Protocol C1221007

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

Statistical Analysis Plan

(SAP)

Version: 2

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C1221007 is based on the protocol dated 19 Nov 2021.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Definition of treatment emergent adverse events	Added and clarified

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C1221007. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary Objective

To assess the pharmacokinetic (PK) comparability of PF-06881894 administered by on-body injector (OBI) versus prefilled syringe (PFS) as a single subcutaneous (SC) dose.

Secondary Objective

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.

2.2. Study Design

The study is a randomized, open-label, 2-treatment, 2-period, crossover single-dose study in healthy adult participants. Approximately 134 healthy participants will be enrolled and randomized to 1 of 2 treatment sequences: PF-06881894 by OBI (Treatment A) followed by PF-06881894 by PFS (Treatment B); or PF-06881894 by PFS (Treatment B) followed by PF-06881894 by OBI (Treatment A); approximately 67 participants per treatment sequence. The

study will be conducted at approximately 4 Clinical Research Units (CRUs) in an in-clinic setting.

There are 2 treatment periods in this study. The washout between treatments will be at least 56 days between study interventions to ensure the complete elimination of the drug.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

C_{max}, AUC_{last} and AUC_{inf} (if data permits).

3.2. Secondary Endpoint(s)

T_{max} and $t_{½}$ (if data permits).

Adverse Events (AEs), including AESIs (Adverse Events of Special Interests) and device-related AEs; Injection Site Reactions (ISRs) and Application Site Reactions (ASRs).

3.3. Other Endpoints

Not applicable.

3.4. Baseline Variables

Baseline is defined as the last observation obtained prior to study intervention. Unless otherwise specified, study intervention is defined as dosing. For a variable that is collected after washout and prior to dosing in the 2nd period, the last value obtained prior to dosing in the 2nd period is the baseline value for that variable in the 2nd period. If a variable's 2nd period baseline is not available yet 1st period baseline is available, the 1st period baseline will be used as the 2nd period baseline. In case time of data collection for a variable cannot be determined relative to dosing, the order of procedures will be assumed to have followed the protocol.

3.5. Safety Endpoints

Safety endpoints include AEs (including AESIs and device related AEs, ISRs, and ASRs), ECGs, vital signs, and safety laboratory data.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to database lock and releasing the database and classifications will be documented per standard operating procedures.

4.1. PK population

The PK population is defined as all participants randomized who are dosed 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. Data impacted by incomplete dosing (including those caused by device failures/malfunctions) as reported on CRF will not be included in the PK analysis set.

4.2. Full Analysis Set

All participants who are randomized and take at least 1 dose of study intervention (regardless of complete or incomplete dose). 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.

4.3. Per Protocol Analysis Set

Not applicable.

4.4. Safety Analysis Set

All participants who are randomized and receive at least 1 dose of study intervention (regardless of complete or incomplete dose). AEs, laboratory tests, vital signs and other safety information will be summarized using the safety analysis set, and by the treatment subjects actually receive.

4.5. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The null hypothesis is PF-06881894 OBI is not equivalent to PF-06881894 PFS. Pharmacokinetic equivalence will be assessed by constructing the 90% confidence intervals (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% for all 3 primary endpoints, the null hypothesis is rejected.

5.2. General Methods

Data will be summarized by treatments based on timing relative to dosing. When exact date/time of a procedure performed is not available and therefore cannot be determined if it is prior to or after dosing, the procedure will be assumed performed according to the protocol. When a variable is collected at multiple time points within a treatment period and needs to be summarized by timepoint, data at scheduled collection timepoints will be used. All data, regardless collected at scheduled time points or not will be listed.

5.3. Methods to Manage Missing Data

Missing values will not be imputed.

5.4. Analysis Methods

5.4.1 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}) in at least 1 treatment period will be included in the PK population. The PK population will be the primary analysis set for the primary PK analyses. Data impacted by incomplete dosing (including those caused by device failures/malfunctions) as reported on CRF will not be included in the PK analysis set. 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 the 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.

Sensitivity analysis of the primary PK parameters will be performed using the full analysis set.

5.4.2 Safety Analysis

Safety variables (adverse events, serious adverse events, vital signs, ECGs, concomitant medication use) will be summarized according to Pfizer's implementation of CDISC standards for safety reporting.

All safety analyses will be performed on the safety population unless otherwise specified.

Treatment emergent adverse events (AEs) are defined as AEs that occur after dosing. AEs including AESIs and device related AEs, ISRs, and ASRs, ECGs, vital signs, and safety laboratory data will be summarized by treatment. AESIs that occur during the study will be identified using the C122 Targeted Medical Events (TME) list in the Pfizer product safety review plan [PF-06881894 (HSP-130) SAFETY SURVEILLANCE REVIEW PLAN (http://gdms.pfizer.com/gdms/drl/objectId/090177e199560eae)]. Safety data will be presented in tabular 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 (documented in the C122 TME list).

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.

As ASRs might occur after device activation and before dosing, an additional ASR summary will be produced for all randomized participants that include ASRs that occur after device activation.

Participants impacted by incomplete dosing (including those caused by device failures/malfunctions) as reported on CRF will be listed.

5.5 Other Endpoint(s) Analysis

Not applicable.

5.6 Subset Analyses

Not planned.

5.7 Baseline Summaries

Summaries of baseline characteristics (demography, medical history, previous medication use) will follow Pfizer's implementation of CDISC standards.

6. INTERIM ANALYSES

Not planned.

7. SAMPLE SIZE ESTIMATION

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.

8. APPENDIX

8.1 Schedule of Activities

The Schedule of Activities (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.

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																														
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
Height and weight	X																																	
Serology testing	X																																	
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

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]**
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	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	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	X

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]**

- Washout period between treatments will be at least 56 days.
- Within 30 days prior to first dose of study intervention
- Telephone visit.
- 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.
- Informed consent must be completed before any study related procedures are performed.
- Period 1 only.
- Record change(s) in medical history and prior medication since screening (Period 1 only)
- 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.
- Sitting BP, PR, respiratory rate and tympanic temperature. To be obtained prior to any procedures, eg, blood draws.
- 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.
- 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).
- FSH for women < 60 years of age who are amenorrheic for at least 12 consecutive months and not using hormonal contraception or HRT.
- This should include eGFR and Cystatin-C.
- Collected pre-dose.
- Assessment of ASR is only applicable to the period in which administration occurs via OBI.
- On Day -1, only participants with OBI applied will need assessment of ISRs and ASRs.
- 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.
- Collected pre-dose, and only collected in period 1.
- 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.
- Check exposure to positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms.

8.2 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.