1.2. Schema

Figure 1: Part A Single Ascending Doses in Healthy Participants

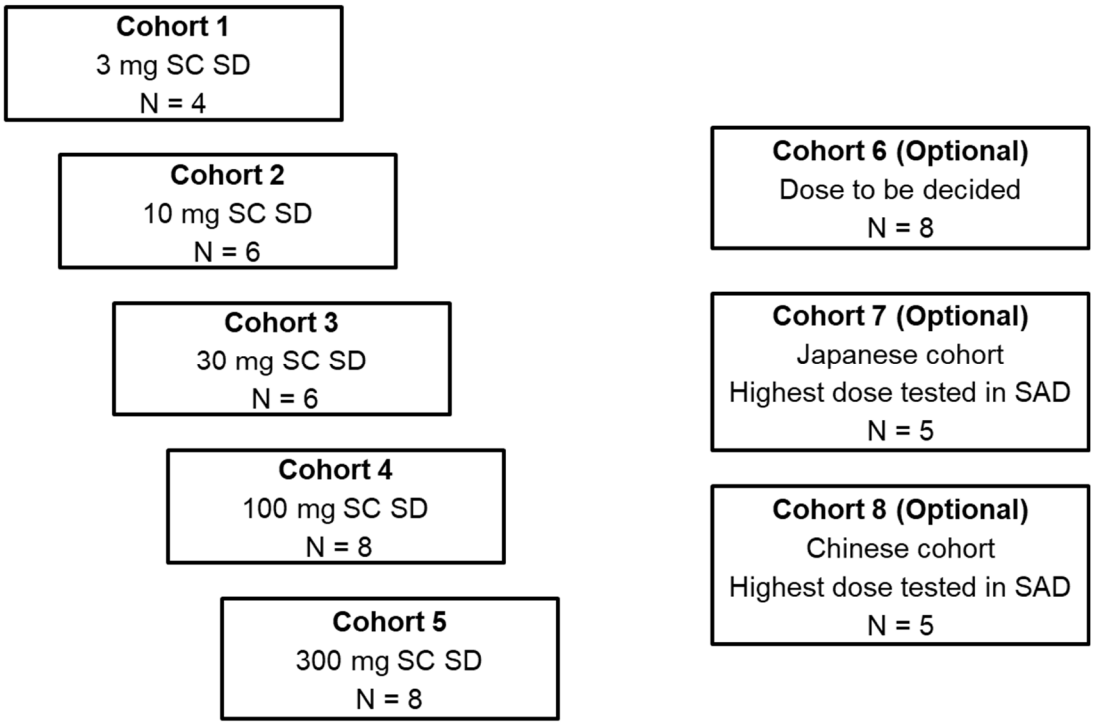
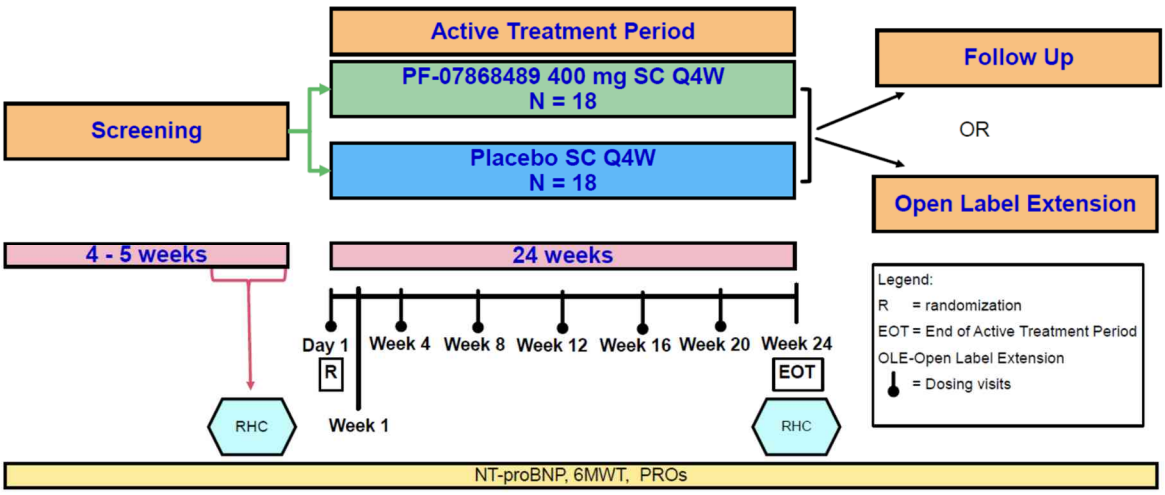


Figure 2: Part B Participants with PAH



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.

1.3.1. Schedule of Activities Part A (Single Ascending Doses in Healthy Participants)

1.3.1.1. Table 1: Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Table 1. Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Treatment Period**										**Notes**
		Clinical Confinement								**Outpatient Visits**		
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**				**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	• Day relative to start of study intervention (Day 1).
Hours After Dose			**-2 h to -5 min**	**0 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	**168 h**	**336 h**	
Visit Window											**±1 days**	**±1 days**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Informed consent	X												• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Review Inclusion/exclusion criteria	X	X											• See Section 5.1 and Section 5.2 for additional information.
Medical history, demography	X	X											

Table 1. Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Treatment Period**										**Notes**
		Clinical Confinement								**Outpatient Visits**		
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**				**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	• Day relative to start of study intervention (Day 1).
Hours After Dose			**-2 h to -5 min**	**0 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	**168 h**	**336 h**	
Visit Window											**±1 days**	**±1 days**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Admission to CRU		X											
Urine drug test	X	X											• The minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines (others are site and study-specific). A positive test for cannabinoid-based compounds (eg, THC, CBD, etc) will not be considered exclusionary.
PE	X	X								X	X	X	• Full PE may be done at screening or deferred to Day -1 at the discretion of the investigator. A brief PE may be performed instead of a full examination, at the discretion of the investigator, at marked study visits. In addition, a full or brief PE may be performed at the discretion of the investigator at any time during the study if there is a new or ongoing AE. See Section 8.3.1 for additional information.
Randomization		X											• Randomization may be performed on Day -1, or prior to the first dose on Day 1.
Height (Screening only), body weight	X												• See Section 8.3.1 for additional information.
History of drug, alcohol, and tobacco use	X	X								X	X	X	

Table 1. Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Treatment Period**										**Notes**
		Clinical Confinement								**Outpatient Visits**		
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**				**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	• Day relative to start of study intervention (Day 1).
Hours After Dose			**-2 h to -5 min**	**0 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	**168 h**	**336 h**	
Visit Window											**±1 days**	**±1 days**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Vital signs	X		X					X		X	X	X	• Vital signs include sitting or semi-recumbent BP, RR, PR, and temperature. For BP, triplicate measurements are required on Day 1 pre-dose. • Temperature check for COVID-19 may be done daily during residence or per CRU policy. See Section 8.3.2 for additional information.
Continuous cardiac monitoring by telemetry			X	X						X	X		• To establish a baseline, telemetry should be recorded for at least 2 hours before dosing while awake. The 2-hour assessment 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. • Continuous cardiac monitoring will be conducted at least 15 minutes pre-dose through 2 hours postdose period. • On Days 5 and 8, continuous cardiac monitoring should be performed for 2 hours.
12-Lead ECG	X		X				X	X		X	X		• ECGs will be collected in triplicate approximately 2-4 minutes apart 3 times pre-dose on Day 1 (at -1.5 h, -1.0 h and -0.5 h pre-dose). One triplicate measurement will be taken post-dose during clinical confinement at each of the times specified in the

Table 1. Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Treatment Period**										**Notes**
		Clinical Confinement								**Outpatient Visits**		
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**				**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	• Day relative to start of study intervention (Day 1).
Hours After Dose			**-2 h to -5 min**	**0 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	**168 h**	**336 h**	
Visit Window											**±1 days**	**±1 days**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													SoA. Single ECGs will be collected at all other designated visits including screening. • See Section 8.3.3 for additional information.
Contraception check	X	X									X	X	
Safety laboratory	X	X					X			X	X	X	• See Appendix 2 for additional information. • At the PI discretion, additional samples may be collected on Day -1 for analysis at local lab if needed to provide data prior to randomization. This data would be kept as source.
Pregnancy test (WOCBP only)	X	X											See Appendix 2 for additional information.
Serum FSH	X												• FSH test is performed only in WONCBP below 60 years of age at screening to confirm postmenopausal status in females who have been amenorrhoeic for at least 12 consecutive months. It will not be required in women with a confirmed history of hysterectomy. • See Appendix 2 for additional information.
HIV, HBsAg, HBcAb, HBsAb, HCVAb testing	X												See Appendix 2 for additional information.

Table 1. Schedule of Activities Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Screening to Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Treatment Period**										**Notes**
		Clinical Confinement								**Outpatient Visits**		
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**				**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	• Day relative to start of study intervention (Day 1).
Hours After Dose			**-2 h to -5 min**	**0 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	**168 h**	**336 h**	
Visit Window											**±1 days**	**±1 days**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
QuantiFERON-TB Gold	X												
Study intervention administration				X									See Sections 6.1 for additional
Injection site reaction assessment				X	→	→	→	→	→	→	X	→	See Sections 6.1 and 8.3.7 for additional information
Prior/concomitant treatment(s)	X	X	→	→	→	→	→	→	→	→	→	→	• See Section 6.9 for additional information
PK blood sample collection			X		X	X	X	X	X	X	X	X	
Immunogenicity sample collection			X									X	
Target engagement biomarker			X				X		X	X	X	X	
NT-proBNP		X											
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	• See Section 8.4 for additional information.
CRU discharge										X			• Discharge should only occur after review of Day 5 (96 hour post-dose) safety labs.

1.3.1.2. Table 2: Schedule of Activities for Follow-up Visits Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Day 29 Until Discharge

Table 2. Schedule of Activities for Follow-up Visits Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Day 29 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix10.	**Follow-up Visits**				**Early Discontinuation**	**Notes**
Days relative to Day 1	**Day 29**	**Day 57**	**Day 85**	**Day 113 (End of study)**		• Day relative to start of study intervention (Day 1).
	Week 4	**Week 8**	**Week 12**	**Week 16**		
Visit Window	**±2 days**	**±2 days**	**±2 days**	**±2 days**		• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
PE	X		X	X	X	• A brief PE is required at discharge. A brief PE may be performed instead of a full examination, at the discretion of the investigator, at marked study visits. A full or brief PE may also be performed at the discretion of the investigator at any time during the study if there is a new or open AE.
Vital signs	X	X	X	X	X	• Vital signs include sitting or semi-recumbent BP, and PR. • See Section 8.3.2 for additional information.
Single 12-Lead ECG		X		X	X	
Contraception check	X	X	X	X	X	
Safety laboratory	X	X	X	X	X	• See Appendix 2 for additional information.
PK blood sample collection	X	X	X	X	X	
Immunogenicity sample collection	X	X	X	X	X	

Table 2. Schedule of Activities for Follow-up Visits Part A (SAD Cohorts 1 to 8, SC Route) in Healthy Participants From Day 29 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix10.	**Follow-up Visits**				**Early Discontinuation**	**Notes**
Days relative to Day 1	**Day 29**	**Day 57**	**Day 85**	**Day 113 (End of study)**		• Day relative to start of study intervention (Day 1).
	Week 4	**Week 8**	**Week 12**	**Week 16**		
Visit Window	**±2 days**	**±2 days**	**±2 days**	**±2 days**		• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Target engagement biomarker	X	X	X	X	X	
NT-proBNP		X		X	X	Note: Early term only if 4 weeks since the last collection of NT-proBNP.
Pregnancy test (WOCBP only)	X	X	X	X	X	
History of drug, alcohol, and tobacco use	X	X	X	X	X	
Serious and nonserious AE monitoring	X	X	X	X	X	See Section 8.4.3 for follow-up AE and SAE assessments.
Concomitant medications	X	X	X	X	X	
Discharge from study				X		Follow-up visit schedule may be changed based on emerging safety, PK, and biomarker data from previous cohorts.

1.4. 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.

1.4.1. Schedule of Activities Part B Participants with PAH

1.4.1.1. Table 3: Schedule of Activities Part B Participants with PAH Treatment period

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Informed consent	X										• Informed consent should be obtained

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Review inclusion/ exclusion criteria	X										• See Section 5.3 and Section 5.4 for additional information.
Registration in IRT	X										• At registration, the participant enrollment number is assigned.
Medical History and PE											
Medical history, demography	X										
PE	X	X			X	X	X	X	X	X	• See Section 8.3.1 for additional information.

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											• PEs to be completed before administration of study intervention.
Height (Screening only), Body Weight	X	X				X			X	X	• See Section 8.3.1 for additional information.
Vital signs	X	X	X	X	X	X	X	X	X	X	• Vital signs include sitting or semi-recumbent BP, respiratory rate, and PR. • See Section 8.3.2 for additional information.
12-Lead ECG	X	X	X			X			X	X	• Single ECGs will be collected at visits specified except for

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											Day 1, which will be in triplicate. • See Section 8.3.3 for additional information.
Spirometry	X										• See Section 8.1.1
O_2 saturation	X	X	X	X	X	X	X	X	X	X	• See Section 8.3.2.3 for additional information. O_2 saturation collected prior to conduct of the 6MWT may be used to satisfy this requirement.
Right heart catheterization (RHC)	X								X		• Need to pass all other I/E before performing pre-randomization

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											RHC. Pre-randomization RHC should be done within 2 weeks of randomization. Data from a RHC performed within 12 weeks of Screening as part of the participant's usual disease monitoring may satisfy this requirement provided all required data are available. • The EOT RHC may be performed within -10 /

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											+5 days of the nominal Week 24 visit. • See Section 8.2.1 for additional information.
Contraception check	X	X	X	X	X	X	X	X	X	X	

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Laboratory Assessments											• See Section 8.3.5 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Safety laboratory	X	X	X	X	X	X	X	X	X	X	• See Appendix 2 for additional information. Coagulation testing should be done so that results are available before RHC at baseline and at Week 24.

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
HIV, HBsAg, HBcAb, HBsAb, HCVAb testing	X										• See Section 8.3.10 and 8.3.11 for additional information.
QuantiFERON-TB Gold In-tube, T-Spot, or equivalent test	X										• See Section 8.3.5 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done.
Serum FSH	X										• FSH test is performed only in WONCBP below 60 years of age at Screening to confirm postmenopausal status

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
											in females who have been amenorrhoeic for at least 12 consecutive months. It will not be required in women with a confirmed history of hysterectomy
Pregnancy test	X	X	X	X	X	X	X	X	X	X	• WOCBP only
Urine drug test	X										
PK blood sample collection		X	X	X	X	X	X	X	X	X	• Samples should be collected pre-dose on dosing days

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Immunogenicity sample collection		X		X	X	X	X	X	X	X	• Samples should be collected pre-dose on dosing days
Target engagement biomarker		X	X	X	X	X	X	X	X	X	• Samples should be collected pre-dose on dosing days
NT-proBNP	X	X	X	X	X	X	X	X	X	X	• Samples should be collected pre-dose on dosing days
Study Intervention and Other Treatments											See Section 6 for additional information.
Randomization		X									
Study intervention administration		X		X	X	X	X	X			See Section 6.1 for additional information.

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	See Section 6.9 For additional information
Assessments											See Section 8 for additional information.
Efficacy											See Section 8.2 for additional information.
6-Minute Walk Test	X	X	X	X	X	X	X	X	X	X	See section 8.2.2 for additional information.
Borg CR10 scale® (pre- and post-6MWT)	X	X	X	X	X	X	X	X	X	X	To be completed before and after each 6MWT. See Section 8.2.4.6. for additional information.
WHO Functional Class Assessment	X	X	X	X	X	X	X	X	X	X	See Section 8.2.3 for additional information
Patient Reported Outcome Measures											See Section 8.2.4 for additional information.

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
SF-36		X				X			X	X	
EQ-5D-5L		X				X			X	X	
PAH-SYMPACT		X		X		X			X	X	
PGI-S		X		X		X			X	X	
PGI-C				X		X			X	X	
Safety											See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	See Section 8.4 for additional information.
Injection site reaction assessment		X	X	X	X	X	X	X		X	See sections 6.1 and 8.3.8. for additional information. Completed at the early discontinuation visit only if study drug was administered on that day.

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Clinical worsening	X	X	X	X	X	X	X	X	X	X	See Section 8.3.12 for additional information.
Biomarker Assessments											See laboratory manual
Retained research sample for genetics (Prep D1)		X									• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
Exploratory serum biomarkers		X	X	X	X	X			X	X	
Retained research samples for biomarkers (Prep B2.5)		X	X			X			X	X	

Table 3. Schedule of Activities Part B Participants with PAH Treatment period

Visit Identifier Abbreviations used in this table may be found in Appendix10.		**Treatment Period**								**Early Discontinuation**	**Notes**
Days relative to Day 1	**Screen (Up to 35 days before Day 1)**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**		• Day relative to start of study intervention (Day 1).
			Week 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 / EOT**		
Visit Window			**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 Days**		• All screening should be done ≤35 days before the first dose. A delay in randomization ≤ 7 days due to the need to acquire RHC, PFT and /or repeat laboratory data will not be considered as a PD. • See Section 8.4.3 for follow-up AE and SAE assessments.
Retained research samples for biomarkers (Prep R1)		X	X			X			X	X	

1.4.1.2. Table 4: Schedule of Activities Part B Participants with PAH-Follow-up

Table 4. Schedule of Activities Part B Participants with PAH-Follow-up

Visit Identifier Abbreviations used in this table may be found in Appendix10.	**Notes**			
Days relative to Day 1	**Day 197**	**Day 225**	**Day 253**	
	Week 28	**Week 32**	**Week 36 (EOS)**	
Visit Window (Days)	**±2**	**±2**	**±2**	• See Section 8.4.3 for follow-up AE and SAE assessments.
PE	X	X	X	• See Section 8.3.1 for additional information
Body Weight			X	• See Section 8.3.1 for additional information.
Vital signs	X	X	X	• See Section 8.3.2 for additional information.
ECG			X	• See Section 8.3.3 for additional information.
O_2 saturation	X		X	• See Section 8.3.2.3 for additional information. O_2 saturation collected prior to conduct of the 6MWT may be used to satisfy this requirement.
Serious and nonserious AE monitoring	X	X	X	• See Section 8.4 for additional information.
Clinical Worsening	X	X	X	
Contraception check	X	X	X	
6MWT	X		X	• See Section 8.2.2 for additional information.
Borg CR10 scale® (pre- and post-6MWT)	X		X	To be completed before and after each 6MWT. See Section 8.2.4.6. for additional information.
Patient Reported Outcome Measures				
SF-36			X	• See Section 8.2.4 for additional information.
PAH-SYMPACT	X		X	• See Section 8.2.4 for additional information.
PGI-S			X	• See Section 8.2.4 for additional information.
PGI-C			X	• See Section 8.2.4 for additional information.
Laboratory Assessments				
Safety laboratory	X	X	X	• See Appendix 2 for additional information.
PK blood sample collection	X	X	X	
Immunogenicity sample collection	X	X	X	

Table 4. Schedule of Activities Part B Participants with PAH-Follow-up

Visit Identifier Abbreviations used in this table may be found in Appendix10.	**Notes**			
Days relative to Day 1	**Day 197**	**Day 225**	**Day 253**	
	Week 28	**Week 32**	**Week 36 (EOS)**	
Visit Window (Days)	**±2**	**±2**	**±2**	• See Section 8.4.3 for follow-up AE and SAE assessments.
NT-proBNP	X	X	X	
Target engagement biomarker	X	X	X	
Biomarker Assessments				
Exploratory biomarkers		X	X	• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
Retained research samples for biomarkers (Prep B2.5)	X			
Retained research samples for biomarkers (Prep R1)	X			

2. INTRODUCTION

PF-07868489 is an anti-BMP9 mAb that is currently being investigated as a potential treatment for patients with PAH. The BMP9 pathway has been implicated in the pathogenesis of PAH and inhibition of BMP9 signaling has the potential to improve clinical outcomes in this disease.

2.1. Study Rationale

This is the first time that PF-07868489 will be given to humans. The purpose of this study is twofold: Part A will evaluate the safety, tolerability, PK, and immunogenicity of single doses of PF-07868489 in healthy adult participants; Part B will evaluate the clinical activity, safety, tolerability, PK, immunogenicity, and PD of repeat doses of PF-07868489 in patients with PAH.

2.2. Background

PAH (WHO Group 1 classification of PH) is a rare debilitating vascular disease in which distal pulmonary arteries become narrowed and ablated. PAH is characterized by an increase in proliferation and resistance to apoptosis of pulmonary arterial eCs, vascular SMCs, and fibroblasts. This leads to progressive vascular remodeling, increases in pulmonary arterial pressure, and adverse remodeling of the right ventricle. More precisely, PAH is defined physiologically as mPAP measured by right heart catheterization >20 mmHg at rest, PAWP ≤15 mmHg, and PVR >2 WU.[7] Ultimately, PAH results in death from right heart failure. [8,12] PAH has a poor prognosis despite established vasoactive therapies targeting the endothelin, prostacyclin, and nitric oxide pathways, with a 5-year survival rate between 57% and 61%.[3,6,8,12]

The BMPRII gene is mutated in approximately 75% of heritable and in 20% of idiopathic/sporadic PAH cases.[4,5,9] Reduced BMPRII expression has also been demonstrated in PAH patients without LOF mutations and in non-genetic rodent models of the disease.[2,10,11,13] Reduced BMPRII levels can promote pathological BMP9 GOF signaling via the compensating Type II Rcs (ActRIIA and ActRIIB). This is thought to drive EC dysfunction, downstream SMC proliferation, and vascular remodeling in PAH.[14,15]

PF-07868489 is a highly potent and selective neutralizing antibody against BMP9 protein that blocks its binding to Type II receptors such as BMPRII and inhibits receptor-mediated pSMAD nuclear translocation in endothelial cells. PF-07868489 has the potential to be disease modifying in patients with PAH by selectively inhibiting BMP9-driven endothelial dysfunction and subsequent pulmonary vascular remodeling.

2.2.1. Nonclinical Pharmacology

In vitro data demonstrated that PF-07868489 is a highly potent and selective monoclonal antibody that neutralizes BMP9 activity. Potent binding affinity of PF-07868489 to rat, monkey, and human recombinant BMP9 proteins was observed. No off-target binding of PF-07868489 to a panel of TGFβ superfamily members (human BMP10, GDF8, GDF9, GDF11, Activin A, and TGFβ1) was detected. PF-07868489 had no effect on either GDF8-

or GDF11-induced luciferase activity in C2C12 mouse myoblasts stably expressing the CAGA-luciferase reporter. PF-07868489 neutralized species-specific BMP9-induced pSMAD1/5/9 and pSMAD2 nuclear translocation in a concentration-dependent manner and inhibited BMP9-induced secretion of ET-1, IL-6, and IL-8 by HPAEC. BMP9-induced inhibition of HPAEC proliferation was blocked by PF-07868489.

In vivo, neutralization of BMP9 by PF-07868489 in the rat SuHx model of PAH led to improved disease endpoints. The magnitude of disease developed in SuHx-treated rats was attenuated upon administration of 0.3 mg/kg or 3 mg/kg of PF-07868489, as evidenced by reduced RVSP and RVH compared to treatment with an isotype control antibody. Serum from PF-07868489-dosed rats inhibited pSMAD nuclear translocation in endothelial cells relative to serum from rats dosed with an isotype control. The observed dose-dependent accumulation of total soluble BMP9, following PF-07868489 administration in rats, supports target engagement.

Additional details regarding nonclinical pharmacology may be found in the current version of the PF-07868489 IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Following single IV dosing of PF-07868489 in female monkeys, the t½ values ranged from ~6.4 to 8.3 days. In the 1-month GLP repeat dose toxicity studies in rats and monkeys and the 26-week GLP repeat dose toxicity study with 60-day recovery in rats, there were no consistent sex-related differences in systemic exposure (as assessed by C_{max} and AUC) following repeat SC or IV dosing. Mean systemic exposure increased with increasing dose (SC dosing), and accumulation was observed after repeat SC or IV dosing in the 1-month studies in rat and monkeys. Accumulation was not observed in the 26-week study in rats after repeat SC dosing. The overall incidence of ADA induction to PF- 07868489 was approximately 6.3% in the 1-month rat study, 62% in the 26-week rat study and 11% in the 1-month monkey study, across all dose groups.

PF-07868489 is expected to be cleared primarily via catabolic degradation in humans; therefore, it is unlikely that concomitant medication can alter the clearance of PF-07868489 even if target expression is affected.

Additional details regarding the nonclinical absorption, distribution, metabolism, and excretion properties of PF-07868489 may be found in the current version of the PF-07868489 IB.

2.2.3. Nonclinical Safety

There were no in-life dose-limiting toxicities or target organs identified in the nonclinical toxicity studies. No adverse hematologic, macroscopic, or microscopic findings were observed in the nonclinical toxicity studies up to 1-month duration in rats and monkeys, and up to 26 weeks (6 months) in rats administered SC or IV PF-07868489. Data from recovery phase of the 26-week repeat dose toxicity study in rats are pending. PF-07868489-related findings were only observed in rats and limited to non-adverse minimal subacute

inflammation at subcutaneous injection site. Additionally, transient non-adverse PF-07868489-related minor hematology and clinical chemistry changes were noted only in rats (and not monkeys). This nonclinical toxicity profile supports the selectivity of PF-07868489 and is consistent with data from BMP9 knockout mice being phenotypically normal[17]. The NOAELs were 175 mg/kg/week (IV) in rats (C_{max} of 5880 µg/mL; AUC_{168} of 321000 µg•h/mL, resulting in C_{av} of 1911 µg/mL) and 125 mg/kg/week (IV) in monkeys (C_{max} of 9460 µg/mL; AUC_{168} of 895000 µg•h/mL, resulting in C_{av} of 5327 µg/mL), which were the highest doses tested in the 1 month toxicity studies. The NOAEL in the 26-week (6-month) SC rat study was 100 mg/kg/dose (C_{max} of 302 µg/mL; AUC_{336} of 42800 µg•h/mL, resulting in C_{av} of 127 µg/mL), the highest dose tested in the study. No immunohistochemical staining was noted in the tissue cross-reactivity study using human, rat, and monkey normal tissues indicating lack of off-target binding across species. No binding was observed in the in vitro C1q and FcγR binding assays. The nonclinical data support the progression of PF-07868489 into human clinical trials with a potentially favorable overall benefit-risk profile.

Further details of the nonclinical safety program may be found in the current version of the PF-07868489 IB.

2.2.4. Clinical Overview

PF-07868489 is being evaluated in Part A in single ascending doses in healthy participants. Ongoing review of emerging, preliminary safety data from this part of the study (single doses up to 800 mg SC) has not revealed any safety signals that would negatively affect the overall benefit-risk of PF-07868489. Observed PK from the doses tested in Part A are presented in Sec 4.3.2 and IB.

2.3. Benefit/Risk Assessment

Since Study C5001001 is the first time that PF-07868489 will be administered to humans, there were no human safety data, and only preclinical data, on which to base an assessment of overall potential benefit-risk at the time the study was initiated. Given that PF-07868489 is a highly selective, high-affinity mAb to BMP9 and that no target organ toxicities were observed in the completed GLP toxicity studies conducted to date, no mechanism-based safety issues are anticipated in humans due to exposure to PF-07868489. A GLP chronic toxicity study in rats was ongoing when the study was initiated. This study has since completed (dosing phase), and no test article – related target organ toxicities were identified that change the overall assessment of safety or potential benefit – risk.

PF-07868489 is not expected to provide any clinical benefit to healthy participants in the single ascending dose part of the study (Part A). This phase of the study is designed primarily to generate safety, tolerability, PK, and immunogenicity prior to exposure of PF-07868489 to participants with PAH. Ongoing review of emerging safety data from Part A of the study has not revealed any safety signals or clinically significant adverse effects.

Part B of the study will be conducted in participants with PAH. Since this will be the first assessment of the clinical activity, safety, tolerability, immunogenicity, PK, and PD of

PF-07868489 in this population, it is not known if participants with PAH will derive clinical benefit from exposure to PF-07868489 but it is possible that they may.

The study design, inclusion/exclusion criteria, and procedures have been developed in a manner to minimize the risks to participants. Evidence for potential benefits comes from data observed in rodent models of PAH and human genetic evidence suggesting a role for altered BMP9 receptor signaling in the pathogenesis of PAH.

As of the date of this protocol, no specific human risks have been identified in preclinical toxicity studies nor in review of emerging preliminary clinical data from the ongoing Part A of the study. Potential risks related to PF-07868489 exposure will be minimized through the use of a cautious dose escalation process in Part A wherein higher doses of PF-07868489 will be administered only after lower doses have been found to be well-tolerated with an acceptable safety profile. In addition, the healthy participant phase of this study includes standard, intensive inpatient monitoring of the participants following administration of the study intervention.

The patient phase (Part B) of the study will only be initiated after adequate safety and tolerability have been established in healthy participants and the GLP chronic toxicity data are available. Evaluation of emerging, preliminary clinical data from Part A of the study has not identified any safety or tolerability issue that would preclude progression into Part B of the study in patients with PAH. Additionally, emerging unblinded safety data from Part B of the study will be monitored periodically by an internal review committee that will provide feedback on the emerging safety profile in participants with PAH.

Given the anticipated risks and risk mitigations, the overall potential benefit-risk profile of PF-07868489 is expected to be favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07868489 may be found in the current version of the PF-07868489 IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07868489 and Placebo		
Potential for anaphylaxis and injection site reactions.	As a protein therapeutic, there is a theoretical potential for immunogenicity. The potential for PF-07868489 to induce significant antibody responses and for such antibody responses, should they occur, to cause clinically significant sequelae has been assessed based on the physical characteristics of PF-07868489, the planned clinical indication, and the design characteristics of the FIH study C5001001. It is also possible that participants will have adverse reactions to other ingredients of the study intervention The overall risk of immunogenicity or adverse reactions to the ingredients of the IP is projected to be low.	Participants will be observed closely for signs and symptoms of immunogenicity using standard clinical monitoring. Injection site reactions will be documented as adverse events. For SC administration of study treatment, injection site reactions will be monitored, and injection sites rotated.
Study Procedures		
Potential for bleeding, arrythmias, lung collapse and death related to the RHC procedure (Part B only).	RHC is an invasive procedure that involves insertion of a catheter into a major vein, through the right atrium and ventricle, and into the pulmonary vasculature.	RHC will be performed only by personnel skilled in performing RHC, under sterile, surgical conditions, and in a facility with controlled monitoring and resources to manage potential complications.

2.3.2. Benefit Assessment

Part A

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

Part B

Given the stage of development of PF-07868489, there are no data attesting to its beneficial effect in patients with PAH. While no clinical benefit from administration of PF-07868489 to participants with PAH in Part B of Study C5001001 can therefore be assumed, inhibition of BMP9 signaling by PF-07868489 may demonstrate clinical activity in this patient population, the assessment of which is an objective of Part B of the study.

2.3.3. Overall Benefit/Risk Conclusion

Given the measures to minimize risk to study participants, the potential risks identified in association with exposure to PF-07868489 are justified by the anticipated benefits that may be afforded to participants with PAH.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Part A

Objectives	Endpoints	Estimands
Primary:	**Primary:**	
• To evaluate the safety and tolerability of escalating single SC injections of PF-07868489 in healthy adult participants.	• Incidence and severity of AE and SAEs. • Change from baseline in vital signs. • Change from baseline in clinical laboratory values. • Change from baseline in ECG parameters (heart rate, QT, QTcF, PR, and QRS intervals).	• NA
Secondary:	**Secondary:**	
• To characterize serum exposure of escalating single SC injections of PF-07868489 in healthy adult participants.	• After single dose: PF-07868489 PK parameters as data permit: AUC_{last}, AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$.	• NA
• To evaluate the immunogenicity profile of PF-07868489 following single dose administration in healthy adult participants.	• Incidence of the development of ADA against PF-07868489 following single dose.	• NA

Objectives	Endpoints	Estimands
Tertiary/exploratory:	**Tertiary/exploratory:**	
• To characterize further the PK profile of PF-07868489 following single doses in healthy adults.	• PF-07868489 PK parameters, as data permit: AUC_{last} (dn), AUC_{inf} (dn), C_{max} (dn), CL/F and V_z/F	NA
• To evaluate the effects of PF-07868489 on target engagement biomarkers.	• Change from baseline in blood levels of biomarkers (if assessed): o Blood target engagement levels	
• To characterize the behavior of NT-proBNP in healthy volunteers.	• Change from baseline in NT-proBNP	• NA

3.2. Part B

Objectives	Endpoints	Estimands
Primary:	**Primary:**	
• To evaluate the safety and tolerability of repeat SC doses of PF-07868489 in participants with PAH.	• Incidence and severity of AE and SAEs. • Change from baseline in vital signs. • Change from baseline in clinical laboratory values. • Change from baseline in ECG parameters (heart rate, QT, QTcF, PR, and QRS intervals).	• NA
• To characterize change in blood concentration of NT-proBNP following repeat SC dose administration of PF-07868489 in participants with PAH.	• Change from baseline at Week 24 of NT-proBNP	• E1: The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in NT-proBNP in PAH patients. This analysis will exclude data after use of rescue medications and after study treatment discontinuation.
Secondary:	**Secondary:**	
• To characterize serum exposure following repeat SC doses of PF-07868489 in participants with PAH.	• PF-07868489 PK parameters after repeat doses; as data permit: C_{min}, and $t_{1/2}$	• NA
• To evaluate the immunogenicity profile of PF-	• Incidence of the development of ADA against PF-07868489 following repeat doses.	• NA

Objectives	Endpoints	Estimands
07868489 following repeat SC doses in participants with PAH.		
• To evaluate the effects of repeated PF-07868489 dosing on 6MWD and PVR in participants with PAH.	• Change from baseline at Week 24 on 6MWD • Change from baseline at Week 24 on PVR	• E2: The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in PVR at Week 24 in PAH patients. This analysis will exclude data after use of rescue medications and after study treatment discontinuation.
Tertiary/exploratory:	**Tertiary/exploratory:**	
• To evaluate the effects of PF-07868489 on target engagement biomarkers	• Change from baseline in blood levels of biomarkers (if assessed): o Blood target engagement levels	
• To evaluate the effects of repeated PF-07868489 dosing on exploratory measures of clinical effect in participants with PAH	• 6MWD at timepoints other than Week 24 • PVR at timepoints other than Week 24. • NT-proBNP at timepoints other than Week 24	• NA
• To assess effect of PF-07868489 on clinical worsening in participants with PAH	• Time to Clinical worsening	• NA
• To evaluate the effect of PF-07868489 on PROs in participants with PAH	Change from baseline in: • SF-36 • EQ-5D-5L • PAH-SYMPACT • PGI-S • PGI-C • Borg CR10 scale®	• NA

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/ 2, randomized, double-blind, placebo-controlled study conducted in 2 sequential parts. Part A is designed to evaluate the safety, tolerability, PK, and immunogenicity of single escalating doses of PF-07868489 in healthy adult participants. Part

B is designed to evaluate the clinical activity, safety, tolerability, PK, immunogenicity, and PD of repeat doses of PF-07868489 in participants with PAH.

4.1.1. Part A: Single ascending doses in healthy participants

Part A of this study is an investigator- and participant-blind, sponsor-open, placebo-controlled, single ascending dose study of PF-07868489 administered SC in healthy adult participants. There are 8 planned cohorts, including optional cohorts of healthy adult Japanese, and Chinese participants. The inclusion of these optional cohorts is to enable the recruitment of Japanese and Chinese patients into future clinical trials and will depend on the operational feasibility of recruiting the relevant populations. These cohorts, if conducted, will be done at a dose that is determined to be safe and well-tolerated in Western participants. Up to approximately 54 participants will be enrolled into Part A of this study and randomly assigned to receive PF-07868489 or placebo as follows:

- Cohort 1 (n = 4): 3 mg SC (n = 2) or placebo (n = 2)
- Cohort 2 (n = 6): 10 mg SC (n = 4) or placebo (n = 2)
- Cohort 3 (n = 6): 30 mg SC (n = 4) or placebo (n = 2)
- Cohort 4 (n = 8): 100 mg SC (n = 6) or placebo (n = 2)
- Cohort 5 (n = 8): 300 mg SC (n = 6) or placebo (n = 2)
- Optional Cohort 6 (n = 8): In Western participants active (n = 6) or placebo (n = 2) at a dose to be determined by emerging safety and PK data in prior cohorts.
- Optional Japanese Cohort 7 (n = 5): at the highest dose tested in the sequence above (n=4) or placebo (n=1).
- Optional Chinese Cohort 8 (n = 5): at the highest dose tested in the sequence above (n=4) or placebo (n=1).

Within approximately 28 days of signing the ICD, eligible participants will be randomized to receive PF-07868489 or placebo as SC injection(s). Single dose cohorts will be enrolled sequentially in a dose escalating fashion starting from the lowest proposed dose.

For Cohort 1, if a single participant dosed with active drug meets one of the dose escalation stopping criteria mentioned in Section 6.6.1, based on a discussion between sponsor and investigator(s), 4 more participants may be added to the cohort (2 active, 2 placebo). If a cohort is extended with 4 additional participants as described above, dose escalation stopping decisions (Section 6.6.1) will be based on the data from all 8 participants.

During Part A of the study, escalation to subsequent dose levels will occur following the sponsor and investigator's review of available safety through a minimum of Study Day 15 and PK data through a minimum of Study Day 8 for the immediately previous cohort (and

emerging clinical and PK data from all enrolled cohorts). Doses in this part may be adjusted depending upon the actual exposure of PF-07868489 observed in humans at lower doses. If, based on the observed data, the subsequent dose-projected group mean C_{max} or AUC_{168} (data permitting) are higher than the PK exposure limit in humans of 946 µg/mL or 89500 µg•hr/mL, respectively (defined as $1/10^{th}$ of the mean exposures observed at NOAEL in the 1-month monkey toxicity study), that dose will not be explored.

Participants will be admitted into the CRU approximately 1 day prior to dosing and will be required to stay overnight in the study center through completion of Day 5 evaluations as per the SoA. Participants will be discharged after Day 5 procedures have been completed and Day 5 safety labs have been reviewed by the PI. The final follow-up visit for all cohorts in Part A is up to Week 16 or until their exposures are below LLOQ.

Based on emerging data from previous and ongoing single dose cohorts, doses may be repeated, modified and other doses may be explored in additional cohorts. If the exposures in the subsequent dose are projected to exceed the prespecified exposure limits, that dose will not be explored.

4.1.2. Part B: Participants with PAH

Part B is a 24-week, randomized, double-blind, placebo-controlled study design (see schema in Section 1.2) in participant with PAH. Up to approximately 36 participants will be randomized into Part B of this study.

Following the Screening period of up to 35 days to confirm eligibility, participants with PAH who meet all eligibility criteria at Screening and Baseline, will be randomized to study intervention (PF-07868489 or placebo) in a 1:1 ratio. Beginning on Day 1, participants will receive of a total of 6 doses administered Q4W SC (through Week 20). Following Day 1, there will be a visit at Week 1 (Day 8) for initial safety monitoring followed by visits at Week 4 and Q4W thereafter. The active treatment period is defined as extending from Day 1 through the Week 24 / EOT visit.

Participants who complete the active treatment period of study C5001001 may be offered the opportunity to enroll in an OLE study. All participants in the OLE study will receive active study intervention (details of the OLE study will be provided in a separate protocol).

Participants who complete the active treatment period should decide whether or not to enter the OLE study by the Week 24 visit of the current protocol. Participants who elect to enroll in the OLE study will enter that study after completion of all Week 24 activities in the current study. Participants enrolling into the OLE study will receive their first dose of PF-07868489 at the Week 24 visit of the current study and will not progress into the follow-up period of the current study.

Participants who discontinue study intervention prematurely will complete the Week 24 / EOT visit 4 weeks after termination of study intervention. Alternatively, in discussion with the PI and with Sponsor agreement, a participant who has completed at least through Week 12, may have the option to enter the OLE.

If participants do not elect to enter the aforementioned optional OLE study, the last dose of study intervention will be at Week 20. Participants who do not elect to enroll in the OLE study will enter a 12-week Follow-Up Period, beginning after completion of the Week 24 visit, after which they will be discharged from the study (EOS visit for these participants being Week 36).

Up to approximately 10 % of participants who are discontinued due to lack of efficacy, may be replaced. Additional follow-up may be conducted for safety evaluation, at the discretion of the investigator.

An IA may be conducted during Part B of the study to assess preliminary efficacy data in participants with PAH. The timing and operating characteristics of the IA, if performed, will be defined as part of an IA charter/plan (to be provided later) and / or as an amendment to the SAP. Additional IAs may also be performed. IA results may be used for decisions regarding stopping for futility, sample size re-estimation, revisions to the dose levels, continuing enrollment into the study, or selective crossover of participants initially assigned to receive placebo to active treatment. If the trial is stopped for futility, participants may discontinue study treatment prematurely and enter the follow-up period.

If a participant withdraws from the study prior to completion of the Week 24 visit for a reason unrelated to efficacy or due a non-treatment-related AE (as determined by the investigator and sponsor) that meets individual participant study intervention stopping criteria (Section 7.1.6), additional participants may be randomized at the discretion of the sponsor to ensure there are sufficient data for analysis.

An independent oversight committee in the form of an IRC will monitor unblinded safety and tolerability data of PF-07868489 in the participants in Part B of the study on an ongoing, regularly scheduled basis. The IRC may also be charged with performance of any planned or unplanned IAs. Additional details will be described in the IRC charter.

Based on emerging data from Part A of the study, the dose, dosing frequency, and the follow-up schedule in Part B may be modified to characterize better the safety, PK and efficacy profile of the molecule.

4.2. Scientific Rationale for Study Design

Study C5001001 represents the first time PF-07868489 will be administered to humans and hence will be conducted initially in healthy participants in Part A of the study employing an escalating single dose design. Once the safety and tolerability of single doses have been demonstrated in healthy participants, participants with PAH will be enrolled into Part B of the study and receive repeat doses of PF-07868489. Repeat dosing in PAH participants allows for the assessment of the safety and tolerability of PF-07868489 under conditions in which a more favorable potential benefit: risk relationship is likely, while also affording the opportunity to explore PD in the target population.

Study C5001001 uses a placebo-controlled, blinded design to minimize bias which is justified in this early clinical study to provide a reference for safety and tolerability.

Additionally, in Part B, all participants with PAH (both participants receiving PF-07868489 and placebo) will be on background standard of care treatment for PAH.

Both adult male and female participants (including WOCBP) are eligible for enrollment into the study. Since human reproductive safety data are not available for PF-07868489, female participants must either be confirmed to be of non-childbearing potential or, if of childbearing potential, to be using at least 1 form of highly effective method of contraception as detailed in Appendix 4. As an additional safety measure, WOCBP will be required to have a negative pregnancy test prior to randomization and at specified visits per the SoA (including before the single dose in Part A and each repeat dose in Part B), and contraception checks will be performed at all outpatient visits. No contraception is warranted for male participants as the potential exposure to PF-07868489 via semen to female partners of male participants is anticipated to be very low.

Since all mAbs have a potential for immunogenicity, all participants will be monitored closely for signs and symptoms of immunogenicity, including injection site reactions and anaphylaxis. Blood samples will be collected for measurement of ADA in all participants.

Currently, all participants in both Part A and B will be followed for approximately 5-half-lives following last dose of study intervention. The follow-up visit schedule may be changed based on safety and PK data emerging from previous cohort(s).

4.2.1. Part A: Single ascending doses in healthy participants:

Part A (SAD phase) of the study will be initiated with a dose of 3 mg SC (see Dose Rationale, Section 4.3) with dose escalation continuing up to the maximum planned dose unless one of the stopping criteria is met.

Part A of the study will be conducted in healthy participants (as defined by the inclusion/exclusion criteria) in order to establish the safety, tolerability, PK and immunogenicity profile of PF-07868489 prior to exposure in patient populations. Although healthy participants can derive no potential benefit from exposure to PF-07868489, nonclinical data suggest that PF-07868489 will be well-tolerated and have an acceptable safety profile in healthy participants.

PF-07868489 is designed to bind to BMP9 and inhibit its interaction with BMP9 receptors. Blood samples will be collected for the assessment of target engagement. Collection times (see SoA) are planned based on expected changes, and target turnover.

Continuous cardiac monitoring by telemetry is planned to monitor any post injection AEs and on Study days 5 and 8 to capture any C_{max} related AEs.

Healthy Japanese and Chinese participants may be enrolled in optional, separate cohorts at the discretion of the sponsor to provide a preliminary characterization of the safety, tolerability, PK and target engagement profile of PF-07868489, to support potential inclusion of Japanese and Chinese patients in future studies. These cohorts may be terminated prematurely if enough participants cannot be recruited.

The safety surveillance, and the dose escalation rules (Section 6.6.1) are expected to minimize risk to study participants while providing key safety, tolerability, PK, and target engagement information.

4.2.2. Part B: Participants with PAH

Part B of the study will be initiated once adequate safety and PK data are available from the highest dose in Part A (see Section 4.1.1).

The dose in Part B is currently planned to be 400 mg SC Q4W.

The population for Part B of Study C5001001 is participants with PAH (WHO Group 1 PH) who are Functional Class II-III, as defined by the Inclusion / Exclusion Criteria. All participants will receive background standard of care treatment for PAH that will include a combination of at least 2 classes of vasodilator drugs. This ensures that participants receiving placebo are still receiving approved PAH therapy appropriate for their disease severity.

The scientific hypothesis being tested in Part B of the study is that inhibition of BMP9 will produce pharmacological effects on the pulmonary vasculature that ultimately improve RV hemodynamics, reduce PVR, and reduce RV wall strain. The selection of the primary, secondary and exploratory PD endpoints is based on potential improvements in pulmonary vascular and RV hemodynamics as a result of treatment with PF-07868489 as predicted by effects in nonclinical studies. These beneficial effects are predicted to be reflected in improvements (reductions) in NT-proBNP which is produced in response to increased RV pressure and wall strain. Therefore, levels of NT-proBNP will be a key primary endpoint in Part B for demonstrating clinical effect of PF-07868489 in PAH participants. Treatment with PF-07868489 would also be expected ultimately to yield measurable reductions in PVR and improvements in exercise capacity as measured by improvements in 6MWD. Assessments of 6MWD and PVR (measured during RHC) will be exploratory endpoints in Part B of the study.

The PROs incorporated into the protocol are designed to measure proximal and distal impacts of PAH, as well as to demonstrate improvements to overall quality of life, with analyses of physical and mental impacts. The endpoints included are intended to inform future clinical trials.

4.2.3. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07868489 have not been conducted. Therefore, the use of a highly effective method of contraception by women of childbearing potential is required (see Appendix 4).

4.3. Justification for Dose

4.3.1. Prediction of Human PK

Based on the pharmacokinetics observed in NHPs, the pharmacokinetics in humans are expected to be biexponential with an expected T_{max} of approximately 4 -7 days based on

experience with a typical mAb. The first order plasma clearance of PF-07868489 (k_{el}) is estimated to be 0.0013 hr^{-1} with a projected half-life of approximately 20 days.

4.3.2. Dose Justification for Parts A and B

The nonclinical safety profile of PF-07868489 has been adequately characterized to support progression into human clinical studies. No test article-related effects or target organs were identified following weekly administration of PF-07868489 in the 1-month monkey toxicity study with the NOAEL defined as the highest dose tested, 125 mg/kg QW (IV). In this study, the C_{max}, and AUC_{168} exposure limit for dose escalation in Part A are set to be 946 µg/mL, and 89500 µg•hr/mL, respectively, determined as the $1/10^{th}$ of the mean exposures observed at NOAEL in the monkey toxicity study. For Part B, dose projections are compared to exposures from the 6-month rat NOAEL of 100 mg/kg given Q2W.

Part A

In Part A, a starting dose of PF-07868489 3 mg SC is planned. The predicted PF-07868489 C_{max} and AUC_{168} at the 3-mg single dose are approximately 4730- and 3442- fold safety margins, respectively, below the pre-defined PK exposure limits. Preliminary modeling using a mechanistic PK/PD model predicts an average BMP9 inhibition over a month of ~30% with maximum BMP9 inhibition ~70% after a 3 mg SC single dose. This level of inhibition is expected to be safe and not expected to induce mechanism-based AEs.

Extensive pharmacology, selectivity, and nonclinical safety data for PF-07868489 support the starting dose and dose escalation schema. First, it hypothesized that abnormal downstream signaling of BMP9 through type 2 receptors (eg, ALK2), rather than elevation in circulating BMP9, leads to the pro-proliferative pathology in PAH. Circulating levels of BMP9 have been identified to be highly variable with similar ranges in PAH patients and in healthy participants with no associated clinical impact. Second, the highest doses of PF-07868489 tested in NHP (125 mg/kg/week IV) and rats (175 mg/kg/week IV) are expected to provide near complete BMP9 suppression (~99%), at which no AEs and test article-related findings were established. Third, no phenotypic abnormalities have been noted in BMP9 knockout mice. Lastly, PF-07868489 is identified to be highly selective to BMP9 and no off-target binding (and associated pharmacology) is expected. This supports safety of high and sustained levels BMP9 suppression projected during dose escalation.

Table 5 presents the observed exposures and safety margins following single and multiple doses of PF-07868489 from Part A. Due to emerging safety and PK, a single dose of 800 mg SC was tested in Part A in an optional cohort. This was the highest dose tested and provides an exposure margin of 13-fold for C_{max} and 10-fold for AUC_{168}, relative to the 1-month exposure limits. The maximum and average BMP9 inhibition over a month after 800 mg SC single dose is predicted to be ~99%, thereby assuring an adequate test of pharmacology.

Table 5. Observed Exposures and Safety Margins Following Single Doses of PF-07868489

Dose (SC)	C_{max} (ug/mL)	AUC_{168} (ug/mL*hr)	SM_C_{max} [a]	SM_AUC_{168} [a]
3 mg	0.15	20	6307	4475
10 mg	0.62	81	1526	1105
30 mg	2.46	331	385	270
100 mg	6.48	838	146	107
300 mg	25.92	2980	36	30
800 mg	70.1	8924	13	10

a. SM is calculated relative the exposure limit (C_{max} = 946 µg/mL and AUC_{168} = 89500 µg•hr/mL) calculated as 1/10th of the NOAEL exposures.

Part B

For Part B, a dose of 400 mg SC administered every 4 weeks for a total of 6 doses is planned. The dosing regimen of every 4 weeks was selected to achieve high exposures of PF-07868489 for adequate safety assessment. The multiple dose period is planned to be initiated after review of data from the 800 mg SC dose level in healthy participants in Part A. At 400 mg SC Q4W at Week 24, the C_{max} and C_{av} are predicted to be 6- and 4-fold respectively, below the chronic tox NOAEL of 100 mg/kg given Q2W (Sec 2.2.3). The C_{max} and AUC_{168} at this dose are also 1.5-fold and 1.2-fold below the exposures observed at the top Part A dose of 800 mg SC, respectively.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of this study including the last scheduled procedure shown in the SoA or, for Part B only, either completed all periods of this study including the last scheduled procedure shown in the SoA, or all activities through Week 24 and have enrolled in the OLE study.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria: Part A – Single Ascending Doses in Healthy Participants

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

Age and Sex:

1. Male and female participants must be 18 to 65 years of age, inclusive, at the time of Screening who are overtly healthy as determined by medical evaluation including medical history, PE, vital sign assessments and laboratory tests and 12-lead ECGs.

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

Other Inclusion Criteria:

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

3. Additional criterion for participants to be enrolled in the optional Japanese cohort only: Participants who have 4 Japanese biologic grandparents born in Japan.

4. Additional criterion for participants to be enrolled in the optional Chinese cohort only: Participants who have 4 Chinese biologic grandparents born in China.

5. BMI of 16 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

6. Additional criterion for participants to be enrolled in the optional Chinese cohort only: BMI of 19 to 27 kg/m^2; and a total body weight >50 kg (110 lb).

7. 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: Part A – Single Ascending Doses in Healthy Participants

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).

   - Have a history of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid tissue disease.

2. Participants with any of the following acute or chronic infections or infection history:

    - Any infection requiring treatment, including those requiring hospitalization, parenteral antimicrobial therapy, within 60 days prior to the first dose of investigational product.

    - Any infection judged to be an opportunistic infection or clinically significant by the investigator, within the past 6 months of the first dose of the investigational product.

    - Known active or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections.

    - Evidence of active, latent, or inadequately treated infection with Mycobacterium TB as defined by either of the following:

        - A positive IGRA (eg, QuantiFERON-TB Gold In-tube or equivalent test) performed within the 12 weeks prior to Screening or a positive test at the Screening visit. If the laboratory reports the test as indeterminate, the test should be repeated.

        - History of either untreated or inadequately treated latent or active TB infection, or current treatment for the same.

    - History of a recurrent (more than one episode of) localized, dermatomal herpes zoster, or history of disseminated (one single episode) herpes simplex or disseminated herpes zoster, HIV infection, or infection with hepatitis B or hepatitis C viruses according to protocol-specific testing algorithm. Refer to Section 8.3.10 and 8.3.11.

    - History of febrile illness within 5 days prior to the first dose of investigational product.

3. Have undergone significant trauma or major surgery within 30 days prior to the first dose of study drug.

4. Any 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 6.9.

6. Current use of any prohibited concomitant medication(s). Refer to Section 6.9.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

8. A positive urine drug test. A single repeat for positive drug screen may be allowed. A positive test for cannabinoid-based compounds (eg, THC, CBD, etc.) will not be considered exclusionary.

9. Screening sitting or semi-recumbent BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of rest. If systolic BP is ≥ 140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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. Renal impairment as defined by an eGFR in adults with < 75 mL/min/1.73 m². Based upon participant age at screening, eGFR, eCrCl normalized to BSA, or eCrCl is calculated using the recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the Screening and Baseline eGFR values may be used.

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

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

    - ALT or AST level ≥ 1.05 × ULN
    - T bili level ≥ 1.05 × ULN
    - Albuminuria as defined by urine albumin/creatinine ratio (UACR) >30 mg/g

Other Exclusion Criteria:

13. Participants who smoke more than 10 cigarettes (or equivalent) per day or have a smoking history ≥10 pack-years.

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

5.3. Inclusion Criteria: Part B, Participants with PAH

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

Age and Sex:

1. Participants aged ≥18 years (or the minimum age of consent in accordance with local regulations) at screening who have signed informed consent.

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

Disease Characteristics:

2. Documented diagnostic RHC prior to Screening confirming diagnosis of PAH (WHO Group 1 PH) including any of the following subtypes:

    - Idiopathic or heritable PAH.
    - Drug- or toxin-induced PAH.
    - PAH associated with connective tissue disease.
    - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair.

3. PAH classified as WHO functional class II or III.

4. Pre-randomization RHC documenting a minimum of PVR ≥ 400 dyn ·sec/cm^5 (5 Wood units); and no contraindication to RHC.

    - RHC performed within 12 weeks of Screening as part of the participants management of PAH can satisfy this criterion, if the requisite hemodynamic data are available. Otherwise, a RHC needs to be performed prior to randomization. In this case, the RHC should only be performed if the potential participant meets all other inclusion / exclusion criteria for eligibility.

5. PFTs (spirometry) performed as part of the diagnostic evaluation of PAH excluding clinically relevant obstructive or restrictive pulmonary physiology (unless the participant is an active smoker of > 10 cigarettes/equivalent per day or a smoking history ≥ 10 pack-years, in which case, the PFTs should be done within 6 months prior to Screening). A high-resolution chest computed tomography within 1 year of Screening indicating no more than minimum emphysematous or interstitial changes may be used to satisfy this requirement.

6. Documentation in the participant's medical history that CTEPH has been excluded.

7. 6MWD ≥ 150 m and ≤ 500 m repeated at least twice during Screening and top two values within 15% of each other, calculated from the highest value.

8. A stable dose of at least 2 SOC PAH vasodilator class therapies (as defined in Section 6.9.5) for 60 days prior to Screening (for infusion prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice)

Other Inclusion Criteria:

9. BMI 16 to 35 kg/m^2.

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

5.4. Exclusion Criteria: Part B, Participants with PAH

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

Medical Conditions:

1. Any 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.

    - Participants with seasonal allergic disease or with allergic reactions to a single avoidable allergen (eg, peanuts, bee stings) may be eligible.

    - History of HIV infection, HIV infection associated with PAH; active or latent infection with hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed. (People with a history of hepatitis C with documentation of completion of treatment and deemed to be cured are eligible.) See Section 8.3.11 for details on testing for hepatitis.

- Evidence of active, latent, or inadequately treated infection with Mycobacterium TB as defined by either of the following:
  - A positive IGRA (eg, QuantiFERON-TB Gold In-tube, T-Spot, or equivalent test) should be performed within the 12 weeks prior to screening. If the laboratory reports the test as indeterminate, the test should be repeated.
  - History of either untreated or inadequately treated latent or active TB infection, or current treatment for the same.
- Known history of portal hypertension or chronic liver disease, including hepatitis Band/or hepatitis C (with evidence of recent infection and/or active virus replication), defined as mild to severe hepatic impairment (Child-Pugh Class A-C).
- History of more than mild, treated, obstructive sleep apnea.
- History of known pericardial constriction.
- History of recent cerebrovascular accident (CVA) within 3 months of Day 1.
- History of restrictive or congestive cardiomyopathy.
- History of personal or family history of long QTc syndrome or sudden cardiac death.

2. Stopped receiving pulmonary hypertension chronic general supportive therapy (eg, diuretics, oxygen, anticoagulants, digoxin) within 90 days prior to Screening.
3. History of atrial septostomy within 180 days prior to Screening.
4. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to Screening or planned initiation during the study (participants who are stable in the maintenance phase of a program and who will continue for the duration of the study are eligible).
5. PCWP/ Pulmonary Arterial Occlusion Pressure (PAOP) > 15 mmHg on RHC conducted during Screening.
6. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain).
7. Acutely decompensated heart failure within 30 days prior to Screening, as per investigator assessment.

8. Significant (≥ 2+ regurgitation) mitral regurgitation (MR) or aortic regurgitation (AR) valvular disease.

9. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in investigational product.

10. Major surgery within 8 weeks prior to randomization. Participants must have completely recovered from any previous surgery prior to randomization.

11. Prior heart or heart-lung transplants, active on the lung transplant list, or life expectancy of < 12 months.

12. History of active malignancy, with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin.

13. History of clinically significant (as determined by the investigator) non-PAH related cardiac, endocrine, hematologic, hepatic, immune, metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or other disease that may limit participation in the study.

Prior/Concomitant Therapy:

14. Current use of any prohibited concomitant medication(s) or participants unwilling or unable to use a required concomitant medication(s). Refer to Section 6.9.

Prior/Concurrent Clinical Study Experience:

15. 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) and not concurrently involved in a clinical trial with another investigational product during the study.

Diagnostic Assessments:

16. Uncontrolled systemic hypertension as evidenced by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg during Screening after a period of rest.

17. Systolic BP < 90 mmHg during Screening or at baseline.

18. ECG with QTcF >490 msec during Screening or Randomization.

19. Any of the following clinical chemistry values during Screening:

    - ALT or AST > 3× ULN (> 5 ULN if solely due to right heart failure) or total bilirubin ≥2 × ULN (For Gilbert's syndrome, direct bilirubin >ULN [or ≥ 2 x ULN if solely due to right heart failure] is exclusionary).

- eGFR < 30 mL/min/1.73 m2 within 30 days prior to randomization or required renal replacement therapy within 90 days of randomization.

20. Hematologic abnormalities defined as:

    - Platelets ≤ 50,000/mm^3

Other Exclusion Criteria:

21. A positive urine drug test. A single repeat for positive drug screen may be allowed. A positive test for cannabinoid-based compounds (eg, THC, CBD, etc) will not be considered exclusionary.

22. Participants with a diagnosis of COPD or other clinically significant lung disease.

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

5.5. Lifestyle Considerations

5.5.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.5.2. Meals and Dietary Restrictions (Part A only)

The following requirements apply ONLY while Part A participants are confined in CRU:

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations. Water is permitted without restriction.

- Breakfast is allowed on dosing days. Breakfast must be completed post-baseline safety measurements (eg. vital signs, ECGs, etc) but prior to dosing.

- Noncaffeinated drinks may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing, on dosing days. Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

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

5.5.3. Caffeine, Alcohol, and Tobacco (Part A only)

The following requirements apply while Part A participants are confined in CRU:

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

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample while confined in the CRU. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Smoking may be allowed according to CRU practices. Smoking will not be permitted during frequent sampling procedures and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Smoking will also not be permitted 2 hours before and 2 hours following the Day 1 dose of study intervention. Use of orally-consumed (eg, nicotine gum and chewing tobacco) and transdermal nicotine (eg, nicotine patch) products are prohibited throughout the duration of clinical confinement and for at least 24 hours (at least 48 hours for ≥ 24 hour sustained release transdermal preparations) prior to any clinic visit.

5.5.4. Activity (Part A only)

The following requirements apply while Part A participants are confined in CRU :

- 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;

- Participants will be confined to the procedure room for the first 2 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 ECG 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).

5.6. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once based on investigator's discretion if there was a reasonable reason for failure (eg. use of prohibited concomitant medications that is not washed out, intercurrent infection, etc.). However, for participants who have met the criteria for participation during Screening but the screening falls outside the Screening window, they may be rescreened.

Participants who would fail Screening based on a single laboratory test with abnormal results (if considered by the investigator to be transient and inconsistent with the participant's clinical condition) may be repeated within the Screening window to confirm abnormal results. If results return to protocol acceptable limits within the Screening period, the participant may enter the study. A delay in randomization up to 7 days beyond the Screening period in order to obtain results from repeat laboratory testing, ECG, or to perform required Screening activities, eg RHC, PFTs, or 6MWT (with Sponsor agreement) will not be considered a protocol deviation.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07868489 and placebo for PF-07868489 administered.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	PF-07868489	Placebo
Type	Biologic	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	PF-07868489 (anti-BMP9) solution for injection 100 mg/mL (single use only)	Placebo solution for injection (single use only)

Study Intervention(s)		
Unit Dose Strength(s)	100 mg/vial	Placebo
Dosage Level(s)	As per Part A and Part B schemas	As per Part A and Part B schemas
Route of Administration	SC	SC
Sourcing	Provided Centrally by the Sponsor. Refer to the IPM for more information.	Provided Centrally by the Sponsor. Refer to the IPM for more information.
Packaging and Labeling	Study intervention will be provided in 6-ml vials with 1.4 ml fill volume. Each vial will be labeled as required per country requirement.	Study intervention will be provided in 6-ml vials with a 1.4 ml fill volume. Each vial will be labeled as required per country requirement.
SRSD	IB	NA
Current/Former Name(s) or Alias(es)	NA	NA

Study Arm(s) Part A		
Arm Title	Experimental	Placebo
Arm Description	Participants in various cohorts will receive single doses of PF-07868489 according to Part A schema	Participants in various cohorts will receive single doses of placebo according to Part A schema

Study Arm(s) Part B		
Arm Title	Experimental	Placebo
Arm Description	Participants will receive doses of PF-07868489 Q4W according to Part B schema	Participants will receive doses of placebo Q4W according to Part B schema

PF-07868489 and matching placebo vials will be supplied by Pfizer as individual sterile vials, which are labeled according to local regulatory requirements, for constitution/reconstitution and subsequent unit dosing, as appropriate.

6.1.1. Administration

Planned PF-07868489 and placebo will be administered SC.

Part A

Participants will receive study intervention as an SC injection at approximately 0800 hours (plus or minus 3 hours). SC injections can be administered in the abdomen, thigh, back of the arms. The preferred body location for the SC injection is the abdomen. If abdominal injections are not possible, arm or thigh locations may also be used. For Part A, the same injection location must be used if multiple injections are required.

Part B

Study intervention should be administered as 2 SC injections every 4 weeks. SC injections can be administered in the abdomen (excluding the 5 cm around the navel), thigh, or upper arm. The preferred body location for the SC injection is the abdomen. The injections can be rotated with each administration for participant comfort.

Refer to the IP manual for details regarding the injection sites and volumes for administration. Signs of infection, inflammation, or injection site reactions in the injection area after discharge should be reported.

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for at least 60 minutes by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IP manual for storage conditions of the study intervention and/or dilution.

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

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

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

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

6.2.1. Preparation and Dispensing

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

See the IP manual 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.

Part A

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. Blinded study intervention will be administered in a blinded fashion to the participant.

Part B

Study intervention and placebo will be prepared by qualified blinded site personnel according to the IP manual. Blinded study intervention will be administered in a blinded fashion to the participant.

6.3. Assignment to Study Intervention

6.3.1. Part A

All participants will be assigned to a randomization list provided to the site by the sponsor. The randomization list will be provided directly and securely to the site, or the site will be provided blind-break envelopes (per randomization number) specifically intended for randomization use. The randomization or blind-break envelopes must be kept by the investigator (or unblinded representative) in a secure location. Once the study is complete, the randomization list or all blind-break envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

Study intervention will be dispensed at the study visit summarized in the SoA.

6.3.2. Part B

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual (Part B only) and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

Part A is a sponsor-open.

Part B is a double-blind study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Part A

Investigators and other site staff will be blinded to participants' assigned study intervention, except for personnel involved in preparation of study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Site staff responsible for receiving, storing, dispensing, and preparing the study intervention will be unblinded.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Part B

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

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

The sponsor staff involved directly with the conduct of the study will be blinded to participants' assigned study intervention in Part A and all sponsor staff will be blinded in Part B.
Sponsor staff who are not directly involved with the conduct of this study will review protocol deviations in an unblinded manner while the study is ongoing.

Sponsor staff who are not directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data while the study is ongoing to support interactions with the IRC (Part B)/regulatory submissions/other reasons.

Part A

The sponsor staff involved directly with the conduct of the study will be blinded to participants' assigned study intervention in Part A.

Sponsor staff who are not directly involved with the conduct of this study will review protocol deviations in an unblinded manner while the study is ongoing.

As Part A of the study is a sponsor-open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose -escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

Part B

All sponsor staff involved directly with the conduct of the study will be blinded to participants' assigned study intervention.

6.4.4. Sensitive Clinical Data

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variables are considered sensitive clinical data:

- Target engagement biomarker (after randomization)
- NT-proBNP (after randomization)

6.4.5. Breaking the Blind

Part A

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 study medical monitor 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 CRF.

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

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.

Part B

The IRT will be programmed with blind-breaking instructions. 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 study medical monitor 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. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

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

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

6.6. Dose Modification

Part A

The decision to proceed to the next dose level of PF-07868489 (either an increase or a decrease) will be made by the study team and the investigators based on safety, tolerability, and preliminary PK data obtained at the prior dose level as described in Section 4.1. Provided no safety concerns or AEs suggesting limits of tolerability have been reached in the current or preceding cohorts, dose escalation may proceed if at least 14 days of safety and 7 days of PK data are available from all 4 participants in Cohort 1, at least 4 (at least 1 placebo) of 6 participants in Cohorts 2 and 3 and at least 6 (at least 1 placebo) of 8 participants in Cohorts 4 and 5. The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, PK, and/or target engagement findings at a given dose level or to add cohorts to evaluate up to 2 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.

Part B

While there are no prespecified dose modifications of study treatment on an individual participant basis, reductions in dose or changes in number of injections per dose and/or changes in dose volume may be considered for tolerability issues with discussion and agreement with Sponsor. See Section 4.1.2.

6.6.1. Dose Escalation and Stopping Rules

Part A

Dose escalation stopping rules will be used to determine whether it is safe to proceed to next dose. 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, in the same organ class, indicating dose-limiting intolerance.

- 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, C_{max} of 946 µg/mL or AUC_{168} of 89500 µg•hr/mL.

- If, based on the observed data, the group mean 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.

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

Part A

Not applicable.

Part B

Participants who have agreed to enter the open label extension, will have continued access to study drug.

6.8. Treatment of Overdose

For this study, any dose of study intervention that could potentially lead to exposures of PF-07868489 that would exceed the NOAEL in the GLP toxicity study would be considered as overdose. Since study intervention is blinded, this would in practice manifest as an administered dose of 12 mL (1200 mg) assuming the maximal concentration of IP (100 mg/mL) within a 30-day time period [±3 days] will be considered an overdose.

There is no specific treatment for an overdose. General supportive care should be provided as needed.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

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

Treatments taken within 28 days before 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.

6.9.1. Prohibited During the Study – Part A

Participants are required to discontinue and avoid using certain medications and treatments. Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications. Use of prescription drugs are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention or as noted below.

Prohibited medications during the study include:

- Oral and parenteral corticosteroids within 4 weeks prior to the first dose of study intervention.

- Oral and parenteral anti-infectives within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study intervention.

- Herbal and prescription medications for treatment of chronic diseases including but not limited to hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease.

- Any other prescription or OTC medications that are known to have an effect on drug metabolism must be discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of study intervention.

- Any other investigational drug(s) within 4 weeks of the first dose of study intervention or 5 half-lives (whichever is longer), or at any time during the study.

A protocol deviation is to be completed for any participant that takes a prohibited treatment or medication during the study and the sponsor is to be notified.

6.9.2. Permitted During the Study – Part A

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.

The following concomitant therapies are permitted during the study:

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

- Vitamins, minerals, and purified food substances of standard potency are allowed in amounts known not to be associated with adverse effects (such as hypervitaminosis).

- Acetaminophen may be used intermittently (not to exceed 2.5 g/day).

- Inhaled treatments (eg, ICS/LABA combination treatments, inhaled nasal corticosteroids) and antihistamines for allergic rhinitis.

- Other OTC formulations (including but not limited to herbal supplements, syrups, suspensions, medicated creams, analgesics, antipyretics, antacids, etc.) believed to not have any effect on drug metabolism or affect the primary endpoints of the study may be permitted on a case-by-case basis following approval by the investigator.

- Unless a prohibited medication or treatment, participants may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician.

- 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 CRU 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.

- Participants should report any changes to permitted medications during the study to the investigator as soon as they occur. Medication changes must be documented in the participant's record and CRF.

- Unless a prohibited medication or treatment, participants may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1 up to 3 months post first dose, the addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

A protocol deviation is to be completed for any participant that takes a prohibited treatment or medication during the study and the sponsor is to be notified.

6.9.3. Prohibited During the Study – Part B

- Sotatercept or other activin inhibitors or ligand trap molecules

6.9.4. Prohibited Prior Treatments-Part B

- Sotatercept or other activin inhibitors or ligand trap molecules (patients who responded to sotatercept, but lost access or who needed to discontinue sotatercept due to an AE related to its MOA, may be eligible for participation with discussion and agreement of Sponsor).

- Any other investigational drug(s) within 4 weeks of the first dose of study intervention or 5 half-lives (whichever is longer), or at any time during the study.

A protocol deviation is to be completed for any participant that takes a prohibited treatment or medication during the study and the sponsor is to be notified.

6.9.5. Permitted PAH Therapies During the Study-Part B

Participants should be on stable (for at least 60 days prior to screening) doses of at least 2 of the following classes of PAH vasodilator treatments:

- ERAs

- PDE5 inhibitors

- Guanyl cyclase activators

- Prostanoids- oral, inhaled, parenteral (for IV prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice).

The following adjunctive PAH treatments are permitted as concomitant medications during the study provided the dose has been stable (for at least 60 days prior to Screening):

- Low flow (≤ 4 L / min) nasal oxygen
- Digoxin
- Diuretics
- Anticoagulants

6.9.6. Other Permitted Therapies During the Study-Part B

The following concomitant therapies are permitted during the study:

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).
- Vitamins, minerals, and purified food substances of standard potency are allowed in amounts known not to be associated with adverse effects (such as hypervitaminosis).
- Acetaminophen may be used intermittently (not to exceed 4 g/day).
- Inhaled treatments (eg, ICS/LABA combination treatments, inhaled nasal corticosteroids) and antihistamines for allergic rhinitis.
- Other OTC formulations (including but not limited to herbal supplements, syrups, suspensions, medicated creams, analgesics, antipyretics, antacids, etc.) believed to not have any effect on drug metabolism or affect the primary endpoints of the study may be permitted on a case-by-case basis following approval by the investigator.
- All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

6.9.7. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07868489; standard medical supportive care must be provided to manage the AEs.

Part B only: Participants randomized are required to be taking a combination at least 2 approved vasodilator drugs for PAH of different classes (noted in Section 6.9.5). In addition, participants enrolled into the study are allowed to take other treatments for their disease as prescribed by the investigator, provided they are not included among the prohibited concomitant medications (noted in Sections 6.9.3 and 6.9.4) and the concomitant drugs and

doses are maintained unchanged throughout the active treatment period (first 24 weeks) of the study.

Although no specific rescue treatment is recommended, participants with PAH randomized into Part B of the study may have access to other standard of care therapies for PAH, that may include prohibited treatments and medications, or may change doses of their concurrent background treatments for PAH, if deemed necessary by the investigator to treat their underlying disease. If possible and clinically appropriate, such modifications in background PAH should be deferred until completion of Week 24 study procedures. Participants who change or add treatments for PAH during the active treatment period will be discontinued from study treatment and enter the follow-up period for safety surveillance (unless the participant withdraws consent).

The study site will not supply rescue medication.

The date and time of additional / revised PAH medication administration as well as the name and dosage regimen of the medication must be recorded.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE
- Physician's decision
- Pregnancy
- Study terminated by Sponsor
- Withdrawal by participant
- Lost to follow-up
- Protocol deviation

Part B only

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study, complete the EOT visit 4 weeks after the study treatment has been discontinued prior to entering the specified follow-up period. See the SoA 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, further study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-Up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include PE, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult Participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either new-onset or worsening albuminuria or proteinuria are detected

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. Liver Injury

A participant who meets the criteria as described in Appendix 6 will be withdrawn from study intervention.

7.1.3. 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 ms.
- Change from baseline QTcF >60 ms and QTcF >450 ms.

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.

7.1.4. Pregnancy

Pregnancy tests are conducted at each visit and dosing of study intervention will occur only in the presence of a negative pregnancy test. If a participant is confirmed to be pregnant (see Section 8.3.6) during any visit, further dosing with study intervention, as applicable, will be discontinued immediately and permanently.

Section 8.4.5 Exposure During Pregnancy describes the follow-up activities if a participant meets the EDP criteria.

7.1.5. Lack of Efficacy (Part B only)

The PI has the discretion to make changes in or additions to a participant's background SOC PAH treatment any time during the study if needed to treat the participant's underlying PAH. If these changes to background PAH treatment are made during the active treatment period, study intervention is to be permanently discontinued and the participant should enter the specified follow-up period (unless the participant withdraws consent).

7.1.6. Individual Participant Study Intervention Stopping Criteria

Any participant who develops a CTCAE Grade 3 or higher TEAE in any SOC should be withdrawn from study intervention. The participant would then enter the follow-up period. The AE should be monitored until resolved or deemed clinically stable by the investigator

7.1.7. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.1.8. Temporary Discontinuation

If a scheduled second or third, etc. dosing visit window (approximately a week) is missed, this will be considered a temporary study intervention interruption and a protocol deviation. The participant will be contacted, and further dosing decisions will be based on discussions between investigator and sponsor.

7.1.9. Rechallenge

Participants who may have had mild/moderate injection site reactions, may receive repeat doses of study intervention unless deemed inappropriate in the opinion of the PI.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and - 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 from the study intervention and the study at that time.

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or 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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

Part A only:

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

Part B only:

Participants will be screened within 35 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 35 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.

Parts A and B:

Laboratory, analyte results (eg, PK, NT-proBNP, target engagement) that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until after the study has been unblinded.

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 180 mL for Part A and 390 mL for Part B. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.1.1. Spirometry

Spirometry, if necessary, will be performed prior to randomization, after the participant has met all other inclusion / exclusion criteria (except those obtained by 6MWT and RHC). It must be performed by trained personnel using standard equipment and techniques in accordance with current ERS/ATS guidelines for measurement of lung volume and interpreted using relevant standard reference values. Data from the spirometry testing will be used to assess eligibility criteria and kept as source documentation. If spirometry is not necessary, historical evidence of the participant's meeting lung function eligibility requirements should be documented in source. performed as part of the participant's usual medical care or as part of the diagnostic assessment of PAH within 1 year of Screening may be used to assess eligibility, provided such data are available in source documentation.

8.2. Efficacy Assessments (Part B only)

Planned time points for all exploratory PD and efficacy assessments are provided in the SoA.

8.2.1. Pulmonary Vascular Resistance by Right Heart Catheterization

Pulmonary vascular resistance (PVR) will be measured by right heart catheterization (RHC) during the Screening period and at the Week 24 visit in accordance with the site's/investigators standard practice (SOPs). The RHC should be performed after confirmation of all other eligibility criteria and within 2 weeks of randomization. The RHC may be performed within -10 to + 5 days of the Week 24 visit. Data from RHC performed as part of the participant's usual medical care or as part of the diagnostic assessment of PAH within 12 weeks of signing the ICD may be used to assess eligibility, provided required data are available for entry into the CRF.

In addition to PVR, the RHC will also assess the following hemodynamic variables:

- RAP, mean PAP, mean PCWP / PAOP, RV SBP, RV DBP, HR
- CO is measured in triplicate either by the Fick method or by the thermodilution method. The same method is to be used at the Screening and Week 24 or ED visits.

These hemodynamic parameters are to be assessed when the participant is at a stable hemodynamic rest state which is defined as 3 consecutive mean PAP and CO measurements within 10% of each other.

PVR is to be calculated and entered in the CRF.

The acquired RHC data, as available, may be reviewed centrally to confirm pulmonary vascular hemodynamic measurements. If performed, details of the central review will be provided separately.

8.2.2. 6-Minute Walk Test

The 6MWT is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes.[18] The 6MWD (distance traveled in meters) provides a measure for integrated global response of multiple cardiopulmonary and musculoskeletal systems involved in exercise. The 6MWT should be performed in accordance with the PI's usual procedure. The 6MWT is to be performed at least twice during the Screening Period at least 4 hours (but no longer than 1 week) apart and distances must be within 15% of each other, calculated from the higher number. The 6MWT is to be performed at Screening, and as additional time points per SoA. If occurring on the same day, 6MWT should be performed before RHC. Detailed instructions on conducting the 6MWT will be provided separately.

The Borg CR10 scale® will be completed before and after each 6MWT as specified in the SoA. (See Section 8.2.4.6.)

8.2.3. WHO Functional Class Assessments

The WHO class system is used to provide information about how affected an individual is by their disease according to 4 functional classes that are detailed in the table below. The WHO functional assessment is to be completed as per the SoA for Part B.

WHO Functional Class Assessment for Pulmonary Arterial Hypertension

WHO Class	Description
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

8.2.4. Quality of Life Assessments

PROs are administered at timepoints as specified in the SoA and should be collected before the participant has had significant interactions with site personnel with the exception of the Borg CR 10 scale® which is to be completed before and after each 6MWT (See Section 8.2.4.6.)

8.2.4.1. SF-36 assessment

The 36-Item Short Form Survey (SF-36) is an outcome measure instrument for the objective measure of the quality of life. It comprises 36 questions that cover eight domains of health:

1) Limitations in physical activities because of health problems.

2) Limitations in social activities because of physical or emotional problems

3) Limitations in usual role activities because of physical health problems

4) Bodily pain

5) General mental health (psychological distress and well-being)

6) Limitations in usual role activities because of emotional problems

7) Vitality (energy and fatigue)

8) General health perceptions

8.2.4.2. EQ-5D-5L

The EQ-5D-5L is a self-assessed, health-related, quality of life questionnaire. The scale measures quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a scale that describes the degree of problems in that area (ie, I have no problems walking about, slight problems, moderate problems, severe problems, or unable to walk). This tool also has an overall health scale where the rater selects a number between 0-100 to describe the condition of their health, 100 being the best imaginable.

8.2.4.3. PAH-SYMPACT

A multi-domain PRO that includes assessments of cardiopulmonary, cognitive/emotional and physical impact symptoms.

8.2.4.4. PGI-S

The Patient Global Impression of Severity (PGI-S) consists of 1 question that asks the participant to evaluate the severity of their PAH symptoms over the past 7 days, on a 5-point verbal response scale that ranges from “None” to “Very Severe”.

8.2.4.5. PGI-C

The Patient Global Impression of Change (PGI-C) consists of 1 question that asks the participant to evaluate the change in the severity of their PAH symptoms since the start of the study medication, on a 5-point verbal response scale that ranges from “much better” to “much worse”.

8.2.4.6. Borg CR10 scale®

This scale is used to assess the perceived exertion and fatigue, breathlessness and difficulties breathing (dyspnea). The scale will be completed before and after each 6MWT as specified in the SoA.

8.3. Safety Assessments

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

If multiple procedures are scheduled at the same time, vital signs (BP, pulse, RR) and ECGs should be done before collection of blood specimens.

8.3.1. PEs

A complete PE is to be performed at Screening and brief PE is to be performed at all other visits as per the SoAs.

A complete PE will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, skin, and neurological systems.

A brief PE will be focused on general appearance, skin, and the respiratory and cardiovascular systems, and as guided by participant-reported symptoms.

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

Height will be measured and recorded in cm and accuracy to the nearest 0.1 cm at the Screening visit only. Body weight will be measured as per the SoAs, in kg, and accuracy to the nearest 0.1 kg. 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.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

For Part B, any physical exam findings related to the participant's underlying disease, and any chronic skin lesions should be recorded in the Past Medical History CRF.

8.3.2. Vital Signs

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

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Sitting or semi-recumbent BP and PR will be measured with the participant's arm supported at the level of the heart with feet flat on the floor and back supported and recorded to the nearest mm Hg after approximately 5 minutes of rest in a quiet setting without distractions. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. The same position should be used for all assessments for a given participant.

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 PR is acceptable; however, when done manually, PR 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 PR should be obtained prior to the nominal time of the blood collection.

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

8.3.2.1.1. Part A

BP and PR will be taken before blood collection for laboratory tests and consist of a single measurement of PR and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 2 minutes apart) on Day 1 pre-dose. A single BP measurement will be taken at all other visits. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP readings will be recorded on the CRF.

8.3.2.1.2. Part B

BP and PR will be taken before collection for laboratory tests and consist of a single BP and PR measurement.

8.3.2.2. Respiratory Rate

8.3.2.2.1. Part A

RR will be measured after approximately 5 minutes of rest in a semi-recumbent or seated 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.

8.3.2.2.2. Part B

RR measurements will be assessed in a semi-recumbent or seated position after approximately 5 minutes of rest. RR findings collected during the study will be collected on the CRF for Part B.

8.3.2.3. Oxygen Saturation: Part B-Participants with PAH

Oxygen saturation will be collected at times specified in the SoA by pulse oximetry and findings collected during the study will be collected on the CRF.

8.3.2.4. Temperature: Part A Only

Temperature will be measured by an oral, tympanic, forehead or temporal artery method, provided the same method is used consistently throughout the study. No eating or drinking is allowed for 15 minutes prior to the measurement. Smoking is not allowed for 2 hours prior to the measurement.

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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

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

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

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

8.3.3.1. Part A

Triplicate 12--lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day 1 will serve as each participant's -time-controlled baseline QTcF value.

8.3.3.2. Part B

Single ECGs will be collected as per SoA. A triplicate ECG will be collected on Day 1. ECGs should be performed prior to 6MWT.

8.3.4. Continuous Cardiac Monitoring by Telemetry (Part A only)

Telemetry will be collected in Part A Cohorts (Cohorts 1-8) only. All abnormal rhythms will be recorded and reviewed by the investigator for the presence of rhythms of potential clinical concern. The time, duration, and description of any clinically significant events 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 cardiac monitoring by 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 prior to dosing while participants are awake. 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. Post-dose telemetry will continue for 2 hours after dosing on Study Day 1 and for 2 hours on Study Day 5 and 8.

8.3.5. Clinical Safety Laboratory Assessments

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

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

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

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

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

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

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.

8.3.5.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations may be conducted at a local laboratory, during a mobile visit, or at-home if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology;
- Blood chemistry;
- Urinalysis;
- Coagulation;
- HIV, HBV DNA (see Appendix 2);
- Pregnancy test.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.6. Pregnancy Testing

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

8.3.6.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at-home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3.7. Anaphylaxis Reaction Monitoring

Participants will be monitored for at least 60 minutes after IP administration on dosing days for signs and symptoms of potential anaphylaxis.

All anaphylactic reactions will be assessed by the Pfizer clinical team according to Sampson's criteria.[16]

8.3.8. Injection Site Reactions

An ISR observed at the clinical study site or reported by a participant after they leave the investigative site (delayed reaction) should be reported as an AE. Injection site reaction manifestations including but not limited to erythema, swelling, bruising, pain, or pruritus should be reported in the database. ISR manifestations should be treated according to the investigator's standard of care.

8.3.9. Interferon Gamma Release Assay Tuberculin Test (Screening only)

All participants will be screened for infection with TB using an approved IGRA TB assay.

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Participants with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, participant would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

Participants adequately treated in the opinion of an appropriately qualified personnel (eg, a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of IGRA results provided the treatment is well documented in the participant's medical records and/or source documentation prior to enrollment in the study and a negative chest x-ray is secured.

A participant who is currently being treated for active or latent TB infection must be excluded. See Appendix 2.

8.3.10. HIV (Screening only)

All participants will be screened for HIV. See Appendix 2.

8.3.11. Hepatitis

All participants will be tested for Hepatitis B and C at Screening. See Appendix 2.

Participants must undergo testing for HBsAg, HBcAb, and HBsAb.

- Participants who are negative for all 3 serology tests may be eligible.
- Participants who are HBsAg positive will be excluded.
- Participants who are HBsAg negative, HBcAb positive, and HBsAb negative will be excluded.
- Participants who are HBsAg negative, HBcAb negative, and HBsAb positive and provide written documentation of prior HB vaccination, may be eligible.
- Participants who are HBsAg negative, HBcAb negative, and HBsAb positive without documentation of prior HB vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at Screening. If HBV DNA is detectable, participants will be excluded. If HBV DNA is not detectable, participants may be eligible. If enrolled, HBV DNA will be assessed at least every 12 weeks.

Participants must undergo testing for HCVAb.

- Participants who are HCVAb negative may be eligible.
- Participants who are HCVAb positive will be reflex tested for HCV RNA. If HCV RNA is detectable, participants will be excluded. If HCV RNA is not detectable, participants may be eligible.

Hepatitis testing (HBsAg, HBcAb, HBsAb, HBV DNA, HCV Ab, and HCV RNA) will be performed by the central laboratory. HBV DNA testing may be performed locally if a country requirement.

8.3.12. Clinical worsening – Part B only

Clinical worsening is defined by the occurrence of one or more of the following:

- Death
- Atrial septostomy
- Lung transplantation, or listing for lung or heart/lung transplantation for progressive PAH
- Initiation of intravenous or subcutaneous prostanoids, or other approved PAH treatment or

- Hospitalization for exacerbation of PAH
- Other worsening of pulmonary arterial hypertension (PAH), including increase in WHO Functional Class and confirmed (on repeat measurement) decrease in 6MWD ≥ 15%.

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of approximately 5 half-lives after the last administration of the study intervention.

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

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

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

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

If a participant permanently discontinues or temporarily discontinues study 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 information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.6.

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and

obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

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

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using 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 at least 5 terminal half-lives 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 an 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 report 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- report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

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

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not

pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Death due to worsening PAH (as opposed to other causes of death), should be captured as clinical worsening AEs in the CRF (See Section 8.3.12).

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

Referral for heart or lung transplantation or atrial septostomy as treatment for worsening PAH should be recorded as AEs in the CRF (See Section 8.3.12).

8.4.8. Adverse Events of Special Interest

Not applicable

8.4.8.1. Lack of Efficacy

AE reporting of "lack of efficacy" is not applicable to this study because efficacy is not expected given the early, pre-approval status of clinical development of PF-07868489.

8.4.9. Medical Device Deficiencies

Not applicable

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples will be collected for measurement of serum concentrations of PF-07868489 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 CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-07868489. Samples collected for analyses of PF-07868489 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Samples collected for measurement of serum concentrations of PF-07868489 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 would 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.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

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

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

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

8.7. Biomarkers

Collection of samples for biomarker research is necessary to meet the secondary endpoint of this study and may be used for further exploratory studies for novel biomarkers associated with cardiac disease.

Blood samples will be collected for biomarker analysis are required and will be collected from participants in this study as specified in the SoA:

- target engagement biomarker
- exploratory biomarkers
- NT-proBNP

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.1. Pharmacodynamic biomarkers

Blood samples will be collected for measurement of plasma or serum concentrations of exploratory biomarkers 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 nominal time relative to dosing.

Samples collected for measurement of plasma or serum biomarker concentrations will be analyzed using a bioanalytical method validated for the context of use. Samples collected for biomarker analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

Samples must be processed and shipped as indicated in the 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.

Biomarker concentration information that would 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.

8.7.2. Target Engagement Biomarker

Blood samples will be collected for measurement of target engagement biomarker as specified in the SoA.

8.7.3. NT-proBNP

Plasma samples will be collected for measurement of NT-proBNP as specified in the SoA.

8.7.4. Specified Gene Expression (RNA) Research

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

8.7.5. Specified Protein Research

Blood samples will be collected for potential exploratory biomarker assessment in serum associated with response as specified in the SoA.

8.7.6. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.7. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- blood for Prep B2.5 optimized for serum
- blood for Prep R1 optimized for serum

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

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

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

See Section 10.5 Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8. Immunogenicity Assessments

Blood samples will be collected for determination of immunogenicity 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.

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

Samples collected for determination of immunogenicity may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes and may not be reported in the CSR.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity 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.

Immunogenicity information that would 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.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

9.1.1. Part A

No formal statistical hypothesis testing will be performed for part A of this study.

9.1.2. Part B

NT-proBNP Endpoint

Null hypothesis for NT-proBNP for Part B of this study is that the mean observed NT-proBNP change from baseline at 24 weeks in PAH patients on PF-07868489 is no different than the mean observed NT-proBNP change from baseline at 24 weeks in PAH patients on placebo. The alternative hypothesis is that mean NT-proBNP levels decline from baseline at 24 weeks for PAH patients on PF-07868489 relative to PAH patients on placebo.

9.1.3. Estimands

Estimands defined below are exclusively for Part B. There are no estimands for Part A.

9.1.3.1. Primary Estimand/Coprimary Estimands

E1 (primary analysis estimand): The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in NT-proBNP at Week 24 in PAH patients. This analysis will utilize the Hypothetical approach, excluding data after use of rescue medications prior to week 24 and after study treatment discontinuation.

9.1.3.2. Secondary Estimands

E2 (secondary efficacy estimand): The estimand is the difference between the PF-07868489 and placebo in mean change from baseline in PVR at Week 24 in PAH patients. This analysis will exclude data after use of rescue medications and after study treatment discontinuation.

9.1.4. Multiplicity Adjustment

Not applicable.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process.
PK Population	The PK concentration population is defined as randomized participants who received at least one dose of PF-07868489 and have at least 1 evaluable concentration. The PK parameter population is defined as all randomized participants who received at least one dose of PF-07868489 and have at least 1 evaluable PK parameter
PD-Biomarker Population	The PD-Biomarker population is defined as all randomized participants treated who have at least one evaluable NT-proBNP result
PD-Hemodynamic	The PD-Hemodynamic population is defined as all randomized participants treated who have at both PVR measurements (pre- and post-baseline)
Safety analysis set	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.
Per-protocol Population	All PAH patients in the PD population with no PIPDs. Patients will be analyzed according to randomized treatment assignment.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Data will be presented – ie, listed and summarized – by treatment and overall. Continuous data will be summarized comprising mean, median, standard deviation, minimum and maximum. Categorical and binary data are summarized will be done via percentages.

9.3.1.1. Analyses for Longitudinal Continuous Endpoints

Linear mixed models will be used. The fixed effects of treatment, visit, and treatment-by-visit interaction will be included. Visit will be modeled as a categorical covariate. Unstructured covariance matrix will be assumed for the model errors. If the above model does not converge, random intercepts and slopes models with different covariance matrix specifications (eg, compound symmetry) will be tried. Moreover, a visit could be treated as a continuous covariate. Details regarding additional specifications will be described in the SAP.

When modeling the change from baseline values, the variable for visit will start with the first post-baseline visit. At each visit, estimates of least square mean (LSM) values and the LSM differences between treatment groups will be derived from the model. The corresponding p-values and 95% confidence intervals will also be derived from the model.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

9.3.2.1. Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Clinical laboratory tests (eg, hematology [including coagulation panel], chemistry and urinalysis);
- ECG changes from baseline;
- Vital signs.

Change from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.

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

9.3.2.1.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTc Assessment

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

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 QTc 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 post-dose QTc value and the average of the time-matched baseline triplicate values on Day 1, or the average of the pre-dose 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 will be examined. Details of said model and analyses will be elucidated in an analysis plan separate from the SAP.

9.3.2.2. Change in NT-proBNP

9.3.2.2.1. Main Analysis

- Estimand strategy: Hypothetical (Section 9.1.1).
- Analysis set: PD-Biomarker Analysis (Section 9.2).
- Analysis methodology: Change from baseline relative to placebo will be analyzed using a linear mixed model including data from Weeks 4, 8, 12, 16, 20 and 24 with treatment and time and fixed effect (Section 9.3.1) with subject (and/or time) as a random effect and an unstructured covariance matrix for random effects – ie, a random intercepts and slopes model. If the above model does not converge, random intercepts and slope models with different covariance matrix specifications (eg, compound symmetry) will be tried.
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed NT-proBNP and change from baseline will be presented for treatment and placebo.
- The least-squares (LS) means, the 95% confidence interval for the LS means, the difference between the LS means for each treatment arm, and the corresponding 95% confidence interval will be presented for change from baseline in NT-proBNP for all post-baseline visits.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

9.3.3.1. Change in PVR

9.3.3.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 9.1.1).
- Analysis set: PD-Hemo Analysis (Section 9.2).
- Analysis methodology: Observed PVR of treatment relative to placebo will be analyzed using a linear mixed model including data from Pre-baseline and Week 24 with treatment and time and fixed effect (Section 9.3.1) with subject (and/or time) as a random effect and an unstructured covariance matrix for random effects – ie, a random intercepts and slopes model.
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed NT-proBNP and change from baseline will be presented for treatment and placebo.

- The least-squares (LS) means, the 95% confidence interval for the LS means, the difference between the LS means for each treatment arm at each visit, and the corresponding 95% confidence interval will be presented.

9.3.3.2. Immunogenicity

If data permit and applicable, the following data will be summarized and listed:

1. Listing of ADA data
2. % ADA positive participants by visit
3. Incidence of ADA

Additional immunogenicity characterization and analysis of clinical impact on PK, PD, efficacy and/or safety may be assessed as deemed appropriate. Further details will be specified in the SAP.

9.3.3.3. Pharmacokinetic Analysis

The PK parameters to be assessed, their definition, and method of determination are detailed in Section 9.3.6. Actual PK sampling times will be used in the derivation of PK parameters.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

All of the exploratory endpoints including, but not limited, to target engagement biomarkers may be summarized by dose and presented separately by each time point presented in tabular form or graphically. In addition, some of the exploratory endpoints (including, but not limited to 6MWD, RV hemodynamics and PROs) may be analyzed longitudinally to study the effect over time. Participant level exploratory endpoints may also be summarized by treatment. For immunogenicity, effect of positive ADA and neutralizing immune response on safety, and PK may be assessed, if appropriate. Details of the analysis of clinical worsening will be defined in the SAP. These data and any subsequent analyses, if performed, may or may not be reported in the CSR.

9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

9.3.5.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

9.3.6. Pharmacokinetic Analysis

Actual PK sampling times will be used in the derivation of PK parameters. The serum concentration of PF-07868489 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual subject, mean, and median profiles of the serum concentration-time data will be plotted by treatment group using actual (for individual) and nominal (for median) times respectively. Mean and median profiles will be presented on both linear and log scales.

Table 6. Serum PK Parameters

Parameter	Definition	Method of Determination
Single Dose		
AUC_{last}	Concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}[a]	Area under the serum concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{inf}(dn)[a]	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}	Maximum serum concentration	Observed directly from data
C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Log^{e}(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear -concentration-time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression

Table 6. Serum PK Parameters

Parameter	Definition	Method of Determination
CL/F^a	Apparent clearance for SC dosing	$Dose/AUC_{inf}$
V_z/F^a	Apparent volume of distribution following SC dosing	$Dose/AUC_{inf} \times k_{el}$
Multiple Dose		
C_{min}	Lowest concentration observed during dosing interval of 672 hours; if measured at end of dosing interval, equivalent to C_{trough}	Observed directly from data
$t_{½}^a$	Terminal elimination half-life	$Log^e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression

a. If data permits

The PK parameters in Table 6 will be summarized descriptively by treatment group in healthy participants in accordance with Pfizer data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max}.

Where data permit, dose normalized (to a 1-mg dose) C_{max}, AUC_{inf}, and AUC_{last}, will be plotted against dose and administration route, as appropriate for single dose and multiple doses (using a logarithmic scale). The plot will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose and/or administration route.

The PK data from Japanese and Chinese participants will be summarized separately.

9.3.7. Other Analyses

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

9.4. Interim Analyses

An IA may be performed to assess efficacy. IA results may be used for internal business decisions regarding future study planning, stopping for futility, conducting a sample size re-estimation, or to guide decisions regarding the possible crossover of PAH patients from placebo to active treatment. A decision will not be made to declare early success as a consequence of the IA. Participants may be discontinued from the study intervention/study as a result of the IA, as described in Section 7.

Details of the objectives, decision criteria, dissemination plan, timing of any IA and method of maintaining the study blind pertaining to the IA (if applicable) as per Pfizer's SOPs will be documented and approved in ac IRC charter or separate IA plan. Criteria for the possible switching of PAH participants from placebo to PF-07868489 will also be detailed in the IRC charter or separate IA plan. In addition, the analysis details will be documented and approved in the IA plan.

9.5. Sample Size Determination

Part A

No formal sample size calculations were performed for part A. Cohort size of approximately 4 to 8 participants have been chosen to ensure appropriate sample size to provide adequate safety, tolerability and PK information at each dose level and to provide a placebo comparison group, while minimizing exposure to humans of a new biologic entity. A sufficient number of participants will be screened to achieve 4 participants to be randomized in Cohort 1. For Cohorts 2 and 3, 6 participants and for Cohorts 4, 5 and 6, 8 participants will be randomized. Cohorts 7 and 8 will only screen and randomize 5 Japanese and Chinese participants respectively. For the first two cohorts in Part A (Cohorts 1 and 2) participants will be randomly assigned to PF-07868489 or placebo in a ratio of 1:1 and randomization ratio, 2:1 for Cohorts 3 and 4, 3:1 for Cohorts 4, 5 and 6; 4:1 in the Japanese (Cohort 7) and Chinese (Cohort 8) cohort. A total of approximately 36 participants will be randomized (without any optional cohorts) or up to 54 (with 3 optional cohorts) will be enrolled into the study.

Part B

Sample size determination for part B is based on the primary endpoint of change in NT-proBNP, of PF-07868489 vs. placebo which will be evaluated at 24 weeks (Section 9.1.2). Assuming an inter-subject correlation of 0.85, 15% of patients drop out for non-study reasons and a type 1 error rate of .05, a total of 36 PAH patients randomized 1:1 to either PF-07868489 or placebo (to obtain 15 evaluable patients per arm) provides greater than 90% power to reject the null hypothesis – that is, the mean observed NT-proBNP change from baseline at 24 weeks in PAH patients on PF-07868489 is no different than the mean observed NT-proBNP change from baseline at 24 weeks in PAH patients on placebo – when the true difference is that the post-baseline decline of NT-proBNP at least 45% greater than placebo.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC that will serve as an IOC. The IRC is independent of the study team and includes only members employed by the Sponsor but who have no involvement in the conduct of the study. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer

will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.5.2. Steering Committee

A Steering Committee may be established to provide guidance to the team on study conduct and data analysis. If established, additional details will be provided separately in a Steering Committee charter.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.8. Source Documents

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

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

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

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

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

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

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.11. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent, which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

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 o*f analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values; for example: calculation of estimated kidney function (ie,* 2021 CKD-EPI eGFR as standard lab safety test for clinical studies. 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 7. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs, %) Eosinophils (Abs, %) Monocytes (Abs, %) Basophils (Abs, %) Lymphocytes (Abs, %) Coagulation (aPTT, PT/INR)	Urea Creatinine Cystatin C[a] eGFR, eCrCl[b] Glucose[c] Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Alkaline phosphatase Uric acid Albumin Total protein Total bilirubin,[d] CK	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[e]	At screening: • FSH[f] • Urine drug screening [g] • HBsAg, HBcAb, HBsAb, and HBV DNA[h] reflexd • Hepatitis C antibody and HCV RNA reflex • HIV[h] • IGRA (eg, QuantiFERON-TB Gold In-tube, T-Spot, or equivalent) • Pregnancy test (β-hCG)[i]

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. If glucose is elevated in non-fasting blood sample, testing may be repeated under fasting conditions.
d. Reflex testing for direct bilirubin for assessment of Gilbert's Syndrome during screening.
e. Only if urine is positive for nitrites or leukocyte esterase or both.
f. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
g. The minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines (others are site and study-specific). A positive test for cannabinoid-based compounds (eg, THC, CBD, etc) will not be considered exclusionary.
h. HIV and HBV DNA may be completed locally if a country requirement.
i. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. See SoA for collection times.

Table 8. Protocol-Required Laboratory Assessments – Reflex Testing

Hematology	Chemistry	Urinalysis on Site	Other
If Hb/RBC abnormal: MCV, MCH, MCHC RBC morphology RBC distribution width	Required: For suspected DILI: AST/ALT T bili (direct and indirect), albumin, CK, GGT, PT/INR, eosinophils (%), alkaline phosphatase. The following additional testing may be warranted: Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) Total bile acids Liver imaging For suspected DICI/DIKI: Creatinine (Screat) Cystatin C[a] (Scys) eGFR (Screat only and combined Screat+Scys) eCrCl[b] Urine albumin-to-creatinine-ratio (UACR)	**Local Laboratory** Microscopy and culture for positive local dipstick tests[c]	Hepatitis B DNA Hepatitis C RNA

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1).
b. Screening and Baseline eGFR or eCrCl is measured with creatinine (Screat)-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected by the investigator and urine dipstick is positive for nitrites or leukocyte esterase or both. Any positive results are to be reported as an AE.

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.

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

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

10.3.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

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

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

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

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

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

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

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

Follow-Up of AEs and SAEs

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

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is one of the preferred methods to transmit this information to Pfizer Safety.
- Facsimile transmission of the CT SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

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

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 15 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

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

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

2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

  - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

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 UserDependent

6. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*
8. Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

- The samples will be retained as indicated:

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

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

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Section 10.7.2.1.) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[1]

eGFR (mL/min/1.73m²)

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if >0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	if ≤0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate

formula (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 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 asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-second 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 major events of potential clinical concern listed above 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 is to be reported as AEs/SAEs.

10.9. Appendix 9: Country-Specific Requirements

10.9.1. European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents.

The sponsor will notify EU Member States concerned of the following:

- Any SUSAR via reporting to the EudraVigilance database.
- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event.
- Any serious breach, as described in Section 10.1.1.1, no later than 7 days of becoming aware of that breach.
- Any urgent safety measure, as described in Section 10.1.1.1, no later than 7 days of the measure being taken.
- Any inspection report of a third-country authority concerning the study.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

10.9.2. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any sub-investigators will complete the Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No be charged for study intervention.

3. Urgent Safety Measures

   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.

4. Termination Rights

   Pfizer retains the right to discontinue development of PF-07868489 at any time.

10.9.3. China

Retained research samples for genetics (Section 8.6.2) and retained research samples for biomarkers (Section 8.7.7) will not be collected for participants in China.

In compliance with HGRAC regulations, below is the list of vendors in China that will conduct testing and analysis of human genetic resource samples or disposal of remaining samples.

Testing Name	Testing and Analysis Unit	Destruction Unit
Hematology	PPD Laboratories (Suzhou) Co., Ltd.	Zhangjiagang Huarui Hazardous Waste Disposal Center Co., Ltd.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ADA	antidrug antibodies
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AUC_{168}	Area under the curve from time 0 to 168 hours post-dose
AUC_{336}	Area under the curve from time 0 to 336 hours post-dose
AV	atrioventricular
AxMP	auxiliary medicinal product
BA	bioavailability
BE	bioequivalence
β-hCG	β-human chorionic gonadotropin
BioMeT	biometric monitoring technology
BMI	Body Mass Index
BMP	Bone morphogenetic protein
BMPR	Bone morphogenetic protein receptor
Borg CR10®	Borg category-ratio
BP	blood pressure
bpm	beats per minute
BSA	body surface area
C_{av}	average concentration
CBD	cannabidiol
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CMC	Chemistry, Manufacturing and Controls

Abbreviation	Term
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTEPH	Chronic thromboembolic pulmonary hypertension
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DHT	digital health technology
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DRE	disease-related event
DU	dispensable unit
EBV	Epstein-Barr virus
EC	ethics committee
eC	Endothelial cell
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOS	End of study
EOT	end of treatment
eSAE	electronic serious adverse event
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ERAs	Endothelin receptor antagonists
ERS	European Respiratory Society (ERS)
ESR	erythrocyte sedimentation rate
EU	European Union

Abbreviation	Term
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FIH	First in Human
FSH	-follicle stimulating hormone
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GOF	gain of function
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HDL	high-density lipoprotein
HGRAC	Human Genetic Resource Administration of China
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRQL	health-related quality of life
HRT	hormone replacement therapy
HRU	healthcare resource utilization
hs-CRP	high-sensitivity C-reactive protein
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
I/E	Inclusion/exclusion
ILD	Interstitial lung disease
IOC	Independent Oversight Committee
IP	Investigational Product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
ISO	International Organization for Standardization
IV	intravenous

Abbreviation	Term
IWR	Interactive Web--based Response
K	Proportionality constant for Schwartz Equations (kidney function)
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LPD	local product document
LS	least-squares
LSM	Least squares mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MOA	Mechanism of action
mPAP	Mean pulmonary artery pressure
MQI	medically qualified individual
NA	not applicable
NAb	neutralizing antibodies
NCT	National clinical trial
NDCMC	newly diagnosed chronic medical condition
NHP	Non-human primate
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal–pro hormone–B-type natriuretic peptide
O_2	oxygen
OLE	Open label extension
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary arterial hypertension-symptoms and impact
PAWP	Pulmonary arterial wedge pressure
PAOP	Pulmonary Arterial Occlusion Pressure
PBMC	peripheral blood mononuclear cell
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PDE5	Phosphodiesterase 5
PE	physical examination
PFS	prefilled syringe
PFT	Pulmonary function test
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PI	principal investigator
PIPD	Potentially important protocol deviation
PK	pharmacokinetic(s)

Abbreviation	Term
PR	pulse rate
PRO	Patient reported outcome
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
PTA	post-trial access
PTH	parathormone
PVC	premature ventricular contraction
PVR	Pulmonary vascular resistance
Q2W	Administered every 2 weeks
Q4W	Administered every 4 weeks
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
QW	Every week
RBC	red blood cell
RCs	Reaction centers
RHC	Right heart catheterization
RNA	ribonucleic acid
RR	respiratory rate
SAD	Single ascending dose
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
Screat	serum creatinine
Scys	serum cystatin C
SF-36	36-Item Short Form Survey
SMC	Smooth muscle cell
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	Standard of Care
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal elimination half-life
T_3	total triiodothyronine
T_4	total thyroxine
TB	tuberculosis
T bili	total bilirubin
TEAE	Treatment emergent adverse event
T_{max}	time to reach Cmax

Abbreviation	Term
THC	tetrahydrocannabinol
TOC	table of contents
TSH	thyroid-stimulating hormone
UACR	urine albumin/creatinine ratio
UADE	unanticipated adverse device effect
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information
UTI	urinary tract infection
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	Woman/women of non-childbearing potential

11. REFERENCES

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