Title Page

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE DOSE, 2-WAY CROSSOVER STUDY ASSESSING PHARMACOKINETIC COMPARABILITY OF TWO PF-06881894 PRESENTATIONS, ON-BODY INJECTOR AND PREFILLED SYRINGE, IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-06881894
Study Intervention Name:	Pegfilgrastim
US IND Number:	CCI
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
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Phase:	1

Brief Title: Pharmacokinetic Comparability Study in Healthy Participants of PF-06881894 On-Body Injector Relative to Prefilled Syringe

Document History

Document	Version Date
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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Pharmacokinetic Comparability Study in Healthy Participants of PF-06881894 On-Body Injector Relative to Prefilled Syringe

Rationale

The PK comparability of PF-06881894 administered by PFS versus by OBI will be assessed in a single-dose comparative PK evaluation in healthy participants enrolled at approximately 4 CRUs. Assessment of PK using a single-dose study design in healthy participants is expected to be the most sensitive setting to detect intrinsic differences in PK between the OBI and PFS presentations of PF-06881894.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• PK comparability • To assess the PK comparability of PF-06881894 administered by OBI versus PFS as a single SC dose.	• C_{max}, AUC_{last} and AUC_{inf} (if data permits).
Secondary:	**Secondary:**
• To characterize the PK of PF-06881894 OBI dosing presentation to PFS dosing presentation in healthy participants. • To assess the safety (including immunogenicity) of PF-06881894 OBI dosing presentation to PFS dosing presentation in healthy participants.	• T_{max} and $t_{½}$ (if data permits). • AEs, including AESIs and device-related AEs; ISRs and ASRs.

Overall Design

Brief Summary

This will be an open-label, randomized, 2-treatment, 2-period, crossover single-dose study in approximately 134 healthy adult participants. Participants will be randomized into 2 sequences of treatment as described in the following table of Intervention Groups and Duration.

Number of Participants

Approximately 134 participants will be enrolled to study intervention, with 67 participants assigned to each treatment sequence. Dropouts may be replaced at the discretion of the investigator upon consultation with the sponsor.

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

Intervention Groups and Duration

Sequence	Period 1	Washout	Period 2
1 (n=67)	Treatment A	At least 56 days	Treatment B
2 (n=67)	Treatment B	At least 56 days	Treatment A

Treatment A: PF-06881894, OBI, 6 mg administered as a single SC injection
Treatment B: PF-06881894, PFS, 6 mg administered as a single SC injection

Screening evaluation will occur within 30 days prior to the first dose of study intervention in Period 1. Day -1 is defined as the day prior to the first day of dosing (Day 1) in each period. Participants will be admitted to the CRU on Day -2, at 36-42 hours prior to Day 1 dosing, and will remain confined in the CRU until completion of all study activities on Day 5 during each period.

There will be at least a 56-day washout period between administration of each study intervention to ensure the complete elimination of the drug. The total duration of participation in the study for each participant, excluding Screening, is approximately 12 weeks.

On Day -1 of each period, the PF-06881894 OBI will be activated and applied on participants randomized in the OBI arm.

On Day 1 of each period, each participant will receive a single SC dose of 6 mg PF-06881894 administered by OBI or by PFS based on the randomization code. For those doses administered via OBI, removal of the device will occur following completion of the infusion.

The same injection site (left or right side of the abdomen) will be used for both OBI and PFS for each participant, keeping at least 2 inches (5 cm) away from the belly button. The same needle angle (90°) for SC injection will be used for each participant in the OBI and PFS arms.

Blood samples for PK (3.0 mL) will be collected by either intravenous catheter or venipuncture into evacuated collection tubes within 1 hour prior to dose administration (Hour 0) and at 0.167 (10 min), 0.5, 1, 3, 6, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288 hours post-dose. For the OBI treatment period, PK collection should resume 10 min (0.167 hrs) following the start of the injection and continue as shown. This

sample collection scheme will adequately characterize the PK of pegfilgrastim following a single SC dose.

Safety will be assessed for all treatments by monitoring AEs and other parameters defined by protocol such as vital signs, laboratory assessments, etc.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

The serum concentration time data from Day 1 through Day 13 from individual participants will be analyzed by non-compartmental methods to determine the PK parameters. The primary PK parameters to be estimated will include C_{max}, AUC_{last} and AUC_{inf} (if data permits). The secondary PK parameters to be estimated will include $T_{max,}$ and $t_{½}$ (if data permits). Descriptive statistics for the PK parameters will be provided.

Ninety percent (90%) CIs for the test to reference ratios (PF-06881894 OBI versus PF-06881894 PFS) for C_{max}, AUC_{last} and AUC_{inf} will be constructed on a natural log scale using ANOVA with treatment, sequence and period as effects. PK similarity for a given test to reference comparison will be considered to be demonstrated if the 90% CIs for the test to reference ratios of C_{max}, AUC_{last} and AUC_{inf} fall within the 80% - 125% BE window.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

Table 1. Schedule of Activities

		Period 1[a]																Period 2[a]															
Visit Identifier/Study Day (Visit Window)	**Screening [b]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) TC[c]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) or Early Withdrawal[d]**
Informed consent	X[e]																																		
CRU confinement			X	X	X	X	X	X	X											X	X	X	X	X	X	X									
Inclusion/exclusion criteria	X			X																															
Randomization[f]				X																		X													
OBI activated and applied to those randomized to this arm				X																	X														
OBI removal after injection completed, as appropriate					X																	X													
Medical history	X		X[g]																																
Medication history	X		X[h]																																
Physical examination including Spleen Assessment	X																			X															X
Demography	X																																		
Vital signs[i]	X			X	X				X	X	X	X	X	X	X	X	X					X	X			X	X	X	X	X	X	X	X	X	X	X
Height and weight	X																																		
Serology testing	X																																		

Table 1. Schedule of Activities

		Period 1[a]																Period 2[a]														
Visit Identifier/Study Day (Visit Window)	**Screening[b]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) TC[c]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) or Early Withdrawal[d]**
Contraception check[j]	X		X							X	X	X	X	X	X	X	X	X		X							X	X	X	X	X	X	X	X	X
Pregnancy test[k]	X			X																	X													X
FSH[l]	X																																	
Urine drug screening	X	X																X																
Urine cotinine	X																																	
Alcohol screening	X			X																	X													
Chest X-ray	X																																	
Resting 12-lead ECG	X																																	X
CBC, Platelets, and Chemistry Panel[m]	X	X				X		X									X	X				X		X										X
Urinalysis	X																X	X																X
Enzyme/Liver Panel only (ALT, AST, LDH, ALP, GGT, TBili)					X[n]				X			X		X							X[n]				X			X		X				
Study treatment administration					X																X													
Assessment of ISRs and ASRs[o]				X[p]	X	X	X	X	X	X	X	X	X	X	X	X	X				X[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood sampling					X[q]	X	X	X	X	X	X	X	X	X	X	X	X				X[q]	X	X	X	X	X	X	X	X	X	X	X	X		
AE monitoring	To be captured from informed consent through to the Period 2 Day 28 Visit																																	
Concomitant medication	To be captured from informed consent through to the Period 2 Day 28 Visit																																	
Retained Research Sample for Genetics (Prep D1)[r]					X																													
COVID-19 testing[s]	X	X																X																
COVID-19 questionnaire[t]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

		Period 1[a]																Period 2[a]														
Visit Identifier/Study Day (Visit Window)	**Screening[b]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) TC[c]**	**-5 to -4**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**28 (+2) or Early Withdrawal[d]**

a. Washout period between treatments will be at least 56 days.

b. Within 30 days prior to first dose of study intervention

c. Telephone visit.

d. In the event of early withdrawal, the participant is to return for an Early Withdrawal visit (Treatment Period 2 Day 28 procedures) at least 28 days after the last dose of study intervention, otherwise participants will return for their final visit on Period 2 Day 28.

e. Informed consent must be completed before any study related procedures are performed.

f. Period 1 only.

g. Record change(s) in medical history and prior medication since screening (Period 1 only)

h. Complete history of all prescription and non-prescription drugs, herbal medicines, and dietary and herbal supplements taken within 30 days prior to the planned first dose. History of drug, alcohol, and tobacco use will also be collected.

i. Sitting BP, PR, respiratory rate and tympanic temperature. To be obtained prior to any procedures, eg, blood draws.

j. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines, and confirm and document that proper contraception is being used for the participant and their partner as appropriate.

k. Pregnancy test (with sensitivity of at least 25 mIU/mL), for females of childbearing potential only, at Screening and Day -1 in Periods 1 and 2 and at Period 2 Day 28/Early withdrawal. Pregnancy tests may also be repeated as per request of IRB/ ECs or if required by local regulations. Pregnancy test results will be obtained prior to dosing during each period. A negative pregnancy result is required before the participant receives study treatment. In the case of a positive β-hCG test, the participant will be withdrawn from the study (Section 8.2.6).

l. FSH for women < 60 years of age who are amenorrheic for at least 12 consecutive months and not using hormonal contraception or HRT.

m. This should include eGFR and Cystatin-C.

n. Collected pre-dose.

o. Assessment of ASR is only applicable to the period in which administration occurs via OBI.

p. On Day -1, only participants with OBI applied will need assessment of ISRs and ASRs.

q. Predose (Hour 0) blood sample collected within 1 hour prior to dose administration. Hour 0 and at 10 min (0.167), 0.5, 1, 3, 6, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288 hours post-dose. Also, see PK sampling schema (Table 2) for the listing of hours for each day for sample collection. For the OBI treatment period, PK collection should resume 10 min (0.167 hrs) following the start of the injection and continue as shown.

r. Collected pre-dose, and only collected in period 1.

s. Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

t. Check exposure to positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms.

Table 2. PK Sampling Schema – Periods 1 and 2

Visit Identifier																				
Study Day	**1**								**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Hours After Dose	**0[a]**	**0.167**	**0.5**	**1**	**3**	**6**	**12**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**	**264**	**288**
Study treatment administration	X																			
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Predose (Hour 0) sample collection within 1 hr prior to dose administration. For the PFS treatment period, Hour 0 is the time of SC injection. For the OBI treatment period, Hour 0 is the time when the OBI starts the injection; PK collection should resume 10 min (0.167 hrs) following the start of the injection and continue as shown.

2. INTRODUCTION

PF-06881894 (pegfilgrastim), a US FDA approved biosimilar (Brand name: Nyvepria, pegfilgrastim-apgf) to US-approved Neulasta (Amgen, pegfilgrastim), is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

The indications for this leukocyte growth factor are to:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

2.1. Study Rationale

The PK comparability of PF-06881894 administered by PFS versus by OBI will be assessed in a single-dose comparative PK evaluation in healthy participants. Assessment of PK using a single-dose study design in healthy participants is expected to be the most sensitive setting to detect intrinsic differences in PK between the OBI and PFS presentations of PF-06881894.

2.2. Background

Neutropenia is a laboratory diagnosis and is defined as the reduction in the absolute number of neutrophils in the peripheral blood or circulation. Neutrophils are mature phagocytic leukocytes of the granulocyte series; are formed by bone marrow and released into circulation; are the predominant component of circulating white cells, and are the predominant leukocyte involved in inflammation. Circulating neutrophils actually represent only approximately 3% of the body's total neutrophil numbers, with the vast majority in the bone marrow reserve pool and the remainder in the tissue and marginated pool attached to vascular endothelial cells.[1]

Neutropenia is generally characterized as mild, moderate, or severe based on the circulating ANC.[2,3,4]

- Mild neutropenia: ANC 1000-1500/µL;
- Moderate neutropenia: ANC 500-1000/µL;
- Severe neutropenia: ANC <500/µL.

In general, only patients with severe neutropenia have been found to be at risk for major pyogenic infections and life-threatening infections, regardless of the underlying etiology of the neutropenia, congenital or acquired.[2]

Myelosuppressive chemotherapy is an important iatrogenic cause of neutropenia. While within a given individual, many chemotherapeutic agents can be associated with neutropenia, there are a number of agents that are consistently associated with elevated risk for its development. These are consistent with the medical literature as well as national and international guidelines for management of CIN.[3]

Low ANC increases the risk of fevers (febrile neutropenia) and life-threatening infections.[5,6] Febrile neutropenia is defined by the CTCAE Version 4.03, categorized as Grades 3 to 5 as follows:[7]

- Grade 3: ANC <1000/mm^3 (=1000/µL) and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death.

Implications of CIN and febrile neutropenia are manifold and include infection and overwhelming sepsis and its associated complications, including death, increased risk for hospitalization as well as compromised oncologic outcomes including treatment delays, reduction in chemotherapeutic dose, or both. Neutropenia is a common dose-limiting adverse effect. As a result, patients can receive suboptimal cancer therapy leading to compromised outcomes, including increased morbidity and mortality and decreased survival.[5,6,8-11] International guidelines for prevention and management of CIN include the consistent recommendation of use of supportive care with myeloid growth factors in patients undergoing myelosuppressive chemotherapy with a specified threshold of risk, generally of risk for at least 20% of patients receiving the myelosuppressive agent or regimen.[2,11,12]

Endogenous G-CSF is the primary regulating factor for neutrophils. The G-CSF acts by binding to G-CSF receptors located on the cell surface of the whole neutrophil lineage, resulting in stimulated proliferation, differentiation, commitment, and end cell functional activation. Endogenous G-CSF is known to stimulate proliferation of the mitotic cells, to reduce the maturation time of the non-mitotic cells in the bone marrow and to prolong the life-span and enhance the function of mature neutrophils. Endogenous G-CSF is produced by different cell types including macrophages, monocytes, fibroblasts, stromal cells in bone marrow, and endothelial cells. Endogenous G-CSF is triggered by inflammatory agents as well as by lipopolysaccharide released from bacteria.[13]

Recombinant human G-CSFs can vary slightly based on whether it is produced in *Escherichia coli* (filgrastim) or CHO cells (lenograstim).

The filgrastim protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E coli*. Because filgrastim is produced in *E coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell or that of lenograstim.[14,15]

Filgrastim is a water soluble 175 amino acid protein with a molecular weight of approximately 19 kD and is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene.

G-CSFs, including filgrastim and pegylated filgrastim are leukocyte growth factors that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. The half-life of filgrastim is approximately 210 minutes, while pegylated filgrastim ranges from 15 to 80 hours after subcutaneous injection.[14,16] Based on its circulating half-life, filgrastim must be given daily to prevent or treat CIN whereas pegylated filgrastim can be administered less frequently; eg, once per chemotherapy cycle.

Protein pegylation is widely utilized to prolong the circulating half-life of biologic agents. Pfizer has developed a pegylated G-CSF, referred to as PF-06881894. The proposed pegylated recombinant human G-CSF is a covalent conjugate of recombinant methionyl G-CSF and a 20 kD mPEG molecule. The mPEG is covalently bound to the N-terminal methionyl residue of filgrastim.

For patients at risk of febrile neutropenia as defined by guidelines or individual patient risk, per label, G-CSF should not be administered until at least 24 hours after administration of cytotoxic chemotherapy. Historically, this meant that the patient would need to return to the healthcare clinic the next day after chemotherapy administration for G-CSF injection. The current presentation of US FDA approved Pfizer pegfilgrastim biosimilar (Nyvepria) is PFS for SC delivery. In order to provide an additional option for pegfilgrastim for patients who cannot or do not wish to return to the clinic the next day after chemotherapy administration for their injection, Pfizer has developed an on-body injector—a small, battery-powered, electromechanical drug delivery system that is applied to the patient's skin on the day of chemotherapy to deliver a SC dose of PF-06881894 on the next day after chemotherapy. The objective of the proposed study is to assess the PK comparability of PF-06881894 administered by OBI versus PFS as a single SC dose.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-06881894 can be found in the current version of the IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical PK and metabolism of PF-06881894 can be found in the current version of the IB.

2.2.3. Nonclinical Safety

Details of the nonclinical safety of PF-06881894 can be found in the current version of the IB.

2.2.4. Clinical Overview

PF-06881894 has been evaluated in 3 completed studies, C1221001 (ZIN-130-1505), C1221002 (ZIN-130-1504), and C1221005. C1221001 was a PD and PK similarity study in which PF-06881894 was administered as 6mg/0.6mL PFS SC to healthy participants. This study demonstrated the PK/PD comparability of PF-06881894 to US-approved Neulasta (pegfilgrastim-US) and EU approved Neulasta (pegfilgrastim-EU). In the evaluable 136 PK participants administered with PF-06881894, the arithmetic means (SD) for AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$ were 6,766,153 (4,880,797) h•pg/mL, 6,751,996 (4,882,297) h•pg/mL, 188,422.1 (112,698.0) pg/mL, 18.61 (5.634) hours, 49.3963 (13.53258) hours, respectively. There were no clinically meaningful differences in safety across the PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU study interventions, which overall were well-tolerated in the healthy participants in this study. The safety results were consistent with the known safety profile of the reference product.

The C1221005 Phase 1 study assessed the immunogenicity of multiple SC doses of PF-06881894 and US-approved Neulasta (pegfilgrastim-US) in healthy volunteers. Results from this comparative immunogenicity study met the pre-specified criteria for non-inferiority of PF-06881894 vs pegfilgrastim-US with respect to immunogenicity, with no clinically meaningful differences in safety between the proposed biosimilar PF-06881894 and pegfilgrastim-US reference product.

The safety data from the 2 comparative clinical studies (C1221001 and C1221005) conducted in healthy participants support the safety of PF-06881894.

All participants who received at least 1 dose of the study drug (PF-06881894, pegfilgrastim-US, or pegfilgrastim-EU) were included in the Safety Population. A total of 358 participants were exposed to at least 1 dose of PF-06881894 (148 participants in Study C1221001 and 210 participants in Study C1221005); 356 participants received at least 1 dose of pegfilgrastim-US (146 participants in Study C1221001 and 210 participants in Study C1221005); 148 participants were exposed to at least 1 dose of pegfilgrastim-EU (Study C1221001 only).

Overall, no clinically meaningful differences between the safety profile of PF-06881894 and Neulasta were observed in the clinical studies, and results were similar to the established safety profile of Neulasta as reflected in the labels.[16,17]

Overall, the review of the TEAEs showed consistent information in participants administered PF-06881894 or pegfilgrastim-US and pegfilgrastim-EU in Studies C1221001 and C1221005. Most TEAEs were mild or moderate in severity in Study C1221001 and all TEAEs were mild or moderate in severity in Study C1221005. Both pegfilgrastim-US and pegfilgrastim-EU had results as anticipated from their known profile. No deaths were reported in the 2 comparative studies. Only 4 participants experienced treatment-emergent SAEs (3 participants in Study C1221001 and 1 participants in Study C1221005).

A low number of participants discontinued the studies due to TEAEs (2 participants in Study C1221001 [1 due to non-drug-related abortion spontaneous and 1 due to drug-related rash generalized] and 2 participants in Study C1221005 [1 due to non-drug-related urinary tract infection and 1 due to drug-related angioedema]).

The safety data from the 2 comparative clinical studies conducted in healthy participants support comparability of the safety profile of PF-06881894 to Neulasta.

The C1221002 study was the IND-opening study when the plan was for development under a 351(a) regulatory pathway and was designed to determine the relevant dose for use in the required Phase 3 efficacy and safety study. This was a Phase 1-2 study with an adaptive design that included assessments of 3 mg/0.3mL, and 6 mg/0.6mL, PF-06881894 PFS, administered as SC injection during Cycle 0 (Phase 1, in patients prior to definitive breast surgery and without background chemotherapy), and at Cycles 1-4 (Phase 2, in patients after definitive breast surgery and treated with TAC chemotherapy). During Cycle 0, 12 participants received a single dose of 3 mg or 6 mg (6 participants for each dose) of PF-06881894; and during Cycles 1-4, 13 participants received multiple doses of 6 mg PF-06881894 (1 dose for each of the 4 cycles). In Phase 1, PD (ANC and $CD34^{+}$) and PK results for the 3 mg dose tended to be lower than the results for the 6 mg dose of PF-06881894 or Neulasta (published data); as a result, 3 mg was not initiated in Phase 2, Cycles 1-4. Overall, the safety results were consistent with the known safety profile in patients treated with Neulasta, with and without myelosuppressive TAC chemotherapy. There were no immunogenicity concerns identified for PF-06881894 in the studied populations of breast cancer patients with and without chemotherapy.

2.3. Benefit/Risk Assessment

PF-06881894 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK data for further clinical development. In this study, PF-06881894 will be administered at single dose of 6 mg by OBI or by PFS.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06881894 may be found in the IB, which is the SRSD for this study. Data from the 2 comparative studies in healthy participants can be found in Section 6 of the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06881894 (pegfilgrastim)		
Potential risks associated with PF-06881894 include but may not be limited to the following: potential allergic reactions; splenomegaly; splenic rupture; acute respiratory distress syndrome; alveolar haemorrhage; hemoptysis; leukocytosis; thrombocytopenia; capillary leak syndrome; cytokine release syndrome; cutaneous vasculitis; glomerulonephritis. These risks represent AESI for PF-06881894 (see Section 8.3.8). Two SC injections will be administered using a PFS and OBI during the study, with a washout period of 56 days between doses. For those doses administered via the OBI, removal of the device will occur following completion of the infusion. The same injection site (left or right side of the abdomen) will be used for both OBI and PFS for each participant, keeping at least 2 inches (5 cm) away from the belly button.	The potential risks for pegylated G-CSF are based on safety information of Neulasta, as described in the Neulasta (Amgen) Package Insert[16], and grouped by similar medical constructs. The AESIs were further informed based on the known extension of the pharmacology of the drug as manifested by known clinical adverse reactions with G-CSFs. ISR has been reported previously in the completed PF-06881894 studies and can be found in Section 6 of the IB. ISRs were identified during the post-approval use of pegfilgrastim products and ASRs (including events such as application site hemorrhage, application site pain, application site discomfort, application site bruise, and application site erythema) have been identified during the post approval use of the on-body injector for Neulasta.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). AEs and clinical laboratory results will be monitored on an ongoing basis. ISR Assessment will be performed daily from day -1* to Day 13. *On Day -1 only participants with OBI applied will need assessment of ISRs and ASRs (see SoA and Section 8.2.7).
Device related risks: Allergies to Acrylics: The OBI for PF-06881894 uses acrylic adhesive. For participants who have reactions to acrylic adhesives, use of this product may result in a significant reaction. Please see IB Section 7.11.1.3. Known Drug Class Effects and Other Human Experience for information regarding allergies to adhesives with the OBI for Neulasta. Potential Device Failures: In the event of a missed or partial dose, study participants should be	Risks and Adverse Drug Reactions seen in Neulasta OBI could also be seen for the OBI used in this study. Missing a dose or receiving a partial dose could impact study results.	Exclusion criteria excludes participants with known hypersensitivity to acrylic adhesive (see Section 5). AEs, ISRs, ASRs and clinical laboratory results will be monitored on an ongoing basis. Confinement will enable increased observation of participants, should a reaction occur. Suspected missed or partial doses due to OBI device malfunction should be reported via the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
instructed to notify the principal investigator. Please see IB Section 7.11.1.3. Known Drug Class Effects and Other Human Experience for information regarding potential device failures with the OBI for Neulasta. **Adverse Drug Reactions**: There have been no adverse reactions to the OBI for PF-06881894 identified at this time. Please see IB Section 7.11.1.3. Known Drug Class Effects and Other Human Experience for information regarding adverse reactions identified during post approval use of the OBI for Neulasta.		Device Medical Complaint form (Section 8.3.10.3).
Potential fetal risk	Studies in animals have shown reproductive toxicity.	WOCBP who are unwilling or unable to use highly effective method of contraception as defined in the study protocol will be excluded (See Section 5.3.4 and Appendix 4).
Potential risk of secreting into human milk	It is not known whether PF-06881894 is secreted into human milk.	PF-06881894 should not be administered to breastfeeding women and exposure during breastfeeding should be reported to Pfizer Safety (See Section 8.3.5.2).

2.3.2. Benefit Assessment

For healthy participants in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-06881894 are clinically acceptable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• PK comparability • To assess the PK comparability of PF-06881894 administered by OBI versus PFS as a single SC dose.	• C_{max}, AUC_{last} and AUC_{inf} (if data permits).
Secondary:	**Secondary:**
• To characterize the PK of PF-06881894 OBI dosing presentation to PFS dosing presentation in healthy participants. • To assess the safety (including immunogenicity) of PF-06881894 OBI dosing presentation to PFS dosing presentation in healthy participants.	• T_{max} and $t_{½}$ (if data permits). • AEs, including AESIs and device-related AEs; ISRs and ASRs.

4. STUDY DESIGN

4.1. Overall Design

This will be an open-label, randomized, 2-treatment, 2-period, crossover single-dose study in approximately 134 healthy adult participants enrolled at approximately 4 CRUs. There will be a washout period of at least 56 days between the 2 treatments. The order of treatment administration will be randomized, with approximately 67 participants assigned to each treatment sequence. Dropouts may be replaced at the discretion of the investigator upon consultation with the sponsor.

Table 3. Treatment Sequences

Sequence	Period 1	Washout	Period 2
1 (n=67)	Treatment A	At least 56 days	Treatment B
2 (n=67)	Treatment B	At least 56 days	Treatment A

Treatment A: PF-06881894, OBI, 6 mg administered as a single SC injection
Treatment B: PF-06881894, PFS, 6 mg administered as a single SC injection

Screening evaluation will occur within 30 days prior to the first dose of study intervention in Period 1. Day -1 is defined as the day prior to the first day of dosing (Day 1) in each period.

Participants will be admitted to the CRU on Day -2, at 36-42 hours prior to Day 1 dosing, and will remain confined in the CRU until completion of all study activities on Day 5 during each period.

There will be at least a 56-day washout period between administration of each study intervention to ensure the complete elimination of the drug. The total duration of participation in the study for each participant, excluding Screening, is approximately 12 weeks.

On Day -1 of each period, the PF-06881894 OBI will be activated and applied on participants randomized in the OBI arm.

On Day 1 of each period, each participant will receive a single SC dose of 6 mg PF-06881894 administered by OBI or by PFS based on the randomization code. For those doses administered via the OBI, removal of the device will occur following completion of the infusion.

The same injection site (left or right side of the abdomen) will be used for both OBI and PFS for each participant, keeping at least 2 inches (5 cm) away from the belly button. The same needle angle (90°) for SC injection will be used for each participant in the OBI and PFS arms.

Blood samples for PK (3.0 mL) will be collected by either intravenous catheter or venipuncture into evacuated collection tubes within 1 hour prior to dose administration (Hour 0) and at 0.167 (10 min), 0.5, 1, 3, 6, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288 hours post-dose. For the OBI treatment period, PK collection should resume 10 min (0.167 hrs) following the start of the injection and continue as shown. This sample collection scheme will adequately characterize the PK of pegfilgrastim following a single SC dose.

Safety will be assessed for all treatments by monitoring AEs and other parameters defined in Section 8.

4.2. Scientific Rationale for Study Design

PF-06881894 (Nyvepria) is a pegylated recombinant human methionyl G-CSF that is a US FDA approved biosimilar to the licensed pegfilgrastim (reference product) approved in US and EU in 2002 marketed as Neulasta® (Amgen). Pfizer is developing an OBI device, which is being designed to have similar features and perform equivalently, where applicable, to the Amgen OBI device from the Neulasta Onpro® Kit. Like the Amgen OBI device, the Pfizer OBI delivery device is intended to provide increased convenience to patients and improved compliance for dose administration at the pre-determined time. PF-06881894 is required to be injected no sooner than 24 hours after a patient receives chemotherapy. The Pfizer OBI device will be pre-programmed to automatically deliver PF-06881894 approximately 27 hours after activation. This would eliminate the patient's need for a return visit to a hospital or other clinical setting the day after chemotherapy to receive PF-06881894,

facilitate the medication administration per the recommended dosing schedule, and provide an alternative for patients who do not wish to self-administer or to be administered by a caregiver. To demonstrate PK equivalence of PF-06881894 whether delivered using the OBI device or the PFS, this single dose study in healthy participants is designed, and is expected to be the most sensitive setting to detect intrinsic differences in PK between the OBI and PFS presentations of PF-06881894.

4.2.1. Reproductive Risk

There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity. In pregnant rabbits, pegfilgrastim has been shown to cause embryo/fetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known. See the IB for more details. Pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception. All male participants who are able to father children and female participants who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of PF-06881894.

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

PF-06881894 6 mg administered by OBI or by PFS will be used in this study, and is the approved dose of the originator product Neulasta® (Amgen). The safety profile for the 6 mg dose is considered acceptable for healthy participants.

4.4. End of Study Definition

The end of the study is defined as the date the last participant completes the Period 2 Day 28 Visit.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the Period 2 Day 28 Visit or Early Withdrawal Visit, shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be

taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Healthy male and/or female participants who, at the time of screening, are between the ages of 18 and 65 years, inclusive.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants, for the definition of Woman of Childbearing Potential (Section 10.4.3), and for contraception methods (Section 10.4.4).

Type of Participant and Disease Characteristics:

2. Participants will include healthy individuals, with healthy being defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including BP and PR measurement, 12-lead ECG, chest X-ray, or clinical laboratory tests.

3. Participants agree to abstain from the use of tobacco- or nicotine-containing products for at least 90 days prior to dosing and have a negative urine screen for cotinine at Screening.

4. Participants agree to abstain from alcohol consumption for at least 48 hours prior to Day 1 of dosing in each study period and have a negative screen for alcohol.

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

Weight:

6. BMI between 19 and 30 kg/m^2, inclusive, and body weight of not<50 kg or >100 kg.

Informed Consent:

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

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, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Any condition possibly affecting drug absorption (eg, injuries to subcutaneous tissue at the injection site).

3. Any clinically significant, as determined by the investigator, abnormal laboratory evaluations, including HIVAb, HBVsAg, HBVcAb, HCVAb and liver function taken at Screening. The negative HIVAb status will be confirmed at Screening, and all HIV results will be maintained confidentially by the study site.

4. History of malignancy, including current malignancy, with the exception of adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ within 5 years.

5. Surgery within the 4 months prior to Screening.

6. History of splenic rupture (or participant who is asplenic), pulmonary infiltrate or pneumonia, sickle cell disease, chronic neutropenia, thrombocytopenia, or vasculitis.

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

Prior/Concomitant Therapy:

8. History of biological growth factor exposure, including but not limited to pegfilgrastim, filgrastim and other G-CSFs in the context of treatment, prophylaxis, peripheral blood stem cell mobilization, or previous investigational study setting. This also includes exclusion for history of interferon, epoetin, and IVIG exposure.

9. Receipt of live vaccination, or exposure to communicable viral diseases such as chicken pox, varicella, mumps, measles, or COVID-19 within the 4 weeks prior to Screening.

10. Use of any prescription medicine (with the exception of contraceptives) within 7 days or at least 5 half-lives, whichever was longer. Use of oral or parenteral anticoagulant or antiplatelet agents and corticosteroids should be specifically queried.

11. Administration of a drug by depot injection (with the exception of depot contraception) within 30 days prior to the initial study drug administration or 5 half-lives of that drug, whichever is longer.

12. Use of over the counter medications, including aspirin and non-steroidal anti-inflammatory drugs, or natural preparations (dietary supplement or herbal product) within 7 days of the first dose of PF-06881894 or at least 5 half-lives, whichever is longer. Vitamins and calcium supplements are allowed (not to exceed 100% Daily Value). As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription 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.

13. Females using post-menopausal hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP.

Prior/Concurrent Clinical Study Experience:

14. Treatment 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 (whichever is longer) prior to study entry and/or during study participation. If a participant receives a vaccine or other medical product for the prevention or treatment of COVID-19 authorized under an Emergency Use Authorization, this would not be considered an investigational medical product.

Diagnostic Assessments:

15. Hematologic laboratory abnormalities at screening or the Day -5 to Day -4 visit including leukocytosis (defined as total leukocytes >11,000/µL), leukopenia (defined as total leukocytes <4000/µL), neutropenia (defined as ANC <1500/µL) or thrombocytopenia (defined as platelet count of <150,000/µL).

16. A positive urine drug test.

17. A positive SARS-CoV-2 infection determined by PCR at screening or Day -5 to Day -4, or determined by a positive COVID-19 antigen test (if performed as part of an investigator site policy).

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

19. Screening supine 12-lead ECG demonstrating QTc >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the participant's eligibility.

20. Participants with the following abnormalities in clinical laboratory tests at screening or the Day -5 to Day -4 visit, as assessed by the study specific laboratory will be confirmed by a single repeat test, if deemed necessary. Then the investigator (in consultation with the medical monitor) will determine if the laboratory abnormality is clinically significant and sufficient to exclude the participant from the study.

    - Lack of adequate hepatic reserve, defined by AST/SGOT **or** ALT/SGPT ≥1.5 × ULN of the reference laboratory;

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

    - Lack of renal reserve, defined by serum creatinine of ≥ 1.2 × ULN for reference laboratory or eGFR of ≤ 80 mL/minute; or known history of glomerulonephritis.

Other Exclusions:

21. Drug sensitivity, allergic reaction to, or known hypersensitivity/idiosyncratic reaction to *E coli* -derived proteins, pegfilgrastim, filgrastim, other G-CSFs or any component of the product or known hypersensitivity to pegylated products or acrylic adhesives. Participants with the rare heredity problem of fructose intolerance are excluded due to the excipient sorbitol.

22. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months of Screening.

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

24. Pregnant female participants, breastfeeding female participants, and male participants able to father children and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of study intervention.

25. Blood donation (including plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing OR had a transfusion of any blood product within 90 days prior to Screening.

26. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol. Male participants with pregnant partners are not to be enrolled in the study, even if the participant is willing to comply with the contraception lifestyle requirements and use a highly effective method of contraception consistently and correctly for the duration of the study and for at least 28 days after the last dose of study intervention.

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose pharmacokinetic sample. Water is permitted until 1 hour prior to study intervention administration.

- Water may be consumed without restriction beginning 1 hour after completion of dosing. Non-caffeinated drinks may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after completion of dosing.

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

- An evening snack may be permitted.

- While confined, the 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.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for 48 hours prior to Day 1 of dosing and continue abstaining from alcohol until collection of the final pharmacokinetic sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Caffeine-containing products are permitted, however participants should abstain within 2 hours of vital sign/ECG measurements.

- Participants will abstain from the use of tobacco- or nicotine-containing products during the study.

5.3.3. Activity

- Participants will avoid getting body lotions, creams, oils or cleaning agents near the OBI as these products may loosen the adhesive; participants will keep the on-body injector dry for the last 3 hours prior to the dose delivery start; participants will be careful not to bump the OBI or knock the OBI off of their body. Refer to the complete OBI Instructions for Use and the IP Manual.

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 72 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- Participants will also be instructed to maintain their usual level of activity during the study when they are not in the study unit, with the exception that participants should refrain from collision sports as defined below and from professional or highly competitive university team contact sports such as basketball or soccer during the study period.

  In collision sports (eg, boxing, ice hockey, rugby, [American] football, lacrosse, roller derby, and rodeo), athletes purposely hit or collide with each other or with inanimate objects (including the ground) with great force. In contact sports (eg, basketball and soccer), athletes routinely make contact with each other or inanimate objects but usually with less force than in collision sports.

- Exposure to communicable viral diseases such as COVID-19, varicella, mumps, or measles should be avoided during the study period. If such exposure occurs, it should be reported to the investigator.

5.3.4. Contraception

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

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to pegfilgrastim-apgf administered by PFS or PF-06881894 administered by OBI.

6.1. Study Intervention(s) Administered

The OBI is to be used with the reference product PF-06881894 PFS 6 mg/0.6 mL solution for injection, 0.63 mL. The OBI and the PFS for OBI will be contained within the same kit.

PF-06881894 PFS 6 mg/0.6 mL solution for injection, 0.63 mL to be used with OBI – Treatment A (Test Product), contains 0.63 mL to deliver 6 mg/0.6 mL subcutaneously with OBI.

Pegfilgrastim-apgf PFS 6 mg/0.6 mL solution for injection, 0.6 mL SC injection - Treatment B (Reference Product).

The pegfilgrastim PFS and OBI kits (containing OBI device and PFS for OBI) will be labeled according to local regulatory requirements and provided to the clinical site for dispensing.

Pivotal BA/BE study PFS and OBI kits will be supplied to the clinical site in single dose labeled containers (in sufficient number to allow unopened containers to be kept as retains).

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention during each period. Administer study intervention according to the IP manual and the OBI Instructions for Use.

The pegfilgrastim-apgf PFS will be administered on Day 1 of Treatment Period 1 or Period 2 based on participant's randomization. The OBI will be applied on Day -1 of Treatment

Period 1 or Period 2, and PF-06881894 will be administered by the OBI on the following day (Day 1).

A qualified staff member will dispense the study intervention via unique numbers on carton containing pegfilgrastim-apgf PFS 6 mg/0.6 mL solution for injection, 0.6mL; and/or PF-06881894 PFS for OBI 6 mg/0.6 mL solution for injection, 0.63mL packaged with OBI device.

The site should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the study intervention is to be administered. The following activities should be recorded by a member of the study site staff for each OBI applied during the study:

Date/time the OBI is activated – to activate the OBI both activation buttons should be pressed and held for 3 seconds, a double-beep will be heard, and then the buttons will flash amber for approximately 10 seconds and then flash green. Subsequent actions should occur as described in the OBI Instructions for Use. Study site staff should avoid delay in the insertion of the soft cannula.

Date/time of the start of injection via OBI – approximately 27 hours after activation the OBI will produce a series of triple beeps, and dose delivery will begin approximately 2 minutes later. The OBI will produce a double beep to indicate the dose is beginning, and the green light will flash (this time should be recorded as the start of injection). The dose takes approximately 30 minutes to complete.

Date/time of the end of injection via OBI – when the dose delivery is complete a long beep will sound, and the status light will be solid green and then turn off.

Please reference the OBI Instructions for Use for complete instructions.

OBI device malfunction should be reported via the Device Medical Complaint form (Section 8.3.10.3).

6.1.2. Medical Devices

1. The manufactured medical devices provided for use in this study are the PFS that is used to administer pegfilgrastim-apgf and the OBI that administers the PF-06881894.

2. Instructions for medical device use are provided in the IP manual and OBI Instructions for Use.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study (see Section 8.3.10) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

7. Further guidance and information for the final disposition of unused study interventions are provided in the 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.

8. All pivotal BA/BE retained PFS and OBI kits should be stored by the investigator site or with a third-party vendor. Sample retention is the responsibility of the entity performing the BA or BE study.

9. OBI devices utilized during the study will need to be stored in their original packaging at the investigator site and subsequently returned to the sponsor or designee.

10. Any PFS or OBI involved in a product complaint should be quarantined in its original packaging, and the site staff should wait for further instruction.

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, or 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 and OBI Instructions for Use 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.

The PFS and PFS for OBI are single use.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

6.4. 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. Study site personnel will examine each PFS and OBI device used for a participant to see whether the study intervention was administered.

For the OBI treatment period, once the OBI medicine port has been filled, study site personnel will inspect the PFS to ensure the contents are empty, then inspect the fill indicator to ensure the yellow line aligns with the “full” icon on the fill indicator (solid drop). If this is not the case, the OBI should not be used; a new OBI kit should be utilized. Following dose delivery and removal of the OBI, study site personnel will check that the OBI is empty; the yellow line will align with the “empty” indicator (empty drop). Please reference the OBI Instructions for Use for complete instructions.

For the PFS treatment period, study site personnel will inspect the PFS to ensure the contents are empty following administration of the PFS.

Suspected missed or partial doses due to OBI device malfunction should be reported via the Device Medical Complaint form (Section 8.3.10.3).

For treatment of overdose please reference Section 6.7.

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

6.5. Dose Modification

Dose modification for PF-06881894 is not allowed.

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

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

6.7. Treatment of Overdose

The maximum amount of PF-06881894 that can be safely administered has not been determined. As per Nyvepria Package Insert, Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. In the event of overdose, the patient should be monitored for adverse reactions.

For this study, any dose of PF-06881894 greater than 6 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06881894 (whichever is longer).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

5. Obtain a blood sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

6.8. Concomitant Therapy

6.8.1. Prior Treatments

Previous medication must be discontinued. Prescription medicine (with the exception of contraceptives) and over the counter medication, including aspirin and non-steroidal anti-inflammatory drugs, or natural preparations (dietary supplement or herbal product) must be discontinued at least 7 days (or 5 half-lives, whichever is longer) prior to the first dose of study intervention. Use of oral or parenteral anticoagulant or antiplatelet agents and corticosteroids should be specifically queried. Vitamins and calcium supplements are allowed and not to exceed 100% Daily Value. Drug by depot injection (with exception of depot contraception) must be discontinued within 30 days prior to the first dose of study intervention or 5 half-lives of that drug, whichever is longer.

Participants who have had treatment with another investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives prior to the first dose of study intervention will not be accepted into the study. All previous medications (prescription and non-prescription drugs) taken within 7 days (or 5 half-lives, whichever is longer) prior to Randomization (drug by depot injection within 30 days or 5 half-lives, whichever is longer) will be documented on the source document and recorded on the eCRFs.

Receipt of live vaccination within the 4 weeks prior to screening is prohibited.

6.8.2. Permitted During the Study

Concomitant therapy refers to therapies used during the investigational period, eg during or after study drug dosing. The Investigator or designee will refrain from prescribing new medications during the study, unless clinically indicated for the treatment of AEs/SAEs. Use of multivitamins and calcium supplements are allowed and not to exceed 100% Daily Value.

Limited use of non-prescription 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

discussion with and approval by the Sponsor. Restrictions on prior and concomitant medication are described in Section 5.2.

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

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

6.8.3. Prohibited During the Study

If medication is required for medical treatment during the study (after study intervention administration), the participant may be discontinued at the discretion of the Investigator or Sponsor.

If administration of any medication becomes necessary after the administration of study intervention through the end of the study, the name of the medication, dosage information including dose and frequency, date(s) of administration including start and end dates, and reason for use must be recorded in the source documents, and the eCRFs completed as appropriate.

Females taking post-menopausal hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study intervention and remain off hormonal therapy for the duration of the study.

Receipt of live vaccination is prohibited during the study period.

No other prohibition for concomitant treatments are required for this study, as there have been no formal drug interaction studies between pegfilgrastim and other drugs performed (Section 10.9).

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 Decision, Pregnancy, Protocol Deviation, No Longer meets an eligibility criteria, Study Terminated By Sponsor, Lost To Follow-Up, Medication Error without Associated AE, Death, Withdrawal By Subject, Refused further study procedures, and Other.

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for 28 days after the last dose of study intervention. 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, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Pregnancy

In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention. Please also see Section 8.2.6 Pregnancy Testing and Section 8.3.5.1 Exposure During Pregnancy.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AE;
- Medication Error without Associated AE
- Physician Decision;
- Pregnancy;
- Protocol Deviation;
- No longer meets an eligibility criteria;
- Withdrawal by Subject;

- Other

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. See the SoA for assessments to be collected at the time of study discontinuation.

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Participants will be screened within 30 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 30 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.

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

ECGs should be obtained prior to vital signs. ECGs and vital signs should be obtained as close as possible to scheduled time and prior to blood specimen collection. If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR, BP, respiratory rate and tympanic temperature) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 240 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 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.

There may be instances when copies of medical records pertaining to follow-up for an abnormal result or AE are requested by Pfizer. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of medical records before submission to Pfizer.

8.1. Efficacy Assessments (Not Applicable)

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

8.2.2. Vital Signs

Vital signs (BP, PR, respiratory rate and tympanic temperature) will be measured at times specified in the SoA. Additional collection times or changes to collection times of vital signs will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.1. BP and PR

Sitting BP 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. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and 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 of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.2. Respiratory Rate

Assessment of respiratory rate should include the following general approach: Measure the respiratory rate after at least 5 minutes at rest. Observe the rise and fall of the subject's chest and count the number of respirations for 1 full minute. One respiration consists of 1 complete rise and fall of the chest or the inhalation and exhalation of air. Observe the rhythm, ease, and strength of the respiration. Accurately document the respiratory rate.

8.2.2.3. Temperature

Temperature will be measured by a tympanic thermometer.

8.2.3. Electrocardiograms and Chest X-ray

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. Whenever possible, ECGs should not be collected within 3 hours after food or beverage consumption. Any abnormalities noted should be documented in the source document as clinically significant or clinically non-significant.

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 there is a new occurrence of ECG abnormalities during the study that is judged to be clinically significant by the investigator, the investigator should report the event as AE and follow-up ECG should be conducted as appropriate. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

A posterior and lateral chest radiograph will be obtained at Screening and will be read by qualified site personnel.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

Minimum requirement for drug screening includes: cocaine, THC, opiates/opioids, barbiturates, benzodiazepines and amphetamines.

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

8.2.5. COVID-19 specific assessments

A COVID-19 questionnaire should be completed at times listed in the SoA for each participant to check for exposure to a positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms. Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator. Sites should follow their individual site practice guidelines for COVID-19 testing for symptomatic participants. If a test result is inconclusive or indeterminate at any visit, a repeat should be performed to gain a result of positive or negative.

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but 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 the participant's receiving 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. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of study intervention.

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.

8.2.7. Assessment ISRs and ASRs

Examinations for ISRs and ASR must occur at timepoints specified according to the SoA. If a participant develops an ISR or ASR, it must be documented at each subsequent time point in the SoA until resolution. In addition, ISRs and ASRs may also be captured during AE monitoring to document those reactions that may occur outside the scheduled assessments. All ISRs and ASRs will be reported as AEs.

Reactions may include but are not limited to: erythema, induration, ecchymosis, pain, and pruritus. The severity of each ISR and ASR will be assessed and documented. If deemed appropriate by the investigator, a consultation with a dermatologist will be performed. Documentation may include a dermatologist report, clinic notes and photographs.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.10.

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 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

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

If a participant permanently discontinues or temporarily discontinues study 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 completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

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

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A 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 exposes a female partner prior to or around the time of conception.

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

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

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

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

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

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

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events (Not Applicable)

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

8.3.8. (Not Applicable)

8.3.9. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

All AEs shall be assessed by the investigator or his/her designee during the administration of the drug to identify immediate reactions and any reaction reported within at least 28 days after last dose to include potential acute and delayed immunogenic reactions.

8.3.9.1. Lack of Efficacy

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

8.3.10. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administration. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.10.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.10.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.10.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint Form.

3. If an AE (either serious or non-serious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the CT SAE Report Form as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

The manufactured medical devices provided for use in this study are the PFS that is used to administer pegfilgrastim-apgf and the OBI that administers the PF-06881894 (Section 6.1.2).

8.3.10.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.11. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of 1.5 mL serum, will be collected for measurement of serum concentrations of PF-06881894 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-06881894. Samples collected for analyses of PF-06881894 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of serum concentrations of PF-06881894 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.

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep 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). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked 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 lab manual and other supporting documentation.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Specified Gene Expression (RNA) Research

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

8.6.2. Specified Protein Research

Specified protein research is not included in this study.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. Retained Research Samples for Biomarkers

Banked biospecimens for biomarkers is not included in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

The null hypothesis is PF-06881894 OBI is not equivalent to PF-06881894 PFS. Pharmacokinetic equivalence will be assessed by constructing the 90% CIs for the GMR (test/reference) for C_{max}, AUC_{last} and AUC_{inf}. When the 90% CIs are completely contained within the acceptance limits of 80%-125%, the null hypothesis is rejected.

9.2. Analysis Sets

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

Participant Analysis Set	Description
PK population	The PK population is defined as all participants randomized who are treated and have valid PK parameters in at least 1 treatment period. Participants will be analyzed according to the treatment they are randomized to receive. This will be the primary population to assess PK equivalence. Participants with device failures/malfunctions that could potentially impact drug delivery may not be included in the PK population analysis. Details will be described in the SAP.
Full Analysis Set	All participants who are randomized and take at least 1 dose of study intervention. Participants will be analyzed according to the treatment they were to receive based on randomization. Sensitivity analysis of PK parameters will be performed using the full analysis set.
Safety population	All participants who are randomized and take at least 1 dose of study intervention. Participants will be analyzed according to the treatment they actually receive based on randomization.

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. Pharmacokinetic Analysis

Participants who receive at least 1 dose of study intervention and have sufficient valid data to calculate the primary PK parameters (C_{max}, AUC_{last} and AUC_{inf}) will be included in the PK population. The PK population will be the primary analysis set for the primary PK analyses. PK comparability determination of the 2 treatments will be made on the PK population.

PK parameters following single dose administration will be derived from the concentration time profiles by noncompartmental analysis as follows:

Parameter[a]	Definition	Method of Determination
AUC_{last}	Area under the serum drug concentration-time profile from time 0 to the last quantifiable concentration (C_{last})	Linear-log trapezoidal method
AUC_{inf}[b]	Area under the serum concentration-time profile from time 0 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
C_{max}	Maximum serum concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[b]	Terminal serum elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by 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. Actual PK sampling times will be used in the derivation of PK parameters
b. If data permits.

The serum concentration time data from Day 1 through Day 13 from individual participants will be analyzed by non-compartmental methods to determine the PK parameters. The primary PK parameters to be estimated will include C_{max}, AUC_{last} and AUC_{inf} (if data permits). The secondary PK parameters to be estimated will include $T_{max,}$ and $t_{½}$ (if data permits). Descriptive statistics for the PK parameters will be provided.

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}.

Ninety percent (90%) CIs for the test to reference ratios (PF-06881894 OBI versus PF-06881894 PFS) for C_{max}, AUC_{last} and AUC_{inf} will be constructed on a natural log scale using ANOVA with treatment, sequence and period as effects. PK similarity for a given test to reference comparison will be considered to be demonstrated if the 90% CIs for the test to reference ratios of C_{max}, AUC_{last} and AUC_{inf} fall within the 80% - 125% BE window.

9.3.2. Safety Analysis

All safety analyses will be performed on the safety population.

AEs including AESIs and device related AEs, ISRs, and ASRs, ECGs, vital signs, 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.

The following data summary tables will be generated to evaluate immunogenicity-related safety events for all participants:

- Number and percentage of participants with ISR and ASR;
- Number and percentage of participants that meet Sampson's Criteria
- Number and percentage of participants who experienced hypersensitivity-related AEs (including anaphylactic reactions) using the relevant SMQs.

Physical examination (including spleen) and neurologic 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 neurologic examinations conducted after the administration of the first dose of study intervention will be captured as an AE, if those findings meet the definition of an AE. In addition to summaries of AEs by treatment that include all AEs, device-related AEs, AESIs, ISRs, and ASRs will also be summarized by treatment.

9.3.3. Other Analyse(s)

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

9.4. Interim Analyses

No formal interim analysis is planned for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.5. Sample Size Determination

The study is powered for assessment of the primary PK parameters C_{max}, AUC_{last} and AUC_{inf}. Assuming a within-participant coefficient of variation of 39% (based on Study C1221001) and a true ratio of 1.05, and an equivalence range of 80 to 125% of the test/reference mean ratio for C_{max}, AUC_{last} and AUC_{inf}, a total of 134 enrolled participants will be required to demonstrate PK equivalence with 100 evaluable participants at approximately 90% power.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the clinical monitoring plan, which is maintained by the sponsor.

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

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

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

10.1.11. Sponsor's Qualified Medical Personnel

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 4. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) ALT, AST, LDH, GGT, TBili ALP Uric acid Albumin Total protein Cystatin-C and eGFR **Enzyme/Liver Panel** ALT, AST, ALP, LDH, GGT, TBili Additional Tests (Needed for Hy's law assessment; See Appendix 6 of the protocol for additional information.): AST, ALT (repeat) TBili (repeat) Albumin (repeat) ALP (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy and Culture[a] Protein:creatinine ratio if urine is positive for protein	FSH[b] Urine drug screening[c] β-hCG[d] Alcohol screening[e] Urine cotinine[f] Serology[f] (anti-HIVAb, anti-HCVAb, HBVsAg, HBVcAb) Screening only SARS-CoV-2 PCR

a. Only if UTI suspected or urine result is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in females <60 years of age who are amenorrheic for at least 12 consecutive months and not using hormonal contraception or HRT.
c. At Screening and the Day -5 to Day -4 visit in Periods 1 and 2 and at the discretion of the investigator.

Table 4. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other

d. Serum or urine β-hCG for females of childbearing potential.
e. At Screening and Day -1 in Periods 1 and 2 and at the discretion of the investigator.
f. At Screening.

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

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

g. Results in death

h. 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.

i. 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.

j. 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.

k. Is a congenital anomaly/birth defect

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

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

m. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

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

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

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

Assessment of Intensity

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

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

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

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

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

Assessment of Causality

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

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

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

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

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

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

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

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

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

Follow-Up of AEs and SAEs

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

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

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Vasectomy:

  - Considered a highly effective contraceptive method provided 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.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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 definitions below in Section 10.4.3);

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at

least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

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.

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential 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.

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

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

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

    - Oral;

    - Injectable.

8. Sexual abstinence.

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

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- 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 PF-06881894 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

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

ECG Findings That May Qualify as SAEs

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

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

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and USADE

SAE Definition:
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition

- A USADE is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.8.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency 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 device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint Form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint Form. • 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. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. 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 in his/her assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• 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 device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint Form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.8.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

No formal drug interaction studies between pegfilgrastim and other drugs have been performed.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
abs	absolute
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASR	application site reaction
AST	aspartate aminotransferase
$AUC_{extrap\%}$	AUC extrapolated as a percentage of AUC_{inf}
AUC_{inf}	area under the serum concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the serum drug concentration time profile from time 0 to the last quantifiable concentration
AV	atrioventricular
β-hCG	β-human chorionic gonadotropin
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CIN	chemotherapy-induced neutropenia
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{last}	last quantifiable concentration
C_{max}	maximum serum concentration
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report

Abbreviation	Term
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Event
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EC	ethics committee
ECC	Emergency Contact Card
ECG	electrocardiogram
eCRF	electronic case report form
E coli	*Escherichia coli*
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
HBVcAb	hepatitis B virus core antibody
HBVsAg	hepatitis B virus surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibody
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ISO	International Organization for Standardization
ISR	injection site reaction
IV	Intravenous(ly)
IVIG	intravenous immunoglobulin

Abbreviation	Term
kD	kilodalton
k_{el}	terminal phase rate constant
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MedDRA	Medical Dictionary for Drug Regulatory Activities
mPEG	monomethoxypolyethylene glycol
N/A	not applicable
OBI	on-body injector
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
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)
SD	standard deviation
SGOT	serum glutamic oxaloacetic transminase
SGPT	serum glutamic pyruvic transminase
SMQ	standardized MedDRA query
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
STOD	Study Team On Demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal serum elimination half life
TAC	taxotere, adriamycin, and cyclophosphamide
TBili	total bilirubin
TC	telephone call
TEAE	treatment-emergent adverse event

Abbreviation	Term
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
ULN	upper limit of normal
US	Unites States
USADE	unanticipated serious adverse device effect
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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