A Phase 1b/2 Open-Label Study to Evaluate Pharmacokinetics, Safety, Efficacy, and Pharmacodynamics of PF-06801591 (PD-1 inhibitor) in Participants with Advanced Malignancies

STATISTICAL ANALYSIS PLAN – B8011007

Compounds: PF-06801591

Compound Name: Sasanlimab

Version: 4.0

Date: 7-APR-2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) version 4 for Study B8011007 is based on the protocol amendment 2 dated 24June2020.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
1	11-Dec-2019	Not applicable.
2	27-Jun-2020	Title page and headers - Sasanlimab has been added since it was officially confirmed as the generic name for PF-06801591. Section 2 "Introduction" - clarified that the primary analysis date to be based on 1 year after Phase 2 last participant's randomization date. The final analysis will be based on last participant's last visit . Section 2.1.1 "Study Objectives and Endpoints" - The term "Japanese participants" was removed from objectives since the Phase 1b includes Asian participants (not limited to Japanese participants) per protocol amendment #2. Section 2.1.2. "Primary Estimands" – clarified that if there are participants non evaluable for DLT in Phase 1b, then additional participants can be enrolled. Section 2.2. "Study Design" - Figure 1 "Study Schema" was updated. Phase 1b includes now escalation and expansion parts per protocol amendment #2. Clarification of stratification by line in phase 2 was added. Section 3.4.1. "Study drug, study treatment and baseline definitions" – "treatment group" definition was updated to reflect escalation and expansion parts in Phase 1b. Section 4. "Analysis Sets" – removed replacement of non-evaluable participants for DLT as not relevant to the definition of the DLT-evaluable analysis set. Section 5.1.1. "Hypotheses and sample size determination" – Sample size in Phase 1b was updated due to an addition of the expansion part. The Phase 2 null and alternative hypotheses were revised. Section 5.1.2. "Decision rules" – the rules for expansion part were added. Section 5.2. "General Methods" – added that the summary of endpoints in Phase 1b will be done by treatment arm and by dose with the escalation and expansion parts combined.
3	17-Dec-2020	Section 3.4.1. "Study drug, study treatment, and baseline definitions"- the rule how to handle missing measurements at baseline for efficacy analysis was clarified, some changes to align with the master SAP. Section 3.4.2. "Baseline characteristics" – Physical measurements were removed. Section 5.2.9. "Unscheduled visits" – It was clarified that descriptive statistics by visit convention will be needed only if such analyses are performed. Section 5.2.11. "Adequate post-baseline tumor assessment" – A clarification was added that time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date. Section 5.3.1.2. "Pharmacokinetic parameters" – Text for how to handle missing pharmacokinetic parameters was updated. Section 5.3.2.1. "Disease history" – The imputation rule for missing dates was added. Section 5.3.2.3. "Prior and concomitant medications" – The section was added. Section 6.2.5. "Endpoints for Immunogenicity Data of PF-06801591" – Updated Table 6 for Participants Characterized Based on Anti-Drug Antibody Results (ADA Status) and Neutralizing Antibody Results (NAb Status) Section 6.2.5.1. "ADA titer" – Ever and baseline ADA positive terms were removed. Section 6.2.6. "PD-L1 Expression in Baseline Tumor Tissue" - PD-L1 status determination was clarified.

		Section 6.5.1.1. “Demographic characteristics” - Physical measurements were removed. Section 6.5.1.3. “Disease characteristics” – CRF page was updated. Section 6.5.1.4. “Prior anti-cancer therapies” – Listing of anti-cancer radiotherapies and listing of anti-cancer surgeries were removed. Section 6.5.2.1. “Participant disposition” – analyses of randomization strata by CRF, randomized versus treated were added. COVID-19 listings were added. Section 6.5.2.2. “Protocol deviations” – A deviation describing participants who received incorrect treatment was added. A listing of COVID-19 related deviations was added. Section 6.5.4. “Concomitant Medications and Non-drug Treatments” – Summary of prior medications and listings prior and concomitant medications and procedures were removed. Section 6.5.5. “Subsequent Anti-Cancer Therapies” – Listing of subsequent anti-cancer therapies was removed. Section 6.6.2. “Deaths” – It was added that deaths related to COVID-19 will be flagged. Section 6.6.5.1. “Hematology and chemistry parameters” – Analyses of laboratory data by visit, summary of individual levorotary grades were removed. Section 6.6.5.2. “Other laboratory parameters” – Listings of abnormal values and other clinical parameters were removed. Section 6.6.6. (previous version). “Vital Signs” – section was removed. Section 6.6.6. “Electrocardiogram” – ECG listings were removed. Log-linear regression method was changed to linear regression methods. Section 6.6.8 (previous version). “ECOG performance status” – The section was removed. Minor editorial and consistency changes.
4	7-Apr-2022	Second and subsequent pages – The header was modified to show the correct study number B8011007. Section 4. “Analysis Sets” –One of the requirements for inclusion into PK parameter analysis set was revised from C_{trough} at 12 weeks to any PK parameter. Section 5.1.2. “Decision rules” – The “escalate” decision rule for 1 DLT in 6 patients was added. Section 5.2.6. “Definition of start of new anti-cancer therapy” – Radiation therapy is included if it is ‘Curative in intent’. Section 5.3.1.2. “Pharmacokinetic parameters” – Definitions of tau and window for Ctrough were added. Section 6.2.5. “Endpoints for immunogenicity data of PF-06801591” - Analyses of ADA and NAb data were updated. Section 6.5.2.1. “Participant disposition” – COVID-19 listings were modified to present participant treatment discontinuations and participants who became not evaluable for the primary study outcome. Section 6.5.3.2. “Dose delays” – categories for dose delays based on number of days were modified. Section 6.6.1.1. “All adverse events” – Summary of TEAEs and Related TEAEs leading to treatment interruptions were added. Section 6.6.1.2. “Adverse events leading to interruption of study treatment” – section was added. Table 7 “Case Definition for irAEs”. - Thyroid disorders were added.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B8011007. 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.

Throughout this document '**non-randomized phase**' refers to Phase 1b and '**randomized phase**' refers to Phase 2 of this study, and '**start date**' refers to first dose of study treatment for non-randomized Phase 1b and date of randomization for randomized Phase 2.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (i.e., pharmacokinetic (PK) concentration, anti-drug antibody (ADA), neutralizing antibody (NAb), biomarker data). The primary analysis will include all data up to a cut-off date corresponding to 1 year after the Phase 2 last participant's 'start date'. The final analysis of the data will be performed after last participant last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• Phase 1b: To assess dose limiting toxicity (DLT) rate of PF-06801591. • Phase 2: To compare PF-06801591 exposure of 600 mg SC Q6W to 300 mg SC Q4W in terms of AUCτ and C_{trough} at steady state	• Phase 1b: DLTs observed in Cycle 1 (28 days for Q4W and 42 days for Q6W) • Phase 2: PK parameters (AUCτ and C_{trough} at steady state, at Week 12)
Secondary	
• To assess the overall safety and tolerability	• AEs (type, severity [as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version (v) 5.0], timing, seriousness, and relationship to study treatments), laboratory test abnormalities (type, severity and timing)
• To characterize the PK (for Phase 1b and Phase 2)	• PK parameters (e.g., AUC and C_{trough} after first dose and C_{trough} at steady state)
• To characterize the immunogenicity	• Immunogenicity (ADA/NAb incidence and titer)
• To assess anti-tumor activity	• Objective response (OR) and Time-to-response (TTR) by investigator assessment using RECIST v1.1
• To assess the correlation between clinical activity and PD-L1 expression in baseline tumor tissue	• PD-L1 expression in baseline tumor tissue.
CCI [redacted]	
[redacted]	[redacted]

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

2.1.2. Primary Estimands

This section defines the estimands associated with the primary endpoints of the study. The populations associated with estimands are as follows:

Phase 1b

- Participants from Asian countries only with advanced solid tumors

Phase 2

- Participants from global sites with 1st line and 2nd line non-small cell lung cancer (1L and 2L NSCLC)

The endpoint definitions, the observations that will be considered in the derivation of the endpoint, and the associated analyses are described or referenced below.

Primary Estimand (DLT): DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1, 28 days for 300 mg Q4W and 42 Days for 600 mg Q6W) in Phase 1b.

- Variable: Occurrence of DLTs. DLTs are defined in Section 3.1.
- Analysis population: DLT-evaluable participants defined as participants who receive at least 1 dose of study treatment in the Phase 1b and either experience DLT during the DLT-evaluation period or complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of study drug in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. If there are participants not evaluable for DLT, then additional participants can be enrolled to ensure that target number of DLT evaluable participants is reached
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

Primary Estimand (AUCτ and C_{trough} at 12 weeks): Ratio of adjusted geometric means for AUCτ and C_{trough} are estimated based on data from PK-evaluable participants in Phase 2.

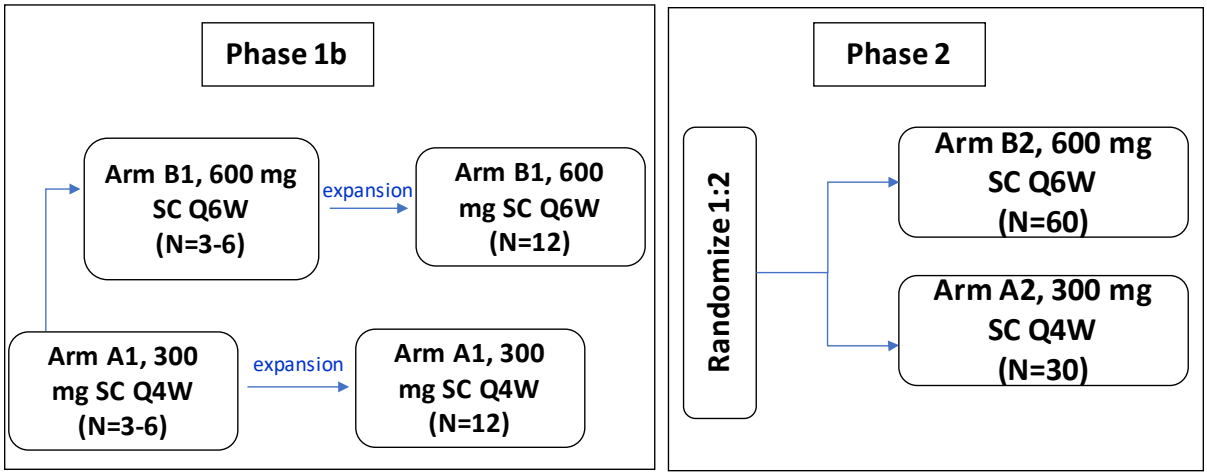
- Variable: values of AUCτ and C_{trough} at steady state, where τ = 4 weeks for Arm A2 and 6 weeks for Arm B2.
- Analysis population: PK-evaluable participants defined as all participants who received at least one dose of study drug in Phase 2 and have a C_{trough} at 12 weeks.

- Population-level summary measure: Ratio of adjusted geometric means for AUCτ and C_{trough}. AUCτ and C_{trough} will be summarized descriptively (n, mean, standard deviation, coefficient of variation [CV], median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval [CI]) by dose, cycle, and day. Dose normalized parameters will be reported as appropriate. The trough concentrations will be plotted for each dose using a box whisker plot by cycle and day in order to assess the attainment of steady state.

2.2. Study Design

The Study schema is presented in Figure 1.

Figure 1. Study Schema



Phase 1b population: Asian participants with advanced solid tumors; Phase 2 population: global participants with 1L and 2L NSCLC.
Phase 1b and Phase 2 will be conducted in parallel.

This is a Phase 1b/2, open-label, multi-center study to evaluate PK, safety, efficacy and pharmacodynamics of PF-06801591 in Asian participants with advanced solid tumors (Phase 1b) and global participants with 1L and 2L NSCLC (Phase 2). The Phase 1b is composed of two parts, a dose escalation part and a dose expansion part. The Asian Phase 1b and global Phase 2 will be conducted in parallel and participants from Japanese sites will be allowed to enter the global Phase 2 after Phase 1b meets safety criteria as defined by the modified toxicity probability interval (mTPI) design (Section 5.1). Chinese participants will be enrolled only in the Phase 1b part of this study

Phase 1b Design

Participants will be enrolled to 2 treatment arms

- Arm A1: PF-06801591 300 mg SC Q4W (up to 6 DLT-evaluable participants in dose escalation and approximately 12 participants in dose expansion part) and

- Arm B1: PF-06801591 600 mg SC Q6W (up to 6 DLT-evaluable participants in dose escalation and approximately 12 participants in dose expansion part)

Dose escalation part: The first dose level of PF-06801591 will be 300 mg SC Q4W (Arm A1). If this dose level is considered safe as per the mTPI design, the participant enrollment will start at the next dose level at 600 mg SC Q6W (Arm B1). Each dose level will start with enrolling a group of 3-4 participants, allowing for additional participants (up to 6 in total) to be enrolled. The DLT observation period will be 1 cycle (i.e., 4 weeks for Arm A1 and 6 weeks for Arm B1).

Dose expansion part: once the safety evaluation is completed in the dose escalation part, an expansion part will be opened and PF-06801591 will be further evaluated sequentially at 300 mg SC Q4W (Arm A1) and at 600 mg SC Q6W (Arm B1) for further PK and safety evaluations. Each expansion dose level will enroll approximately 12 participants as long as DLT rate is below 0.35. After the enrollment in Arm A1 expansion part for DLT monitoring is completed and DLT rate is below 0.35, then Arm B1 expansion enrollment will be initiated. The DLT observation period will be 1 cycle (i.e. 4 weeks for Arm A1 and 6 weeks for Arm B1). In the event of participant discontinuations prior to obtaining steady state PK at Cycle 4 for Q4W or Cycle 3 for Q6W, additional participants may be enrolled to achieve a minimum of 8 participants from mainland China at each dose level with evaluable PK at

Phase 2 Design

Participants will be randomized to Arm A2:Arm B2 in a 1:2 ratio.

- Arm A2: PF-06801591 300 mg SC Q4W (30 participants) and
- Arm B2: PF-06801591 600 mg SC Q6W (60 participants)

The study will use interactive response technology (IRT) for participant randomization/treatment allocation in Phase 2. The randomization will be stratified by line of therapy (1st line vs 2nd line).

- 1st line: no prior therapy for advanced or metastatic disease
- 2nd line: one prior therapy for advanced or metastatic disease

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- **Phase 1b:** DLTs observed in Cycle 1 (28 days for Q4W and 42 days for Q6W)

  For the Phase 1b, any of the following AEs occurring during the DLT observation period (the first cycle of treatment) which are attributable to the investigational product will be classified as DLTs. The DLT observation period will be 1 cycle. Cycle 1 is defined as the time from the first dose to the next expected dose of PF-06801591. The planned treatment cycle duration is 4 weeks (28 days) for Arm A1 and 6 weeks (42 days) for Arm B1.

- Grade 5 AE not clearly due to the underlying disease or extraneous causes
- Hematologic toxicity:
  - Following Grade 3-4 hematologic AE:
    - Grade 4 neutropenia lasting for > 7 days;
    - Febrile neutropenia (defined as absolute neutrophil count (ANC) < 1000/mm3 with a single temperature of >38.5°C (101.3°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour;
    - Grade ≥ 3 neutropenic infection (defined as ANC < 1000/mm^3 or < 1.0 × 10^9/L and Grade ≥ 3 infection);
    - Grade 4 thrombocytopenia;
    - Grade 3 thrombocytopenia with clinically significant bleeding or requiring medical intervention (e.g., transfusion);
    - Grade 4 anemia;
    - Grade 3 anemia requiring transfusion or steroids.
- Non-Hematologic Toxicity:
  - Grade 4 non-hematologic AE;
  - Grade 3 AE lasting > 3 days despite optimal supportive care;
  - Grade 3 central nervous system AE regardless of duration;
  - Meets criteria for drug-induced liver injury (see Protocol Appendix 6).
- Delay of ≥ 3 weeks in receiving the next scheduled administration due to persisting treatment-related toxicities;

The following AEs will not be adjudicated as DLTs:

- Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement.
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
- Isolated Grade 3-4 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade ≤ 3 injection reactions and allergic reactions will not be considered dose limiting as they are unlikely to be dose related, but all available information on these events will be collected.

In addition, clinically important persistent toxicities that are not included in the above criteria may be considered a DLT following review by the investigators and Pfizer. All DLTs need to represent a clinically significant change from baseline.

- **Phase 2:** PK parameters (AUC_{τ} and C_{trough} at steady state, at Week 12)

Table 2. Primary PK Parameters to be Determined for PF-06801591

Parameter	Definition	Method of Determination
AUC_{τ}	Area under the plasma concentration-time profile after single dose and at steady state, starting at Week 12 (Arm A2: Cycle 4, Arm B2: Cycle 3)	Linear/Log trapezoidal method
C_{trough}	Pre-dose concentration after single dose and during multiple dosing at steady state, at Week 12	Observed directly from data

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- AEs (type, severity [as graded by NCI CTCAE v5.0], timing, seriousness, and relationship to study treatments)

  AEs will be graded by the investigator according to the CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory test abnormalities (type, severity, and timing).

3.2.2. Efficacy endpoints

- OR by investigator assessment using RECIST v1.1

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the ‘start date’ until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- TTR by investigator assessment using RECIST v1.1

  TTR is defined, for participants with an OR, as the time from the ‘start date’ to the first documentation of objective response (CR or PR) which is subsequently confirmed.

3.2.3. Pharmacokinetics endpoints

- PK parameters (e.g., AUC and C_{trough} after first dose and C_{trough} at steady state)

Table 3. Additional PK Parameters to be Determined for PF-06801591

Parameter	Definition	Method of Determination
AUCsd,τ AUCss,τ	Area under the plasma concentration-time profile from time zero to the next dose (after single dose and at steady state)	Linear/Log trapezoidal method
Cmax	Maximum observed plasma concentration	Observed directly from data
Tmax	Time for Cmax	Observed directly from data as time of first occurrence
t½[a]	Terminal half-life	Log(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
C_{trough}	Pre-dose concentration during multiple dosing	Observed directly from data
CL/F[a]	Apparent clearance	Dose / AUCτ for steady state
Vz/F[a]	Apparent volume of distribution	Dose / (AUCτ ·kel) for steady state
AUCsd,τ (dn) AUCss,τ (dn)	Dose normalized AUC	AUC / Dose
Cmax(dn)	Dose normalized Cmax	Cmax / Dose

[a] If data permit

3.2.4. Immunogenicity endpoints

- Immunogenicity (ADA/NAb incidence and titer)

3.2.5. Biomarker endpoint

- PD-L1 expression in baseline tumor tissue.

Table 4. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest that are defined by tumor cell morphology	Pathologist, assisted by image analysis

CCI

[redacted]

[redacted]

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to PF-06801591 and '**study treatment**' refers to one of the following:

- PF-06801591 300 mg SC Q4W
- PF-06801591 600 mg SC Q6W

In this study '**treatment group**' refers to one of the following:

Phase 1b

- Arm A1 Escalation: PF-06801591 300 mg SC Q4W
- Arm A1 Expansion: PF-06801591 300 mg SC Q4W
- Arm B1 Escalation: PF-06801591 600 mg SC Q6W
- Arm B1 Expansion: PF-06801591 600 mg SC Q6W

Phase 2

- Arm A2: PF-06801591 300 mg SC Q4W
- Arm B2: PF-06801591 600 mg SC Q6W

Start and end dates of study treatment

The date/time of first dose of study treatment is the earliest date/time of non-zero dosing of the study drug.

The date/time of last dose of study treatment is the latest date/time of non-zero dosing of the study drug.

Definition of baseline

Definition of baseline for efficacy analyses

The last measurement prior to the 'start date' will serve as the baseline assessment for efficacy analyses. If such a value is missing, the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessments data in Phase 2 where the baseline assessment would be considered as missing.

Definition of baseline for safety analyses

The last measurement prior to the start of study treatment is defined as 'baseline' for safety analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 (day of first dose of study treatment) for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose assessment.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. QTcB and QTcF will be derived based on RR and QT.

Definition of baseline for immunogenicity analyses

The last available assessment prior to the start of treatment with study drug is defined as 'baseline' for immunogenicity analyses. If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first dose of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing.

Definition of baseline for biomarker analyses

The last assessment prior to first dose of study treatment will serve as the baseline assessment for biomarker analyses. For biomarkers that are planned to be assessed on Cycle 1 Day 1, it will be assumed that the assessment was performed prior to study treatment administration, if the assessment time point is not collected or is missing.

3.4.2. Baseline characteristics

Randomization in Phase 2 is stratified by line of therapy (1st line vs 2nd line), as recorded in the IRT.

Other baseline characteristics (including demographics, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE). The criteria for classification of an AE as an irAE are described in Appendix 1.

4. ANALYSIS SETS

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

Only participants who signed informed consent will be included in the analysis sets below.

Table 5. Analysis Sets

Population	Description
Enrolled	All participants who sign the informed consent document (ICD)
Full analysis set (FAS)	Phase 1b: All enrolled participants who take at least 1 dose of study drug. Participants will be classified according to the study treatment actually received. If a participant receives more than one treatment the participant will be classified according to the first study treatment received. Phase 2: All participants who are randomized. Participants will be classified according to the treatment assigned at randomization.
Safety analysis set	All enrolled participants who receive at least 1 dose of study drug. Participants will be classified according to the study treatment actually received. If a participant receives more than one study treatment, the participant will be classified according to the first study treatment received. In the non-randomized phase of the study, the FAS and the safety analysis set are identical.
DLT-evaluable analysis set	The DLT-evaluable analysis set includes all participants who receive at least 1 dose of study treatment in the Phase 1b and either experience DLT during the DLT-evaluation period or complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of each study drug in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT.
Biomarker analysis set	The biomarker analysis set is a subset of the safety analysis set and will include participants who have at least 1 baseline biomarker assessment.

Immunogenicity analysis set	The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least 1 ADA/NAb sample collected.
PK analysis sets	Phase 1b and Phase 2: The PK concentration analysis set is a subset of the safety analysis set and will include participants who have at least 1 reportable concentration measurement. The PK parameter analysis set is a subset of the safety analysis set and will include participants who have at least 1 PK parameter reported.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

Approximately 126 participants will be assigned to study intervention based on eligibility, for an estimated total of 3-6 DLT-evaluable participants at each dose level (6-12 in total) in the dose escalation part and approximately 12 additional participants at each dose level (24 in total) in the expansion part of Phase 1b and approximately 90 randomized participants in 1:2 ratio between two treatment arms in Phase 2.

Phase 1b

The primary objective of the Phase 1b of the study is to assess the DLT rate of PF 06801591 in Asian participants.

Approximately 36 participants in total will be enrolled in Phase 1b with 3-6 participants at each dose level (6-12 in total) will be enrolled in the dose escalation part and approximately 12 additional participants at each dose level (24 in total) in the expansion part. However, the final number of participants in Phase 1b will depend on the number of participants evaluable for DLT at each dose level. Each dose level in the dose escalation part will start with enrolling a group of 3-4 participants, allowing for additional participants (up to 6 in total) to be enrolled. Once the safety evaluation is completed in the dose escalation part, the expansion part will be opened and PF-06801591 will be evaluated sequentially at 300 mg SC Q4W (Arm A1) and at 600 mg SC Q6W (Arm B1). Each expansion dose level will enroll approximately 12 participants as long as the DLT rate is below 0.35. After the enrollment in Arm A1 expansion part for DLT monitoring is completed and DLT rate is below 0.35, then Arm B1 expansion enrollment will be initiated. The DLT observation period will be 1 cycle (i.e. 4 weeks for Arm A1 and 6 weeks for Arm B1). In the event of participant discontinuations prior to obtaining steady state PK at Cycle 4 for Q4W or Cycle 3 for Q6W, additional participants may be enrolled to achieve a minimum of 8 participants in the expansion part at each dose level with evaluable PK at steady state.

Phase 2

The primary objective of the Phase 2 of the study is to compare PK exposure between arms A2 and B2 in terms of AUCτ and C_{trough} at Week 12 (at approximately steady state). The objective of the exposure comparison is to demonstrate that the mean PK exposure obtained

from 600 mg SC Q6W regimen (Arm B2, Test) is not lower than 80% of the mean PK exposure obtained from the reference regimen of 300 mg SC Q4W (Arm A2, Reference).

The following hypothesis will be tested at a one-sided α= 0.05 level of significance separately for log-transformed AUCτ and for log-transformed C_{trough}

H_0: $\mu_T - \mu_R \leq \theta_L$ (Ratio $\leq$ 0.8)

H_A: $\mu_T - \mu_R > 0$ (Ratio > 1)

where μ_T and μ_R represent the average bioavailability on a log scale for the treatments from Arms A2 and B2 respectively and $[\theta_L, \infty)$ defines the bioequivalence range.

Since $\mu T - \mu R$ = ln (Ratio) and θ_L=ln (0.8) = -0.223, the hypotheses can be expressed as

H_0: $\mu_T - \mu_R \leq -0.223$

H_A: $\mu_T - \mu_R > 0$

The standard deviation can be expressed through the Coefficient of Variation (*CV*) on the log scale in the following way:

$$SD = \sqrt{\ln(CV^2 + 1)}$$

Assuming $CV = 0.4$ for C_{trough} and $CV = 0.26$ for AUCτ, then

SD (C_{trough}) = 0.385,

SD (AUCτ) = 0.256.

Assuming that the true ratio between Arm B2 and Arm A2 for both AUCτ and C_{trough} is 1.0 and assuming the CVs above for each of C_{trough} and AUC, a sample size of 90 participants (1:2 randomization ratio, 30 and 60 participants in Arm A2 and B2, respectively) will provide at least 80% power that the lower bound for the 90% CI for the ratio of Test to Reference treatment for the geometric mean of AUCτ and C_{trough} at steady-state will be at least 80%.

5.1.2. Decision rules

Phase 1b

The dosing decision and safety assessment will be guided by the estimation of the probability of DLT in Cycle 1. However, other evidence such as safety data beyond DLT, clinical activity, PK, and pharmacodynamic data will play an important role in the final decision. A safe dose will be determined using the adaptive mTPI design. The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 toxicity intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (pT) rate (pT=0.30). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the

current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. The mTPI dose de-escalation/escalation recommendation will be based on the estimated toxicity rate and 3 intervals (underdosing, target toxicity, and excessive toxicity) as shown below:

- If a dose is in the underdosing [0, 0.25) toxicity interval: escalate to next higher dose;
- If a dose is in the target toxicity [0.25, 0.35) toxicity interval: stay at current dose;
- If a dose is in the excessive toxicity or overdosing [0.35, 1] toxicity interval: de-escalate to a lower dose.

Each dose level will start with enrolling a group of 3-4 participants, allowing for additional participants (up to 6 in total) to be enrolled in the dose escalation part. Once the safety evaluation is completed in the dose escalation part, the expansion part will be opened and PF-06801591 will be evaluated sequentially at 300 mg SC Q4W (Arm A1) and at 600 mg SC Q6W (Arm B1) as long as the DLT rate is below 0.35.

The following table defines the dose finding scenarios:

		Number of participants treated at current dose									
		3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Number of dose limiting toxicities (DLTs)	**0**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
	1	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
	2	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**E**	**E**
	3	**DU**	**DU**	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
	4		**DU**	**DU**	**DU**	**D**	**D**	**S**	**S**	**S**	**S**
	5			**DU**	**DU**	**DU**	**DU**	**DU**	**D**	**S**	**S**
	6				**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**
	7					**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
	8						**DU**	**DU**	**DU**	**DU**	**DU**
	9							**DU**	**DU**	**DU**	**DU**
	10								**DU**	**DU**	**DU**
	11									**DU**	**DU**
	12										**DU**

Escalation/De-escalation algorithms for total number of participants treated at the current dose level (current and previous cohorts)

With 3 participants treated at current dose level:

- 0 DLT → escalate;
- 1 DLT → remain at the same dose;
- 2 DLTs → de-escalate;

- 3 DLTs → de-escalate and consider current dose as intolerable.

With 4 participants treated at current dose level:

- 0 DLT → escalate;
- 1-2 DLTs → remain at the same dose;
- 3-4 DLTs → de-escalate and consider current dose as intolerable.

With 5 participants treated at current dose level:

- 0 DLT → escalate;
- 1-2 DLTs → remain at the same dose;
- 3 DLTs → de-escalate;
- 4-5 DLTs → de-escalate and consider current dose as intolerable.

With 6 participants treated at current dose level:

- 0-1 DLT → escalate;
- 2-3 DLTs → remain at the same dose;
- 4-6 DLTs → de-escalate and consider current dose as intolerable.

Phase 2

Bioequivalence of Test and Reference will be demonstrated if the estimated lower bound of the two-sided 90% CI for the ratios (Test/Reference) of adjusted geometric means for both AUCτ and C_{trough} exceed 80%.

5.2. General Methods

As described in Section 3.4, in this study '**treatment arm**' refers to one of the following:

- Arm A1 Escalation: PF-06801591 administered as 300 mg SC Q4W in Phase 1b
- Arm A1 Expansion: PF-06801591 administered as 300 mg SC Q4W in Phase 1b
- Arm B1 Escalation: PF-06801591 administered as 600 mg SC Q6W in Phase 1b
- Arm B1 Expansion: PF-06801591 administered as 600 mg SC Q6W in Phase 1b
- Arm A2: PF-06801591 administered as 300 mg SC Q4W in Phase 2
- Arm B2: PF-06801591 administered as 600 mg SC Q6W in Phase 2

Endpoints will be summarized based on the analysis sets described in Table 5 by treatment arm and by dose with Escalation and Expansion parts combined in Phase 1b, unless otherwise specified as follows.

- Arm A1 Escalation part

- Arm A1 Expansion part
- Arm A1 Escalation and Expansion combined
- Arm B1 Escalation part
- Arm B1 Expansion part
- Arm B1 Escalation and Expansion combined
- Arm A2
- Arm B2

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values [i.e., n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (e.g., adverse event onset, tumor measurement) will be calculated as:

$$\text{Study day} = \text{Date of the assessment/event} - \text{start of study treatment} + 1.$$

The study day for assessments occurring prior to the first dose of study treatment (e.g., baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event − start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Response to regimen' eCRF page that is after the first dose of study treatment.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used to select tumor assessments in the derivation of BOR (see Section 6.2.2.2).

The start date of new anti-cancer therapy is the earliest date after the 'start date' amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Response to regimen' eCRF page
- Start date of radiation therapy recorded in 'Radiation Treatment' eCRF page with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'Non-drug Treatments (Surgery)' eCRF page when 'Outcome of Procedure' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Response to regimen', 'Radiation Treatment ', and 'Non-drug Treatments (Surgery)' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, electrocardiograms (ECGs) and vital signs will include only data from scheduled visits (if such analyses are performed).

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 31 days prior to and including the ‘start date’.
- All documented lesions must have non-missing assessments (i.e., non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, stable disease (SD), non-CR/non-PD, or PD can be determined (see Section 6.2.2.2). Time points where the response is not evaluable (NE) or no assessment is performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1) A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample);

2) A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

The actual time of sample collection will be used in PK parameter calculation. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal.

If available, the next cycle predose (0hr) concentration will be included in the PK analysis as tau:
For Cycle 1

- For Q4W, tau = 672 hrs (28 days) Cycle 2 predose (0hr) included at the end of the concentration-time profiles for Cycle 1 single dose analysis.
- For Q6W, tau = 1008 hrs (42 days) Cycle 2 predose (0hr) included at the end of the concentration-time profiles for Cycle 1 single dose analysis.

For Cycle 3 and Cycle 4

- For Q4W, tau = 672 hrs (28 days) Cycle 5 predose (0hr) included at the end of the concentration-time profiles for Cycle 4 (84 days or 12 weeks) steady state analysis.
- For Q6W, tau = 1008 hrs (42 days) Cycle 4 predose (0hr) included at the end of the concentration-time profiles for Cycle 3 (84 days or 12 weeks) steady state analysis.

For inclusion in Ctrough estimates, a +/- 5 day window from the planned nominal time relative to previous dose (28 days for a Q4W regimen or 42 days for a Q6W regimen) will be applied to all treatment groups for inclusion in summary statistics and statistical comparisons.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e., not calculated). NC values will not be generated beyond the day that a participant discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment, if more than 50% of the data are NC. For statistical analyses (i.e., analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the participant should be considered to be ongoing and use the cutoff date for the analysis as the last dosing date.
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date (non-imputed) among the following:

- All participant assessment dates (blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, radiation, surgery)
- Start and end dates of anti-cancer therapies
- Start and stop dates of concomitant therapies including non-drug treatments or procedures
- AE start and end dates
- Study drug start and end dates
- Randomization date
- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

If there is a record for death, but the date is missing or is partial, it will be imputed based on the last contact date.

- If the date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - 1st day of the month and year of death, if day of death is missing, OR
  - January 1st of the year of death, if both the day and month of death are missing.

5.3.3.3. Tumor assessments

All investigation dates (e.g., X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g., X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date, then the imputed start date should be set to the end date.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For participants who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN imputed start date = 01JANYYYY

- Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

5.3.4. Other missing or partial dates

Imputation methods generally apply to partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

These rules are used unless the calculations result in negative time durations (e.g., date of resolution cannot be prior to date of onset). In this case, the resolution and onset dates will be the same and the duration will be set to 1 day.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary analysis

DLT during the DLT evaluation period (Cycle 1) is the primary endpoint of the Phase 1b. Analyses of DLT will be based on the DLT-evaluable analysis set as shown in Table 5. The occurrence of DLTs and AEs constituting DLTs will be listed and summarized by treatment group in Phase 1b as described in Section 2.1.2.

6.1.2. AUCτ and C_{trough} at 12 weeks for Phase 2

6.1.2.1. Primary analysis

Ratio of adjusted geometric means for AUCτ and C_{trough} are estimated based on data from PK-evaluable participants in Phase 2 as described in Section 2.1.2.

For participants enrolled in Phase 2 of the study, the individual concentration-time data of PF-06801591 during Cycle 1 for both arms, Cycle 4 for Arm A2 and Cycle 3 for Arm B2 will be analyzed separately by non-compartmental methods to estimate the PK parameters. The PK parameters will include C_{trough} at 12 weeks and AUCτ (where τ = 4 weeks for Arm A2 and 6 weeks for Arm B2). C_{max}, T_{max}, and AUC_{last} will also be calculated. If data permit PK parameters such as $t_{½}$, clearance (CL), volume of distribution (V_d) will also be estimated using data from for Cycle 1 (both arms), Cycle 4 (for Arm A2) and Cycle 3 (for Arm B2).

For the primary PK objectives of AUCτ or C_{trough} at steady-state, estimates of the adjusted mean differences (Test [Arm B2] – Reference [Arm A2]) and the corresponding 90% CIs will be obtained from the model. The adjusted mean differences and the 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% CIs for the ratios. Test treatment relative to Reference treatment will be concluded if the lower bound of the 90% CIs for the ratio of adjusted geometric means of Test treatment relative to Reference treatment for AUCτ or C_{trough} at steady-state fall is greater than equal to 80%. PF-06801591 300 mg SC Q4W will be the Reference treatment, while PF-06801591 600 mg SC Q6W will be the Test treatment.

6.2. Secondary Endpoints

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS as shown in Table 5 by treatment group unless otherwise specified. Tumor endpoints (OR and TTR) will be analyzed based on investigator assessment

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- [(Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline] × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each participant with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Objective response

Best Overall Response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the 'start date' until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)

- SD (applicable only to participants with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 16 weeks after the 'start date' (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR–SD–PR is considered a confirmed PR. A sequence of PR–SD–SD–PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Participants who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of participants with OR in the analysis set.

ORR by treatment group will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method [1] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of participants with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to participants with non-measurable disease at baseline), PD, and NE will be tabulated. Participants with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No evidence of disease at baseline
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the 'start date' without further evaluable tumor assessments)

- PD too late (>16 weeks after the 'start date')

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (i.e., SD of insufficient duration).

6.2.2.3. Time to response

Time to Response (TTR) is defined for participants with confirmed objective response (CR or PR) as the time from the 'start date' to the date of first documentation of objective tumor response which is subsequently confirmed.

TTR (in months) = [first date of OR – 'start date' +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group. Pharmacokinetic parameters for PF-06801591 will be taken from observed values or derived from plasma concentration-time data as described in Section 3.2.3.

Natural log transformed PK parameters (AUCτ or Ctrough at steady-state) will be analyzed using an Analysis of variance (ANOVA) model with treatment as fixed effects and participant as random effect. For the primary PK objectives of AUCτ or Ctrough at steady-state, estimates of the adjusted mean differences (Test – Reference) and the corresponding 90% CIs will be obtained from the model. The adjusted mean differences and the 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% CIs for the ratios. Bioequivalence will be concluded if the lower bound of the 90% CIs for the ratio of adjusted geometric means of Test treatment relative to Reference treatment for AUCτ or Ctrough at steady-state is greater than or equal to 80%. PF-06801591 300 mg SC Q4W will be the Reference treatment, while PF-06801591 600 mg SC Q6W will be the Test treatment.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI) of plasma concentrations and pharmacokinetic parameters will be presented in tabular form by treatment arm, dose level, cycle, day and nominal time. For T_{max}, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV.
- Additionally, similar descriptive statistics will also be generated for dose-normalized C_{max} and AUC parameters.

  Log-linear plots of geometric mean plasma concentrations by nominal time for PF-06801591 will be presented for PK sampling days by treatment arm, cycle, and study day.

- Box plots for AUC and C_{trough} for PF-06801591 will be generated by cycle. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing changes in AUC and C_{trough} for each drug in individual participants will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to explore any association between study drug exposure and biomarkers or significant safety endpoints. Details of these analyses will be outlined in a separate pharmacometric analysis plan (PMAP). The results of these analyses may be reported separately.

6.2.5. Endpoints for immunogenicity data of PF-06801591

ADA/NAb data will be listed and summarized by treatment arm and, if deemed appropriate, combined across treatments. Participants will be characterized into different ADA and NAb categories based on the criteria defined in Table 6.

Table 6. Participants Characterized Based on Anti-Drug Antibody Results (ADA Status) and Neutralizing Antibody Results (NAb Status)

Term	Definition
ADA-positive sample	ADA sample titer (log10) ≥ 2.00
ADA-negative sample	ADA sample titer (log10) < 2.00
NAb-positive sample	NAb sample titer (log10) ≥ 0.602
NAb-negative sample	NAb sample titer (log10) < 0.602
Pre-existing ADA/NAb	Positive ADA/NAb at baseline (e.g. day 1 pre-dose)
Cross-reactivity	This often refers to immunogenicity testing against an endogenous antigen, biosimilar reference product or another biotherapeutic within the same therapeutic class.
Subject-level immunogenicity analysis population	
ADA evaluable population	All subjects with ≥ 1 post-treatment ADA result.
NAb evaluable population	ADA-positive subjects with ≥ 1 post-treatment NAb result, plus all ADA-negative subjects. An ADA-positive subject without any post-treatment NAb data is excluded from the analysis population.
Subject-level definitions	
Treatment-induced ADA	Baseline ADA titer is missing or negative and subject has ≥ 1 post-treatment positive ADA titer.
Treatment-boosted ADA	Baseline ADA titer is positive and subject has a ≥ 4-fold dilution increase in ADA titer from baseline in ≥ 1 post-treatment sample. Since the ADA titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline.
ADA-positive subject	A subject with ≥ 1 treatment-induced or treatment-boosted ADA response.
ADA-negative subject	An ADA evaluable subject without treatment-induced or treatment-boosted ADA response. Subject either has (1) all ADA-negative results throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post dose.
ADA incidence	The percent of ADA-positive subjects in a treatment group/cohort or study.
Treatment-induced NAb	Baseline NAb titer is missing or negative or ADA-negative and subject has ≥ 1 post-treatment positive NAb titer.

Term	Definition
Treatment-boosted NAb	Baseline NAb titer is positive and subject has a ≥ 4-fold dilution increase in NAb titer from baseline in ≥ 1 post-treatment sample. Since the NAb titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline.
NAb-positive subject	An ADA-positive subject with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) subjects, subject is NAb positive only if the subject has ≥ 1 treatment-induced or treatment-boosted NAb response at the visit where the subject has a treatment-boosted ADA response. For visits where the subject did not show a boosted ADA response, the subject is classified as NAb-negative for the visit even if the subject has post-treatment positive NAb titer for that visit.
NAb-negative subject	(1) an ADA-negative subject or (2) an ADA-positive subject without treatment-induced or treatment-boosted NAb response (i.e. subject has all NAb-negative results throughout the study or subject is NAb positive at baseline but did not become treatment-boosted post dose).
NAb incidence	The percent of NAb-positive subjects in a treatment group/cohort or study.
Duration of ADA and NAb response (subject-level definitions)	
Transient ADA	An ADA-positive subject with (1) a treatment-induced or treatment-boosted ADA sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted ADA samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is ADA negative.
Persistent ADA	An ADA-positive subject with first and last positive ADA samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate ADA	An ADA-positive subject who is not persistent or transient.
Transient NAb	A NAb-positive subject with (1) a treatment-induced or treatment-boosted NAb sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted NAb samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is NAb negative or ADA negative.
Persistent NAb	A NAb-positive subject with first and last positive NAb samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate NAb	A NAb-positive subject who is not persistent or transient.

Note: Duration of response (persistent, transient or indeterminate), on-treatment and off-treatment definitions are only applicable to ADA (or NAb)-positive subjects.

All ADA and NAb data will be listed, and the number and percentage of participants in each ADA and NAb category will be summarized by treatment arm. Incidence of ADA and NAb positive participants and time to first ADA and NAb detection will also be summarized by treatment arm. For participants who are ADA positive (treatment-induced or treatment-boosted), the maximum observed ADA titer for a participant will be summarized. Incidence may also be presented graphically and, if ≥ 10% in a treatment arm, immunogenicity titer data may also be summarized and box plots of PK concentrations by ADA and NAb status may be presented.

Where data are summarized by visit, results will be summarized as windowed visit (i.e., cumulatively from the day/time of prior visit to the day/time of current visit) to allow inclusion of results from unplanned visits. Data from samples collected at EOT will be presented in individual listings and will be included in categorical assessments and summaries.

6.2.6. PD-L1 expression in baseline tumor tissue

Descriptive statistics (Section 5.2.3) for levels of PD-L1 expression, and number and percentage of participants with tumors categorized with baseline PD-L1 expression level (high vs low) will be presented by treatment group. Summaries of BOR will be presented by treatment group and by PD-L1 status (high vs low). PD-L1 status determination will utilize an approved algorithm and cutoff for its respective assay if one exists. Tumor cells expression with cutoff of 25% will be used for NSCLC patients tested with SP263.

CCI

6.4. Subset Analyses

Applicable to Phase 2 only. OR and TTR (if meaningful) will be summarized in the following subsets:

- Randomization stratification factor per IRT:
  - 1st line of therapy
  - 2nd line of therapy
- Geography
  - Europe
  - Asia
    - Japan
    - China
    - Other
- Age
  - Age < 65 years
  - Age ≥ 65 years
- Gender
  - Male
  - Female
- Race

- White
- Asian
- Black or African American
- Other

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS overall and separately by treatment group.

6.5.1.1. Demographic characteristics

Demographic characteristics and physical measurements will be summarized as applicable by treatment group using the following information from the 'Demography', 'ECOG Performance Status', and 'Vital Signs' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, Multiracial, Not Reported
  - Ethnic origin:
    - Hispanic or Latino or of Spanish origin
    - Not Hispanic or Latino or of Spanish origin
    - Not Reported
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years
    - < 65, 65 -< 75, 75 -< 85, ≥ 85 years
  - Geographic Region (as applicable):
    - North America
    - Latin America
    - Western Europe
    - Eastern Europe
    - Middle East
    - Australasia
    - Asia
    - Africa
  - Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

Center codes will be used for the determination of the participant's geographic region.

The listing of demographics and baseline characteristics will include the following information: participant identifier, treatment group, age, sex, race, ethnicity, and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'General Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of participants by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis' and disease assessment eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Primary diagnosis
- Time since initial diagnosis to 'start date' (months), defined as ('start date' – date of initial diagnosis)/30.4375

From RECIST eCRF pages:

- Measurable disease (lesions) at baseline (Yes, No, No disease)
- Involved disease sites at baseline

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' eCRF page) and derived variables as above.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Response to Regimen', 'Radiation Treatment' and 'Non-drug Treatments (Surgery)' eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer therapy
- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy

- Participants with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥ 4
- Intent of prior anti-cancer drug therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic, Local regional Disease-Recurrence

The prior anti-cancer drugs will also be summarized based on the number and percentage of participants by the drug class and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer drug therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

6.5.2. Study conduct and participant disposition

The following analyses will be performed based on the FAS overall and by treatment group.

6.5.2.1. Participant disposition

The percentages below will be calculated based on the number of participants screened. The following will be summarized:

- Total number of participants screened overall
- n (%) of participants who discontinued prior to first dose of PF-06810591(non-randomized Phase 1b) or prior to randomization (randomized Phase 2) overall and by reasons for discontinuation.

The percentages below will be calculated based on the number of participants in the FAS. Discontinuations will be presented overall and by reason for discontinuation:

- n (%) in each of the analysis sets defined in Section 4
- n (%) discontinued prior to receiving PF-06810591 (applicable only to randomized Phase 2)
- PF-06810591 disposition
    - n (%) entered the treatment period (i.e., received at least one dose of one of PF-06810591)
    - n (%) discontinued treatment with PF-06810591

  - n (%) ongoing treatment with PF-06810591
  - n (%) completed treatment with PF-06810591
- Follow-up
  - n (%) entered follow-up
  - n (%) discontinued follow-up
  - n (%) completed follow-up

The following will be summarized:

- Number and percentage of treated (non-randomized Phase 1b) or randomized (randomized Phase 2) participants overall, by region, by country, and by center
- Applicable to the randomized Phase 2 only:
  - Number and percentage of randomized participants by randomization strata (IRT)
  - Number and percentage of randomized participants by randomization strata (CRF)
  - Cross tabulation: stratum by IRT vs. stratum by eCRF
  - Cross tabulation: patients randomized (Arm A2/Arm B2/none) vs. patients treated (Arm A2/Arm B2/none)

A listing of participant treatment discontinuations related to COVID-19 will be presented. The listing will present those patients that have reported a TEAE of COVID19 with action taken=”Drug withdrawn”.

A listing of all participants affected by COVID-19 related study disruption who became not evaluable for the primary study outcome (DLT for Phase 1b participants and AUC or Ctrough at steady state for Phase 2 participants) by unique subject number identifier and investigational site along with a description of how the individual’s participation was altered.

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the participants and/or the conduct of the study and/or its evaluation will be reported. These include:

- Participants who are dosed on the study despite not satisfying the inclusion criteria
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn
- Participants who received the wrong treatment or an incorrect dose
- Participants who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

A listing of Protocol Deviations related to COVID-19 will be provided.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set by treatment group.

6.5.3.1. Exposure to PF-06801591

The derivations below are provided assuming 1 cycle = 4 weeks or 6 weeks for the following regimens:

- PF-06801591 administered as a SC at a dose of 300 mg once every 4 weeks in 4-week cycles (Q4W).
- PF-06801591 administered as a SC at a dose of 600 mg once every 6 weeks in 6-week cycles (Q6W).

Duration of exposure to study drug with Q4W regimen (weeks) =

(last dose date of study drug – first dose date of study drug + 28)/7

Duration of exposure to study drug with Q6W regimen (weeks) =

(last dose date of study drug – first dose date of study drug + 42)/7

Doses of PF-06801591 may be recorded in the eCRF as 600 mg, 300 mg, 0 mg or 'Unknown'. An 'Unknown' dose amount should not be considered a 0 mg dose and must be included in the derivations for first and last dose of study drug In addition, the number and percentage of participants who receive a non-zero dose different from that assigned will be summarized overall and by the number (1, 2, 3, 4, 5, ≥6) of non-zero doses different from that assigned. For participants assigned to 600 mg, a non-zero dose different from that assigned can be 300 mg or 'Unknown'. For participants assigned to 300 mg, a non-zero dose different from that assigned can be 'Unknown'.

6.5.3.2. Dose delays

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses. 'Unknown' dose amounts for PF-06801591 are considered a non-zero dose.

Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – Planned days between two consecutive doses.

Dose delays will be grouped into the following categories:

- No delay
- 1-3 days delay
- 4-6 days delay
- 7 or more days delay

No delay and 1-3 days delay will also be summarized together.

The number and percentage of participants with delayed study drug administration and maximum length of delay, i.e., the worst case of delay if participants have multiple dose delays will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set by treatment group.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study drugs, which are started before the first dose of study treatment.

Concomitant medications will be summarized from the 'Concomitant Medications' eCRF page.

Summary of concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

6.5.5. Subsequent anti-cancer therapies

Participants are not required to be followed until subsequent anti-cancer therapy unless the subsequent therapy starts during post-treatment observation period.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group.

6.6.1. Adverse events

TEAEs are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by

the investigator and those of unknown relationship (i.e., no answer to the question 'Relationship with study treatment').

- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event= Yes).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted).
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current study data prior to DB lock)

Unless otherwise specified, AEs will be summarized by number and percentage of participants with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency based on the frequencies observed for Arm B1 for Phase 1b or for Arm B2 for Phase 2.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE v5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3

  - TEAEs leading to interruption of PF-06801591
  - Related TEAEs leading to interruption of PF-06801591
  - TEAEs leading to discontinuation of PF-06801591
  - Related TEAEs leading to discontinuation of PF-06801591
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
  - irAEs
- TEAEs by SOC and PT and worst grade
- Related TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to interruption of study treatment

AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of Drug interrupted'.

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of PF-06801591 by SOC and PT
- Related TEAEs leading to interruption of PF-06801591 by SOC and PT

6.6.1.3. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to permanent discontinuation of PF-06801591, by treatment group:

- TEAEs leading to discontinuation of PF-06801591 by SOC and PT
- Related TEAEs leading to discontinuation of PF-06801591 by SOC and PT

The listing of all AEs leading to discontinuation of PF-06801591 will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' eCRF, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity
  - AE not related to study treatment
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.
- Flag for deaths related to COVID-19.

6.6.3. Serious adverse events

The frequency (number and percentage) of participants with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of participants with each of the following will be presented for irAEs, by treatment group:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- irAEs leading to discontinuation of PF-06801591, by Cluster and PT

- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria. Additional laboratory results that are not part of NCI-CTCAE v5.0 will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v5.0 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 800/mm^3$
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 1500/mm^3$

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and (ALP ≤2×ULN or missing) will be provided.

Parameters with NCI-CTCAE v5.0 grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages

for each laboratory parameter is the number of participants evaluable for CTCAE grading (i.e., those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of participants with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE v5.0.

Parameters with NCI-CTCAE grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period.

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

6.6.6. Electrocardiogram

QTcB and QTcF will be derived based on RR and QT (see below).

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of participants (e.g., >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression method which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} \times (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, heart rate and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of participants evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments
- Frequency (number and percentage) of participants with notable ECG values according to the following categories:
  - QT/ QTc increase from baseline > 30 ms, > 60 ms
  - QT/ QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Participants with notable ECG interval values and qualitative ECG abnormalities will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted in this study. However, as this is an open-label Phase 1b/2 study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-finding decisions, facilitating PK/Pharmacodynamic modeling, or to support clinical development.

7.2. Interim Analyses and Summaries

None.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413, 1934.

9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for PF-06801591.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 7. This case definition is hierarchical, i.e., each step is only checked for participants and events that have already met the prior step.

Table 7. Case Definition for irAEs

Step	Selection Criteria	
1	Adverse Event (AE) selected based on a list of pre-specified MeDRA PTs within clusters. These are included in the SRP. If AE matches the list, then it is included in the next step.	
2	AE onset on or after the first dose of study drug and on or before 90 days after last dose of study drug.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications.
3	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement.	Look in the conmed pages for AEs where concomitant medications match any of the following A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies: Thyroid disorders" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (e.g., addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATC	anatomic therapeutic chemical
AUC	area under the curve
bpm	beats per minute
CI	confidence interval
Cmax	maximum observed concentration
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DB	database
DLT	Dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FAS	full analysis set
GCP	Good Clinical Practice
HR	heart rate
ICD	informed consent document
IRT	interactive response technology
LLN	lower limit normal
LLQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mTPI	modified toxicity probability interval
NAb	neutralizing antibodies
NC	not calculated
NCI	National Cancer Institute
ND	not done
NE	not evaluable
NR	not reached / not reportable
NS	no sample
NSCLC	non-small cell lung cancer

Abbreviation	Term
PD	progressive disease
PK	pharmacokinetic
PR	partial response
PT	preferred term
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT corrected for heart rate using Fridericia's formula
QTcB	QT corrected for heart rate using Bazett’s formula
QTcP	QT corrected for heart rate using linear population correction
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease, standard deviation
SOC	system organ class
SRP	safety review plan
TBILI	total bilirubin
ULN	upper limit of normal
WBC	white blood cell