TITLE PAGE

Protocol Title: 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

Protocol Number: B8011007

Amendment Number: Amendment 2

Compound Number: Sasanlimab (PF-06801591)

Study Phase: Phase 1b/Phase 2

Short Title: A Phase 1b/2 Study of Sasanlimab (PF-06801591, PD-1 inhibitor) in Participants with Advanced Malignancies

Acronym: N/A

Sponsor Name: Pfizer Inc

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Regulatory Agency Identifier Number(s)

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EudraCT	2019-003818-14

Approval Date: 24 June 2020

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	24-June-2020
Amendment 1	13 December 2019
Original Protocol	12 October 2019

Amendment 2 (24-June-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	**Description of Change**	**Brief Rationale**
Title page and Section 1.1 Synopsis	Sasanlimab has been added in the short title. The short title has been aligned with the protocol title: "With" has been replaced by "with".	Sasanlimab is officially confirmed as the generic name for PF-06801591 in the newest recommended International Nonproprietary Names list. Adjusted typo.
Section 1.1 Synopsis, Section 2.0 Introduction, Section 2.1 Study Rationale, Section 3 Objectives, estimands and endpoints, Section 4.1 Overall Design and Section 4.2 Scientific Rationale for Study Design	The sections have been updated to extend the enrollment from only Japanese participants to also include Asian participants. Therefore, the Phase 1b is composed of two parts, dose escalation part and dose expansion part.	Asian participants, in addition to Japanese participants, will be enrolled to further characterize safety profile in this population. .
Section 1.1 Synopsis, Section 2.1 Study Rationale, Section 5.1 Inclusion Criteria, Section 6.3. Measures to Minimize Bias: Randomization and Blinding, Section 8.8.5 Specified Gene Expression Protein Research and Section 10.13 Appendix 13 Japan-specific Requirements	"Patient" has been replaced by "participant".	To be consistent with study protocol template version.
Section 1.1 Synopsis, Section 2, Introduction, Headers, Title page	"Sasanlimab" has been added in addition to "PF-06801591".	Sasanlimab is officially confirmed as the generic name for PF-06801591 in the newest

Section # and Name	Description of Change	Brief Rationale
		recommended International Nonproprietary Names list.
Section 1.1 Synopsis, 3. OBJECTIVES, ESTIMANDS AND ENDPOINTS Section 9.1.1 Estimands and Section 9.3. Populations for Analyses	The DLT-Evaluable analysis set has been updated.	Further clarity was added reporting that in case participants are non-evaluable for DLT, additional participants can be enrolled to ensure that target number of DLT evaluable participants is reached.
Section 1.3 Schedule of Activities	Reference to the study assessments and procedures section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol has been added.	This sentence has been added for further clarity.
Schedule of Activities for Phase 1b and Phase 2 (Q4W) and (Q6W).	The sentence related to the time frame between study treatment and randomization/treatment allocation has been added.. Moreover as per Section 10.1.3. Informed Consent Process, the Japanese participants enrolled in the Phase 1b of the trial will be asked to sign an additional consent document after completion of Cycle 1. It has been clarified that the end of treatment: safety assessments are not required if completed in the prior week, except for tumor assessment, which need not to be repeated if performed within the prior 12 weeks. The post-treatment period has been defined at 30, 90 and 180 days after last dose. The post treatment period ends at 180 days or at the time	To add clarity.

Section # and Name	Description of Change	Brief Rationale
	a new anticancer treatment starts whichever comes first.	
Schedule of Activities for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q4W dosing (Phase 1b and Phase 2) and for Q6W dosing (Phase 1b and Phase 2) and Section 8.8.1.2. Tumor Tissue at the End of Treatment	The sentence related to the collection of the study biopsy within "± 14 days" after the end of treatment has been removed because not consistent with the time window for the EOT (+ 7 days). Moreover, as per local regulations in China, sample collection for biobanking purpose is not allowed.	Adjusted typos and to add clarity.
Section 4.0 Overall design	It has been further clarified that the randomization will be stratified by line of therapy (1st line vs 2nd line).	To add further clarity
Section 4.1 Overall design and Section 9.4.1. DLT rate assessment	The sections have been updated to clarify that the Phase 1b is composed of two parts, dose escalation part and dose expansion part.	A dose expansion part has been added in the current amendment to further evaluate the safety profile in Asian participants. Therefore, it has been clarified that the dose expansion part will be opened once the dose escalation part is completed and dose(s) safety is confirmed.
Section 1.1 Synopsis and Section 4.4 End of study definition	The end of study definition has been updated.	The expectation is that the participants may benefit from treatment and can remain on study longer than 1 year as previously reported. Therefore, the end of study has been updated up to 3 years after the last participant is randomized or if the Sponsor determines the study should end earlier. Moreover, the sentence related to options for continuing study treatment outside the study has been removed since the duration of the study has been extended up to 3 years.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	The schema has been revised	The schema has been revised to add the dose expansion part in the Phase 1b.
Section 5.1 Inclusion Criteria	Inclusion Criteria N°1: "≥ 19 years of age in South Korea" has been added.	Since the age of consent in South Korea is 19 years, this sentence has been added for consistency.
	Inclusion Criteria N°2e: A neoadjuvant/adjuvant treatment will be counted as a line for advanced or metastatic disease if the development of recurrent or metastasis disease occurs during treatment or within 6 months after last dose.	A clear definition has been added regarding previous neoadjuvant/adjuvant treatment.
	Inclusion Criteria N°10. As for participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception.	This sentence has been added to be aligned with study protocol template.
Section 5.2 Exclusion Criteria	Exclusion Criteria N°5: "sero-positivity" has been added	Exclusion Criteria N°5: Further clarity has been added to the exclusion criteria specifying that seropositive participants cannot be enrolled.
	Exclusion Criteria N°6: This exclusion criteria has been streamlined.	Exclusion Criteria N°6: the exclusion criteria has been rephrased and is now more simple and understandable.
	Exclusion Criteria N°7: It has been clarified that the participants are not eligible if both systolic	Exclusion Criteria N°7: Further clarity has been added for

Section # and Name	Description of Change	Brief Rationale
	and diastolic blood pressures are higher than 150 and 90 mmHg, respectively.	participants' eligibility regarding blood pressure measurements.
Section 5.2 Exclusion Criteria	Live attenuated vaccines have been reported as prohibited medication within 4 weeks prior to study entry.	It has been clarified that live attenuated vaccines are not allowed within 4 weeks prior to study entry.
Section 5.3. Lifestyle Considerations	This section has been updated reporting that a second method of contraception is needed in the event a highly effective methods that is user dependent is selected.	Updated for consistency with appendix 4.
Section 6.1 Study Intervention(s) Administered	One sentence has been rephrased for adding clarity.	To add further clarity.
Section 6.1.1. Medical Devices	The paragraph has been rephrased to be aligned with study protocol template. Moreover, the sentence related to the medical device used to deliver PF-06801591 has been rephrased for further clarity.	To be aligned with study protocol template.
Section 6.2 Preparation/Handling/Storage/Accountability	The sentence "and information the site should report for each excursion" has been removed because reported as duplication.	Adjusted typos.
Section 6.5.1. Other Anti tumor/Anti cancer or Experimental Drugs	Cancer vaccination therapy has been reported as prohibited medication during study conduction.	To add clarity
Section 6.5.3. Hematopoietic Growth Factors	It has been clarified that for the countries,	The paragraph has been rephrased to add further clarity.

Section # and Name	Description of Change	Brief Rationale
	including Japan, where the indication and dosage of G-CSF compounds may differ from ASCO guidelines, local package insert or clinical practice in their countries should be followed. "During screening window (ie, within 28 days prior to Day 1)" has been replaced by "during screening"	The participants can be screened at any time during the screening time window (within 28 days). Therefore, it has been clarified that granulocyte Colony-Stimulating Factor (G-CSF) is not permitted to qualify a participant with low ANC counts during screening and not during screening window.
Section 6.5.7. Vaccines	Live attenuated vaccines within 4 weeks prior to the first dose of PF-06801591 and through 30 days following the last dose of PF 06801591 are not allowed.	The paragraph has been added for further clarity.
Section 6.5.9 Rescue Medicine	The reference sections have been added.	To add further clarity the reference sections have been added.
Section 7.1. Discontinuation of Study Intervention	This section has been updated regarding the reason of treatment discontinuation. The sentence related to options for continuing study treatment outside the study has been removed.	There is no limitation in the treatment of patients in complete response. Therefore, this sentence has been removed. Moreover the sentence related to options for continuing study treatment outside the study has been removed since the duration of the study has been extended up to 3 years.
Section 7.1.1. Treatment after Initial Evidence of Radiological Disease Progression	A sentence was added to clarify that participants should be considered for discontinuation from study treatment if the repeat imaging confirms	To give the opportunity to continue treatment beyond progressive disease if the participant is still experiencing clinical benefit.

Section # and Name	Description of Change	Brief Rationale
	progressive disease. However, if a participant with evidence of progressive disease is still experiencing clinical benefit, the participant may be eligible for continued treatment with PF-06801591.	
Section 7.2. Participant Discontinuation/Withdrawal from the Study	The paragraph has been rephrased to be aligned with study protocol template.	To be aligned with study protocol template.
Section 7.2.1 Withdrawal of Consent	This section has been updated.	To be aligned with the mandatory language reported in the new version of the study protocol template.
Section 8.2.3. Electrocardiograms	The interval for the 3 consecutive ECGs at baseline has been added.	Three consecutive ECGs will be performed at approximately [2-4] minutes apart to determine the mean QTc interval.
Section 8.2.4. Clinical Safety Laboratory Assessments	Assessments performed on C2D1 and each subsequent cycle should be performed within 72 hours prior to dosing. Moreover, the assessments to be reviewed prior to dosing have also been reported.	Changes has been made to be consistent with the time window reported in the Schedule of activities and to clarify the assessments to be reviewed prior to dosing.
Section 8.2.5. Pregnancy Testing	A sentence related to the pregnancy test has been added.	The protocol has been aligned with the new version of the study protocol template.
Section 8.3. Adverse Events and Serious Adverse Events and Subsections	This section and subsections have been updated.	The protocol has been aligned with the new version of the study protocol template.
Section 8.3.9 Medical Device Deficiencies and Subsections	This section and subsections have been updated.	The protocol has been aligned with the new version of the study protocol template.
Section 8.3.10. Medication Errors	This section has been updated.	The protocol has been aligned with the new version of the study protocol template.
Section 8.4. Treatment of Overdose	This section has been updated.	Prefilled syringes are not graduated, and the percentage of the overdose cannot be calculated. Therefore, the

Section # and Name	Description of Change	Brief Rationale
		definition of the overdose has been updated and defined as the dose higher than the assigned dose level. Moreover, this section has been aligned with the new version of the study protocol template.
Section 8.5 Pharmacokinetic	It has been added that the PK samples for further analysis will be used unless prohibited by local regulations or ethics committee decision.	To add further clarity
Section 8.6.2. Collection of Samples for Pharmacodynamic Analysis	The total volume of samples has been updated. Moreover the sample for pharmacodynamics analysis will be used unless prohibited by local regulations or ethics committee decision.	Adjusted typos and to add further clarity.
Section 8.8 Biomarkers	The sample for pharmacodynamics analysis will be used unless prohibited by local regulations or ethics committee decision.	To add further clarity
Section 8.8.1.1 Baseline Tumor Tissue	It has been further clarified that the baseline tumor tissue is mandatory for Phase 2 part of the study.	To add further clarity
Section 8.8.1.2. Tumor Tissue at the End of Treatment	The time frame of "± 14 days" for the biopsy collection at the end of treatment has been removed because not consistent with the End of treatment visit window (+ 7 days).	Adjusted typo

Section # and Name	Description of Change	Brief Rationale
Section 8.8.4. Specified Gene Expression (RNA) Research	It has been clarified that two blood samples will be collected for RNA analyses.	This section has been updated as per consistency with the Schedule of Activities.
Section 9.2 Sample size and Section 9.2.1 Phase 1b	Since the Phase 1b has been extended to Asian participant, in addition to Japanese participants, the sample size has been modified.	Asian participants, in addition to Japanese participants, will be treated to assess the safety profile in the Phase 1b part of the trial. Therefore, the total number of participants has been increased.
Section 9.4. Statistical Analyses	The primary analysis will include all data up to a clinical cut-off date corresponding to 12 months after the last participant randomized in Phase 2. The final analysis of the data will be performed after last participant last visit (LPLV).	The end of study has been extended to 3 years after last participant is randomized. Therefore, it has been clarified that the primary analysis will be done prior to the end of study and will be performed 12 months after the last participant randomized in Phase 2.
Section 10.1.5 Dissemination of Clinical Study Data	The appendix has been updated to be aligned with study protocol template.	The protocol has been aligned with the study protocol template.
Section 10.2. Appendix 2: Clinical Laboratory Tests	A sentence related to the urine test has been added in this section.	The protocol has been aligned with the new version of the study protocol template.
Section 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The appendix has been updated to be aligned with study protocol template.	The protocol has been aligned with the new version of the study protocol template.
Section 10.4. Appendix 4: Contraceptive Guidance	The appendix has been updated to be aligned with study protocol template.	The protocol has been aligned with the new version of protocol template.
Section 10.7. Appendix 7: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow up, and Reporting	The appendix has been updated to be aligned with study protocol template.	The protocol has been aligned with the new version of protocol template
Section 10.10. Appendix 10	Non-target disease: Indeterminate has been replaced by inevaluable; present by present without unequivocal	The evaluation of the non-target lesions has been updated consistently with the terms reported in the CRF.

Section # and Name	Description of Change	Brief Rationale
	progression; increased by unequivocal progression. Moreover, a table reporting the determination of tumor response at each assessment for participants with no-measurable lesions has been added.	In the Phase 1b part participants can be enrolled without measurable lesions.
Section 10.12. Appendix 12 Management of Immune-related Adverse Event (irAEs)	Cardiac IRAE section has been updated: Troponin I has been specified and abatacept has been added	To add clarity and to be aligned with program level decision.
10.13. Appendix 13 Japan-specific Requirements	A subsection 10.13.1 has been added.	Definition of serious adverse event caused by medical device was added. Japan requires this language to comply with their local GCP requirements for trials involving a medical device.
10.14. Appendix 14. Alternative Measures During Public Emergencies	This appendix was added to provide alternative study measures followed during public emergencies, including the COVID-19 pandemic.	To add clarity and guidelines.
Section 10.15. Appendix 15 Abbreviations	PMAP (pharmacometric analysis plan) has been removed because reported twice. Moreover E/D (early discontinuation) has been removed because not applicable to this study.	Adjusted typo.
Section 11.0 References	The section has been updated	A reference is not applicable anymore and has been removed.

Amendment 1 (13-Dec-2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis and Section 4.1 Overall design; DLT determination	Adjusted typos. Febrile neutropenia definition: the single temperature was changed from 38.5 °C (101.3°F) to 38.3°C (101 °F).	The single temperature of >38.5°C (101.3°F) was not consistent CTCAE version 5.0.
Schedule of Activities (Tables 1 and 3)	To add that re-consent is needed for Japan participants on Cycle 2 Day 1 in Phase 1b	The reconsent after DLT evaluation period (cycle 1) is a requirement in Japan.
Schedule of Activities (Tables 2, 3 and Section 1.3.4)	Adjusted typos. The end of treatment time frame has been updated to + 7 days instead of ± 7 days previously reported.	The end of treatment visit can occur only + 7 days.
Schedule of Activities (Tables 1, 2, 3 and Section 1.3.4)	The time window has been updated from ± 5 days to ± 3 days.	As per consistency with the other studies of this program, the time window has been updated to ± 3 days.
Schedule of Activities (Tables 1 and 3) and Appendix 2 Clinical Laboratory Tests	The pulmonary function KL-6 and SpO2 tests have been added.	As per Pharmaceuticals and Medical Devices Agency (PMDA) request, KL-6 and SpO2 tests have been added to detect potential Interstitial Lung Disease (ILD)
Section 5.2 Exclusion Criteria	The exclusion criteria to not allow participants with ILD history or complication to be enrolled has been added.	As per PMDA request this exclusion criterion has been added.
Section 5.4 Screen Failures	The following sentence has been removed: "Rescreened participants should be assigned the same participant number as for the initial screening"	As per consistency with the last version of the protocol template the language that indicates rescreened participant should be assigned the same participant number has been removed.
Section 6.5.3 Hematopoietic Growth Factors	Adjusted typos. To specify that the screening period is within 28 days prior cycle 1 Day 1. In addition, it has also been clarified that	A typo was adjusted and additional clarity was added about the use erythropoietin in Japan.

Section # and Name	Description of Change	Brief Rationale
	erythropoietin is not approved in Japan for anemia caused by cancer treatment.	
Section 9.4.1. DLT rate assessment	It has been clarified that evidence such as safety data beyond DLT, including safety data from treated participants who are not DLT evaluable, clinical activity, PK, and PD data will play an important role in the final decision.	As per PMDA requirement, it has been added that safety data from treated participants who are not DLT evaluable will play an important role in the final decision.
Section 9.4.4.3 Analysis of Immunogenicity Data	Adjusted typos. Avelumab has been replaced with PF-06801591.	Avelumab was a leftover.
Appendix 2 Clinical Laboratory Tests	Amylase and lipase tests have been added.	As per PMDA request amylase and lipase tests have been added for the purpose of early detection of pancreatic disease (eg, pancreatitis) after treatment start.
Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	To add that the states of high FSH level should be confirmed if there is no other medical cause.	As per PMDA request, confirmation of high FSH level is needed if there is no other medical cause.
Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	An asterisk was added to “implantable progestogen-only hormone contraception associated with inhibition of ovulation” to clarify that is not commercially available in Japan	Adjusted typo.
Appendix 13 Japan specific requirement	A Japan specific appendix has been added to report the management of the participants during the DLT observation period and the disclosure of biomarker tests results to participants.	As per PMDA request the management of the participant during the DLT observation period and the disclosure of biomarker tests results to participants are clarified.
Section 2.2.4 Clinical Overview	The acronym of vaccine-based	Adjusted typo.

Section # and Name	Description of Change	Brief Rationale
	immunotherapy regimen has been adjusted.	
Appendix 14 Abbreviations	The abbreviations of the terms Interstitial Lung Disease/Pharmaceuticals and Medical Devices Agency/ sialylated carbohydrate antigen/ arterial oxygen saturation were added. The abbreviation of VBIR was updated.	Some abbreviations were added/updated to reflect the changes in the amendment.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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

Short Title: A Phase 1b/2 Study of Sasanlimab (PF-06801591, PD-1 inhibitor) in Participants with Advanced Malignancies

Rationale:

This is a Phase 1b/2 protocol to evaluate pharmacokinetics (PK), safety, efficacy, and pharmacodynamics of sasanlimab (PF-06801591), a programmed death-1(PD-1) antagonist monoclonal antibody (mAb) in participants with advanced malignancies. This study consists of 2 parts: Phase 1b for participants with advanced malignancies in Asia only and a global Phase 2 in participants with non-small cell lung cancer (NSCLC).

The primary purpose is to assess the safety and tolerability of PF-06801591 in Asian participants (Phase 1b) and to support modeling and simulation approaches for optimizing the dosing interval for PF-06801591.

The treatments with PD-1/PD-L1 inhibitors have demonstrated significant survival benefit for multiple tumor types. To date, all approved PD-1/PD-L1 inhibitors are administered intravenously (IV) [1-5]. As participants receiving these agents achieve durable responses and long-term survival, the subcutaneous (SC) treatment administration offers an innovative approach decreasing medical costs and making more efficient use of resources while simultaneously improving participant experience and satisfaction [6-8].

In Study B8011001, an open-label, multi-center Phase 1 study, the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics and efficacy of PF-06801591 were evaluated after IV or SC administration in participants with locally advanced or metastatic solid tumors. PF-06801591, a PD-1 inhibitor, has shown safety and efficacy in tumor types tested, regardless of route of administration (Section 2.2.4). Based on Study B8011001, the safety and tolerability of the PF-06801591, 300 mg Q4W, administered SC was selected for further evaluation in Phase 3 studies.

In the Phase 1b part of this study, 300 mg Q4W SC will be evaluated in Asian participants. Participants with advanced solid tumor will be enrolled for safety and PK evaluations. Since no dose-limiting toxicities (DLTs) occurred in Study B8011001 and no ethnic differences have been identified for PF-06801591 or other PD-1 or PD-L1 inhibitors, no safety concerns are expected.

A second dose level with a longer dosing interval (600 mg Q6W) will be also investigated in Asian participants in Phase 1b to support potential future schedule optimization for Asian population. The Asian Phase 1b and global Phase 2 will be conducted in parallel. Participants from Japan sites will be allowed to enter the global Phase 2 after Phase 1b meets safety criteria as defined by modified Toxicity Probability Interval (mTPI) design. Chinese participants will be enrolled only in the Phase 1b part of this study.

Phase 1b is composed of two parts, a dose escalation part and a dose expansion part. Once the safety evaluation is completed in the dose escalation part, the expansion part will be opened for further safety and PK assessment in Asian participants.

In the global Phase 2 part of this study, the PK profile of PF-06801591 is planned to be characterized at 2 different dose levels and intervals (300 mg Q4W and 600 mg Q6W) to support further optimization of dosing schedule. Participants will be randomized in a 1:2 ratio between 300 mg Q4W and 600 mg Q6W. The aim of the randomized Phase 2 is to explore and compare the PK exposure of PF-06801591 between those two regimens. The findings will support a modeling and simulation approach for extending the dosing interval from Q4W to Q6W and for enabling a flexible dosing interval for future combination programs.

Recently, the PD-1 inhibitors, pembrolizumab and nivolumab, are also being evaluated at different dose intervals using a similar approach[9,10].

The study will enroll participants with NSCLC, a tumor with clinical evidence of response to PD-1/PD-L1 inhibitors [13,14], including PF-06801591. The single tumor homogenous participant population is considered suitable for the collection of robust PK, safety and efficacy data.

In summary, the proposed dose of 600 mg Q6W will be investigated in addition to the previously studied dose 300 mg Q4W to support a modeling and simulation approach for extending the dosing interval from Q4W to Q6W.

Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• Phase 1b: To assess 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 area under the concentration-time curve during the dosing interval (τ) (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	• Adverse events (AEs) (type, severity [as graded by National Cancer Institute (NCI) CTCAE version 5.0], timing, seriousness, and relationship to study treatments), laboratory test abnormalities (type, severity and timing)

Objectives	Endpoints
• To characterize the PK (for Phase 1b and Phase 2)	• PK parameters (e.g., Area Under the Curve (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	• OR and time to response (TTR) by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1
• To assess the correlation between clinical activity and PD-L1 expression in baseline tumor tissue	• PD-L1 expression in baseline tumor tissue
CCI	

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 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.

- Analysis population: DLT-evaluable participants defined as participants who receive at least one 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 non 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 Estimands (AUCτ and concentration at the end of the dosing interval ($C_{trough)}$ 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) 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.

Overall Design:

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 Japan sites will be allowed to enter the global Phase 2 after Phase 1b meets safety criteria as defined by mTPI design. 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 Modified Toxicity Probability Interval (mTPI)[12] 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).

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

Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-4 participants during the 28-day or 42-day dose-limiting toxicity (DLT) evaluation period (Cycle 1) for Arms A1 and B1 respectively.

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 steady state.

Phase 2 Design

Participants will be randomized to 2 treatment arms 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 randomization will be stratified by line of therapy (1^{st} line vs 2^{nd} line).

The primary objective is to compare PK exposure in terms of area under the curve over the dosing interval (AUCτ) and C_{trough} at Week 12 (at steady state). The objective of the exposure comparison is to demonstrate that the mean PK exposure obtained from 600 mg Q6W regimen is not lower than 20% of the PK exposure obtained from the reference regimen of 300 mg Q4W.

For the primary PK objectives, a sample size of 90 participants (30 and 60 participants for Arms A2 (Reference) and B2 (Test), respectively) will provide at least 80% power that the lower bound for the 90% confidence interval (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%. This estimate is based on the assumption that the true ratio between (Test: PF-06801591 600 mg SC Q6W) and (Reference: PF-06801591 300 mg SC Q4W) treatments for both AUCτ and C_{trough} is 1.0 and also assumes a CV of 26% for AUCτ and a CV of 40% for C_{trough}.

The study will use interactive response technology (IRT) for participant randomization/treatment allocation in Phase 2.

DLT determination

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/mm^3 with a single temperature of >38.3°C (101 °F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour;
- Grade ≥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 (eg, 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 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.

Disclosure Statement:

The Phase 1b is Dose Finding Treatment study with 2 arms. No masking will be used.

The Phase 2 is Parallel Treatment study with 2 arms. No masking will be used.

Number of Participants:
Approximately 126 participants will be assigned to study intervention.
Intervention Groups and Duration:

In the dose escalation part of Phase 1b, 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). Once the safety evaluation is completed in the dose escalation part, an 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).

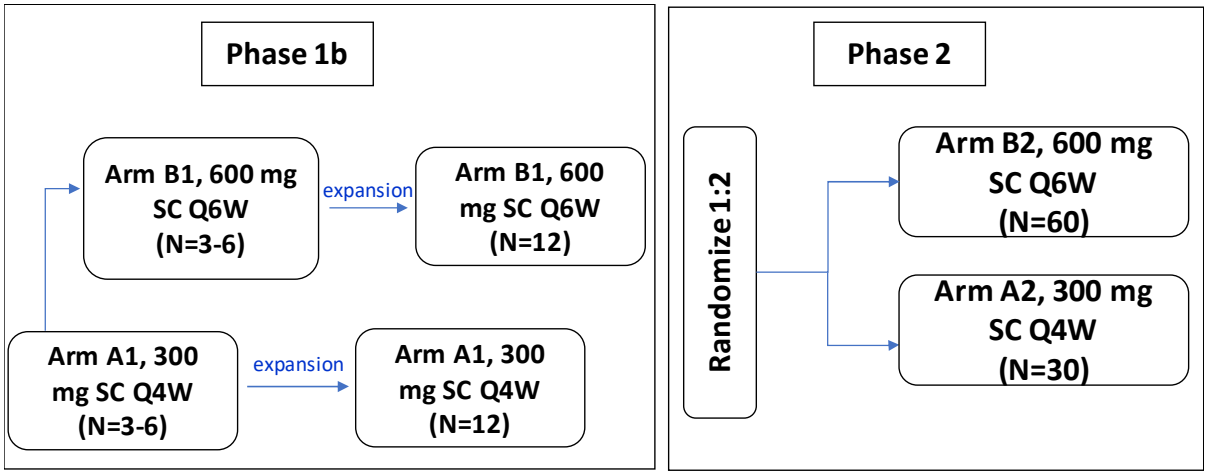
In the Phase 2, approximately 90 participants will be randomized in 1:2 ratio between 2 treatment arms (in 1:2 ratio to 300 Q4W Arm A2 and 600 mg Q6W Arm B2).
The end of the study is defined up to 3 years after the last participant is randomized or if Sponsor determines the study should end earlier.

Data Monitoring Committee: No

1.2. Schema

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.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures.

Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

1.3.1. SoA for Phase 1b and Phase 2 (Q4W)

Table 1. SoA for Phase 1b and Phase 2 for Q4W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 28 days)						Post-Treatment Period				Notes
		Cycle 1				Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D1	D1					
Visit Window		±0	±1	±2	±2	±3	±3	+7	+7	+7	+7	
Informed Consent	X					X (re-consent needed on Cycle 2 Day 1 in Phase 1b in Japan)						Refer to Section 10.1.3
Inclusion and exclusion criteria	X											
Tumor and Medical History	X											**Tumor History**: Includes history of disease under study including details of primary diagnosis, treatment history and staging. **Medical History**: Includes history other than the cancer under study. Includes prior and concurrent treatments. Abnormalities observed during screening are to be considered as medical history.
Physical Examination	X	X	X*	X*	X*	X	X	X	X			Refer to Section 8.2.1.
Height	X											

Table 1. SoA for Phase 1b and Phase 2 for Q4W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 28 days)						Post-Treatment Period				Notes
		Cycle 1				Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D1	D1					
Visit Window		±0	±1	±2	±2	±3	±3	+7	+7	+7	+7	
Weight	X	X				X	X	X				
Vital Signs (BP/pulse rate/Temp)	X	X	X*	X*	X*	X	X	X	X			Refer to Section 8.2.2. In Japanese participants SpO2 test should be done at the same time as vital signs collection.
ECOG Performance Status	X	X				X	X	X				Refer to Appendix 11.
Single/Triplicate 12-Lead ECG	X	X	X			X	X	X	X			Refer to Section 8.2.3. Triplicate ECG is required only at screening
Hematology	X	X	X*	X*	X*	X	X	X	X			Refer to Section 8.2.4 and Appendix 2.
Clinical Chemistry	X	X	X*	X*	X*	X	X	X	X			Refer to Section 8.2.4 and Appendix 2.
Coagulation	X											Refer to Section 8.2.4 and Appendix 2. Additional coagulation tests may be performed as clinically indicated.
ACTH/TSH	X	X					X (on cycle 4 and then every 3 cycles)	X	X			Refer to Section 8.2.4 and Appendix 2
KL-6/SpO2	If clinically indicated											Refer to Section 8.2.4 and Appendix 2. In Japanese participants SpO2 test should be done at the same time as vital signs collection.
Urinalysis	X											Refer to Section 8.2.4 and Appendix 2. Dipstick is acceptable. Microscopic analyses if clinically indicated (eg, only after positive dipstick result). If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24-hour urine. Additional urinalysis tests may be performed as clinically indicated.

Table 1. SoA for Phase 1b and Phase 2 for Q4W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 28 days)						Post-Treatment Period				Notes
		Cycle 1				Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose.
		D1	D8	D15	D22	D1	D1					Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
Visit Window		±0	±1	±2	±2	±3	±3	+7	+7	+7	+7	
Pregnancy Test (WOBCP only)	X	X				X	X	X	X			At 90 and 180 post-treatment period pregnancy status should be examined (allowed also by telephone call, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. Refer to Section 8.2.5 and Appendix 2.
Randomization/Treatment allocation		X										The participant randomization number and treatment in Phase 2 will be assigned using an IRT system. Study treatment should begin within 3 days from randomization/treatment allocation.
Study Treatment (PF-06801591)		X				X	X					Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation. Refer to Section 6.1.
Local Site Injection Tolerability Assessment		X				X						Refer to Section 8.2.7. At Cycles > 3, the assessment will only be performed if clinically necessary.
Tumor Assessment	X	Every 12 weeks (±7 days) from C1D1 according to calendar, regardless of treatment delays and until progressive disease assessed by Investigator using RECIST v1.1 or start of new anti-cancer therapy.										Refer to Section 8.1.
AE	X	==========										Assessment at 90 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 8.3.
SAE	X	==========										Assessment at 90 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 8.3.

Table 1. SoA for Phase 1b and Phase 2 for Q4W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 28 days)						Post-Treatment Period				Notes
		Cycle 1				Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D1	D1					
Visit Window		±0	±1	±2	±2	±3	±3	+7	+7	+7	+7	
Prior and Concomitant Medication/Surgery /Radiation and non-drug supportive interventions	X	==========										To be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Reporting period for concomitant medications for AEs and SAEs should follow respective guidance for AE and SAE reporting period. Refer to Section 6.5.
Contraception check	X	X				X	X	X	X	X	X	Assessments at 90 and 180 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 5.3 and Appendix 4.

* Assessments required only for participants enrolled in the Phase 1b.
[#] End of treatment: Obtain these assessments if not completed in the prior week, except for tumor assessment, which need not to be repeated if performed within the prior 12 weeks.

1.3.2. SoA for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q4W dosing (Phase 1b and Phase 2)

Table 2. SoA for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q4W dosing

Visit Identifiers	Screening	Cycle 1 (Days 1 to 28)				Cycle 2	Cycle 3	Cycle 4				Cycle 5	Cycles >5	EOT	Notes
	(up to 28 days before D1)	D1	D8	D15	D22	D1	D1	D1	D8	D15	D22	D1	D1		
Visit Window		±0	±1	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	+7	
PF-06801591 PK*		X (predose)	X	X	X	X (predose)	X (predose)	X (predose)	X	X	X	X (predose)	X (predose) only for cycles 6, 8, 10)	X	Blood samples (3 mL) will be collected at each time point for PK analysis of PF-06801591. Refer to Section 8.5.
PF-06801591 ADA/NAb		X (predose)				X (predose)	X (predose)	X (predose)					X (predose) only for cycles 6, 8, 10)	X	Blood samples (6 mL) will be collected for ADA/NAb assessment. Refer to Section 8.8.3.
CCI [redacted]		[redacted]													[redacted]

Table 2. SoA for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q4W dosing

Visit Identifiers	Screening	Cycle 1 (Days 1 to 28)				Cycle 2	Cycle 3	Cycle 4				Cycle 5	Cycles >5	EOT	Notes
	(up to 28 days before D1)	D1	D8	D15	D22	D1	D1	D1	D8	D15	D22	D1	D1		
Visit Window		±0	±1	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	+7	
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Table 2. SoA for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q4W dosing

Visit Identifiers	Screening	Cycle 1 (Days 1 to 28)				Cycle 2	Cycle 3	Cycle 4				Cycle 5	Cycles >5	EOT	Notes
	(up to 28 days before D1)	D1	D8	D15	D22	D1	D1	D1	D8	D15	D22	D1	D1		
Visit Window		±0	±1	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	+7	
															CCI
CCI															

* For participants in Japan, overnight stay from Day 1 cycle 1 is allowed.

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1.3.3. SoA for Phase 1b and 2 (Q6W)

Table 3. Schedule of Activities for Phase 1b and Phase 2 for Q6W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 42 days)								Post-Treatment Period				Notes
		Cycle 1						Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D29	D36	D1	D1					
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	+7	+7	+7	+7	
Informed Consent	X							X (re-consent needed on Cycle 2 Day 1 in Phase 1b in Japan)						Refer to Section 10.1.3.
Inclusion and exclusion criteria	X													
Tumor and Medical History	X													**Tumor History:** Includes history of disease under study including details of primary diagnosis, treatment history and staging. **Medical History:** Includes history other than the cancer under study. Includes prior and concurrent treatments. Abnormalities observed during screening are to be considered as medical history.
Physical Examination	X	X	X*	X*	X*	X*	X*	X	X	X	X			Refer to Section 8.2.1.
Height	X													
Weight	X	X						X	X	X				
Vital Signs (BP/pulse rate/Temp)	X	X	X*	X*	X*	X*	X*	X	X	X	X			Refer to Section 8.2.2. In Japanese participants SpO2 test should be done at the same time as vital signs collection.
ECOG Performance Status	X	X						X	X	X				Refer to Appendix 11.
Single/Triplicate 12-Lead ECG	X	X	X					X	X	X	X			Refer to Section 8.2.3. Triplicate ECG is required only at screening
Hematology	X	X	X*	X*	X*	X*	X*	X	X	X	X			Refer to Section 8.2.4 and Appendix 2.

Table 3. Schedule of Activities for Phase 1b and Phase 2 for Q6W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 42 days)								Post-Treatment Period				Notes
		Cycle 1						Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D29	D36	D1	D1					
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	+7	+7	+7	+7	
Clinical Chemistry	X	X	X*	X*	X*	X*	X*	X	X	X	X			Refer to Section 8.2.4 and Appendix 2.
Coagulation	X													Refer to Section 8.2.4 and Appendix 2. Additional coagulation tests may be performed as clinically indicated.
ACTH/TSH	X	X							X (on Cycle 4 and then every 2 cycles)	X	X			Refer to Section 8.2.4 and Appendix 2.
KL-6/SpO2	If clinically indicated													Refer to Section 8.2.4 and Appendix 2. In Japanese participants SpO2 test should be done at the same time as vital signs collection.
Urinalysis	X													Refer to Section 8.2.4 and Appendix 2. Dipstick is acceptable. Microscopic analyses if clinically indicated (eg, only after the positive dipstick result). If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24-hour urine. Additional urinalysis tests may be performed as clinically indicated.
Pregnancy Test (WOBCP only)	X	X						X	X	X	X			At 90 and 180 post-treatment period pregnancy status should be examined (allowed also by telephone call, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. Refer to Section 8.2.5 and Appendix 2.
Randomization/Treatment allocation		X												The participant randomization number and treatment in Phase 2 will be assigned using an IRT system. Study treatment should begin within 3 days from randomization/treatment allocation.

Table 3. Schedule of Activities for Phase 1b and Phase 2 for Q6W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 42 days)								Post-Treatment Period				Notes
		Cycle 1						Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D29	D36	D1	D1					
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	+7	+7	+7	+7	
Study Treatment (PF-06801591)		X						X	X					Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation. Refer to Section 6.1.
Local Site Injection Tolerability Assessment		X						X						Refer to Section 8.2.7. At Cycles > 3, the assessment will only be performed if clinically necessary.
Tumor Assessment	X	Every 12 weeks (±7 days) from C1D1 according to calendar, regardless of treatment delays and until progressive disease assessed by Investigator using RECIST v1.1 or start of new anti-cancer therapy.												Refer to Section 8.1.
AE	X	==========												Assessment at 90 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 8.3.
SAE	X	==========												Assessment at 90 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 8.3.
Prior and Concomitant Medication/Surgery /Radiation and non-drug supportive interventions	X	==========												To be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Reporting period for concomitant medications for AEs and SAEs should follow respective guidance for AE and SAE reporting period. Refer to Section 6.5.
Contraception check	X	X						X	X	X	X	X	X	Assessments at 90 and 180 day post-treatment period may be done by telephone call, unless the participant is visiting the site for other reasons. Refer to Section 5.3 and Appendix 4.

Table 3. Schedule of Activities for Phase 1b and Phase 2 for Q6W dosing

Procedure	Screening (up to 28 days before D1)	Treatment Period (One Cycle = 42 days)								Post-Treatment Period				Notes
		Cycle 1						Cycle 2-3	Cycles ≥4	EOT[#]	D 30	D 90	D 180	Post-treatment period: visits at 30, 90, and 180 days after last dose. Post-treatment period ends at 180 days after last dose or at the time a new anticancer treatment starts whichever comes first (Refer to Section 8.3.1.1 for SAEs).
		D1	D8	D15	D22	D29	D36	D1	D1					
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	+7	+7	+7	+7	

* Assessments required only for participants enrolled in the Phase 1b

[#] End of treatment: Obtain these assessments if not completed in the prior week, except for tumor assessment, which need not to be repeated if performed within the prior 12 weeks.

1.3.4. SoA for Pharmacokinetics, Pharmacodynamics and Immunogenicity Assessments for Q6W dosing (Phase 1b and Phase 2)

Visit identifiers	Screening	Cycle 1 (Days 1 to 42)						Cycle 2	Cycle 3 (Days 1 to 42)						Cycle ≥ 4	EOT	Notes
	(up to 28 days before D1)	D1	D8	D15	D22	D29	D36	D1	D1	D8	D15	D22	D29	D36	D1		
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	+7	
PF-06801591 PK*		X (predose)	X	X		X		X (predose)	X (predose)	X	X		X		X (predose) only for cycles 4, 5, 7	X	Blood samples (3 mL) will be collected for PK analysis of PF-06801591. Refer to Section 8.5
PF-06801591 ADA/ NAb		X (predose)						X (predose)	X (predose)						X (predose) only for cycles 4, 5, 7	X	Blood samples (6 mL) will be collected for ADA/NAb assessment. Refer to Section 8.8.3.
CCI																	
CCI																CCI	
CCI																	
CCI																	

Visit identifiers	Screening	Cycle 1 (Days 1 to 42)						Cycle 2	Cycle 3 (Days 1 to 42)						Cycle ≥ 4	EOT	Notes
	(up to 28 days before D1)	D1	D8	D15	D22	D29	D36	D1	D1	D8	D15	D22	D29	D36	D1		
Visit Window		±0	±1	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	+7	
CCI																	
CCI																	

* For participants in Japan, overnight stay from Day 1 cycle 1 is allowed

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2. INTRODUCTION

This is a Phase 1b/2 protocol to evaluate pharmacokinetics (PK), safety, efficacy, and pharmacodynamics of sasanlimab (PF-06801591), a programmed death-1(PD-1) antagonist monoclonal antibody (mAb) in participants with advanced malignancies. The primary purpose of this study is to assess the safety and tolerability of PF-06801591 in Asian participants (Phase 1b) and to compare PK exposure of 2 PF-06801591 subcutaneous (SC) regimens: 300 mg Q4W and 600 mg Q6W (Phase 2). Data gathered from this study will support modeling and simulation approaches for optimizing the dosing interval for PF-06801591.

2.1. Study Rationale

This is a Phase 1b/2 protocol to evaluate pharmacokinetics (PK), safety, efficacy, and pharmacodynamics of PF-06801591, a programmed death-1(PD-1) antagonist monoclonal antibody (mAb) in participants with advanced malignancies. This study consists of 2 parts: Phase 1b for participants with advanced malignancies in Asia only and a global Phase 2 in participants with non-small cell lung cancer (NSCLC).

The primary purpose is to assess the safety and tolerability of PF-06801591 in Asian participants (Phase 1b) and to support modeling and simulation approaches for optimizing the dosing interval for PF-06801591.

The treatments with PD-1/PD-L1 inhibitors have demonstrated significant survival benefit for multiple tumor types. To date, all approved PD-1/PD-L1 inhibitors are administered intravenously (IV) [1-5]. As participants receiving these agents achieve durable responses and long-term survival, the subcutaneous (SC) treatment administration offers an innovative approach decreasing medical costs and making more efficient use of resources while simultaneously improving participant experience and satisfaction [6-8].

In Study B8011001, an open-label, multi-center Phase 1 study, the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics and efficacy of PF-06801591 were evaluated after IV or SC administration in participants with locally advanced or metastatic solid tumors. PF-06801591, a PD-1 inhibitor, has shown safety and efficacy in tumor types tested, regardless of route of administration (Section 2.2.4). Based on Study B8011001, the safety and tolerability of the PF-06801591, 300 mg Q4W, administered SC was selected for further evaluation in Phase 3 studies.

In the Phase 1b part of this study, 300 mg Q4W SC will be evaluated in Asian participants. Participants with advanced solid tumor will be enrolled for safety and PK evaluations. Since no dose-limiting toxicities (DLTs) occurred in Study B8011001 and no ethnic differences have been identified for PF-06801591 or other PD-1 or PD-L1 inhibitors, no safety concerns are expected.

A second dose level with a longer dosing interval (600 mg Q6W) will be also investigated in Asian participants in Phase 1b to support potential future schedule optimization for Asian population. The Asian Phase 1b and global Phase 2 will be conducted in parallel. Participants from Japan sites will be allowed to enter the global Phase 2 after Phase 1b meets safety criteria as defined by modified Toxicity Probability Interval (mTPI) design. Chinese participants will be enrolled only in the Phase 1b part of this study.

Phase 1b is composed of two parts, a dose escalation part and a dose expansion part. Once the safety evaluation is completed in the dose escalation part, the expansion part will be opened for further safety and PK assessment in Asian participants.

In the global Phase 2 part of this study, the PK profile of PF-06801591 is planned to be characterized at 2 different dose levels and intervals (300 mg Q4W and 600 mg Q6W) to support further optimization of dosing schedule. Participants will be randomized in a 1:2 ratio between 300 mg Q4W and 600 mg Q6W. The aim of the randomized Phase 2 is to explore and compare the PK exposure of PF-06801591 between those two regimens. The findings will support a modeling and simulation approach for extending the dosing interval from Q4W to Q6W and for enabling a flexible dosing interval for future combination programs.

Recently, the PD-1 inhibitors, pembrolizumab and nivolumab, are also being evaluated at different dose intervals using a similar approach[9,10].

The study will enroll participants with NSCLC, a tumor with clinical evidence of response to PD-1/PD-L1 inhibitors [13,14], including PF-06801591. The single tumor homogenous participant population is considered suitable for the collection of robust PK, safety and efficacy data.

In summary, the proposed dose of 600 mg Q6W will be investigated in addition to the previously studied dose 300 mg Q4W to support a modeling and simulation approach for extending the dosing interval from Q4W to Q6W.

2.2. Background

PF-06801591 is a humanized, hinge region-stabilized IgG4 mAb, with antagonistic activities specific for human PD-1. It can selectively and reversibly bind to human PD-1 and block the interaction between PD-1 and PD-L1/PD-L2. PF-06801591 has shown to increase human T-cell proliferation and cytokine secretion (interferon gamma [IFN-γ] and interleukin [IL]-2) when PD-L1 is highly expressed in both in-vitro and in-vivo systems. PF-06801591 blockade of the interaction between PD-1 on T cells and its ligands on tumor cells is expected to restore anti-tumor immunity and form the basis for an immunotherapeutic approach to treat cancer.

2.2.1. Nonclinical Pharmacology

Results from PF-06801591 nonclinical pharmacology studies are consistent with the expected effects of blocking the PD-1 pathway and demonstrate the potential to enhance tumor immuno-surveillance and anti-tumor immune responses.

PF-06801591 binds to human PD-1 with high affinity to both recombinant PD-1 protein and cell surface expressed PD-1. Binding affinity to cynomolgus monkey PD-1 was similar to human PD-1. The ability of PF-06801591 to block the PD-1 pathway, as measured on primary human and primary cynomolgus monkey T cells, was shown by increased T-cell proliferation and cytokine secretion in both of these systems.

See Section 5.1 of the PF-06801591 Investigator's Brochure (IB)[11] for detailed information on in vitro and in vivo nonclinical studies.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Single- and repeat-dose PK were assessed after IV dosing of PF-06801591 in monkeys. Following single or repeat IV dosing, systemic exposure (as assessed by the maximum observed concentration [C_{max}] and area under the concentration-time curve [AUC]) increased with increasing dose. In the GLP toxicity studies, systemic exposure was higher after repeat dosing, and there were no sex-related differences observed in exposure. Anti-drug antibody (ADA) was observed after repeat IV dosing in monkeys.

PF-06801591 has been shown to induce cytokine production (IFNγ, tumor necrosis factor (TNF)α, IL-2). However, cytokine-mediated drug interactions observed in the clinic for other drugs have been modest, resulting in less than 2-fold changes in the exposure of a co-administered small molecule drug.

See Section 5.2 of the PF-06801591 IB [11] for detailed information on nonclinical studies.

2.2.3. Nonclinical Safety

The nonclinical safety profile of PF-06801591 has been well-characterized in repeat-dose toxicity studies in cynomolgus monkeys up to 1 month in duration. The IV and SC routes of exposure were assessed as these are the intended routes of administration in initial clinical studies.

In repeat-dose toxicity studies up to 1-month duration in which PF-06801591 was administered via the intravenous or subcutaneous routes, no direct target organ toxicities were observed. The key changes associated with PF-06801591 treatment of cynomolgus monkeys was minimal to mild mononuclear cellular infiltration of various tissues that persisted and were likely a result of prolonged exposure to PF-06801591 throughout the entire recovery phase. These findings are both consistent with expected pharmacology, and previously described in monkey toxicity studies with similar compounds targeting the PD-1 receptor.

See Section 5.3 of the PF-06801591 IB [11] for detailed information regarding nonclinical toxicology studies.

2.2.4. Clinical Overview

PF-06801591 is being evaluated as a single-agent in Study B8011001; in combination with PF-06753512, a vaccine-based immunotherapy regimen (VBIR) for prostate cancer, in Study B7791001; and in combination with PF-06936308, a VBIR-2 for advanced NSCLC and metastatic triple negative breast cancer (mTNBC), in Study C3621001.

Study B8011001 is an ongoing Phase 1, open-label, dose escalation and expansion study of PF-06801591 in participants with locally advanced or metastatic melanoma, squamous cell carcinoma of the head and neck (SCCHN), ovarian cancer, sarcoma, non-small cell lung

carcinoma (NSCLC), urothelial carcinoma (UC) or other solid tumors. The primary purpose of Study B8011001 is to evaluate safety and early signs of efficacy of PF-06801591. This clinical study was divided into a dose escalation (Part 1) Phase, and a dose expansion (Part 2) Phase. One hundred forty-six (146) participants have been dosed on the study. Forty (40) participants were enrolled into Part 1 and 106 participants (68 with NSCLC and 38 with urothelial carcinoma [UC]) were enrolled into Part 2. In Part 1, 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered every 3 weeks [Q3W]), and 1 subcutaneous (SC) dose level (300 mg administered every 4 weeks [Q4W]) was evaluated for safety. No DLTs were observed and thus, there was no maximum tolerated dose (MTD) identified.

Efficacy

As of the latest data cut-off date of 27 December 2018, in Part 1, objective response (OR) was achieved in 8 out of 40 (20%) participants; partial response (PR) was observed for ovarian cancer (3 of 15), SCCHN (2 of 7), sarcoma (1 of 6), small-cell lung cancer (1 of 3), and microsatellite instability-high endometrial adenocarcinoma (1 of 1); The median duration of treatment was 4.0 months; Disease control rate (DCR; best overall response of complete or partial response, or stable disease [SD] with minimum duration of 35 days) was achieved in 52.5% (21 out of 40 participants). Three (3) participants are still receiving treatment in Part 1. In Part 2, 11 out of 67 participants with NSCLC (one patient was not included because did not have any post-baseline tumor assessment) achieved PR (objective response rate [ORR] 16.4%) and 7 participants out of 37 with UC (one patient was not included because did not have any post-baseline tumor assessment) achieved PR (ORR 18.9%). The median duration of treatment was 2.8 months. The ORR was 25% (7 of 28) in participants with NSCLC with ≥ 1% tumor cell PD-L1 expression by SP263 antibody testing. Additionally, 26 participants with NSCLC achieved the best overall response of SD, for a DCR of 55.2%. A total of 12 participants with UC achieved the best overall response of SD, resulting in a DCR of 51.4%. The median duration of follow up was 5.1 months for participants with NSCLC and 3.0 months for participants with UC. Fifty-five (55) participants are still receiving treatment in Part 2.

Safety

A total of 52 (35.6%) participants in Part 1 and Part 2 (regardless of IV or SC treatment) reported all-causality serious adverse events (SAEs), including 4 (2.7%) participants with treatment-related SAEs (3 pneumonitis and 1 arrhythmia).

Of 106 participants exposed to 1 or more 300 mg SC injections of study drug, 98 participants (92.5%) experienced at least one treatment-emergent AE while on the study. The most common AEs experienced by ≥ 10% of participants were anemia (n = 23, 21.7%) followed by disease progression (n = 13, 12.3%), dyspnea (n = 13, 12.3%), amylase increase (n = 11, 10.4%), decreased appetite (n = 11, 10.4%), and pruritis (n = 11, 10.4%). Thirteen (13) participants (12.3%) experienced maximum Grade 3 AEs, and 6 (5.7%) experienced maximum Grade 4 AEs. Grade 5 AEs (n = 23, 21.7%), reportable within 150 days from last study treatment, were disease progression (n = 13), death not otherwise specified (n = 2), cerebral infarction, urinary tract infection, arrhythmia, gastric ulcer hemorrhage, cognitive

disorder, urosepsis, general health deterioration and cardiac failure (n = 1 each). A total of 58 participants (54.7%) had a least one treatment related adverse event (TRAE) while on study. The most common TRAEs (experienced by ≥5% of participants) were hyperthyroidism (n = 10, 9.4%), hypothyroidism (n = 7, 6.6%), lipase increase (n = 7, 6.6%), pruritis (n = 7, 6.6%), and amylase increase (n = 6, 5.7%). Nine (9) participants had maximum Grade 3 TRAEs and 1 had maximum Grade 4 TRAE. Grade 3 TRAEs were lipase increase, (n = 3) amylase increase (n = 2), pneumonitis, decreased appetite, lymphocyte count decrease, and creatinine increased (n = 1 each). There was one Grade 4 TRAE of white blood cell count/neutrophil decrease. One Grade 5 treatment-related arrhythmia was reported. The Grade 5 arrhythmia was assessed as unrelated by the sponsor.

No significant injection site reactions were reported. Safety data including possible irAE are mostly consistent with the known safety profile of anti-PD-1 treatment.

Detailed information about these events can be found in the PF-06801591 IB [11].

Pharmacokinetics

Single- and multiple-dose pharmacokinetics (PK) of PF-06801591 is being evaluated in Study B8011001. Preliminary PK data suggest PF-06801591 exhibits PK characteristics typical of IgG4 monoclonal antibodies. The mean maximum serum concentration (C_{max}) and area under the serum concentration-time curve over the dosing interval (AUCτ) of PF-06801591 increased in an approximately dose-proportional manner over the dose range of 0.5 -10 mg/kg following IV administration. After SC administration at 300 mg, PF-06801591 was slowly absorbed, with a median T_{max} of approximately 8 days. The estimated median terminal half-life of PF-06801591 is ~ 20 days for IV, ~ 30 days for SC (data on file).

Initial PK modeling suggests that C_{trough} levels can be maintained with longer dosing intervals. AUC_{ss} at 600 mg every 6 weeks (Q6W) has been estimated to be ~30% and C_{trough} ~ 11% higher compared to the 300 mg Q4W dose level, with exposure expected to be well below the highest dose level tested in humans (10 mg/kg Q3W, highest dose level investigated in Study B8011001; no DLT were observed).

Immunogenicity

Based on a preliminary immunogenicity assessment in participants from Study B8011001, 3 participants (8.6%) were positive for treatment-emergent ADAs following IV (n=21) or SC (n=14) administration of PF-06801591. The presence of ADAs was not associated with hypersensitivity or infusion reactions nor significantly affected PF-06801591 clearance. No neutralizing antibodies (NAbs) against PF-06801591 were detected in any of the ADA positive participants.

No clinical data from Study B7791001 and Study C3621001 are available.

2.3. Benefit/Risk Assessment

Based on the nonclinical and Phase 1 clinical data available to date, the conduct of the trial with the proposed single agent PF-06801591 doses and regimens is considered justifiable.

Single-agent PF-06801591 has been evaluated in Study B8011001 after IV (0.5, 1, 3, or 10 mg/kg Q3W) and SC (300 mg Q4W) administration and the clinical safety data available to date, in participants with advanced or metastatic solid tumors, suggest an acceptable safety profile. PF-06801591 is well-tolerated and with a low frequency of treatment-related SAEs.

Most of the observed events were either in line with those expected in participants with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. No relevant injection site AEs were observed.

However, measures including guidelines for treatment interruption and permanent discontinuation in case of toxicities, guidelines for steroid treatment, have been implemented.

The dose of 600 mg Q6W has been selected to support a modeling and simulation approach for extending the dosing interval of any approved indication to Q6W and to support future combination development across indications. As per initial PK modeling evaluation the expected PF-06801591 exposure with this regimen is well below the highest dose level tested in humans (10 mg/kg Q3W, with no DLTs) and therefore safety concerns are not expected.

Additionally, responses to PF-06801591 have been observed in Study B8011001 in a range of tumor types, including NSCLC, bladder cancer, ovarian cancer, SCCHN, sarcoma, SCLC and microsatellite instability-high endometrial adenocarcinoma (see PF-06801591 IB [11]). The significant clinical benefit in terms of ORR and DCR (See Section 2.2.4) is consistent with the ORR and DCR in the same tumor types reported for other agents of the same class.

These results, together with the acceptable safety profile, as currently demonstrated by the ongoing Phase 1 trial B8011001, support the hypothesis that PF-06801591 may represent an important therapeutic approach in participants with advanced solid tumors. Thus, the projected benefit/risk of B8011001 is favorable for investigation in this advanced cancer participant population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study drug may be found in the PF-06801591 IB [11], which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• Phase 1b: To assess 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 • To characterize the PK (for Phase 1b and Phase 2) • To characterize the immunogenicity • To assess anti-tumor activity • To assess the correlation between clinical activity and PD-L1 expression in baseline tumor tissue	• AEs (type, severity [as graded by NCI CTCAE version 5.0], timing, seriousness, and relationship to study treatments), laboratory test abnormalities (type, severity and timing) • PK parameters (e.g., AUC and C_{trough} after first dose and C_{trough} at steady state. • Immunogenicity (ADA/NAb incidence and titer) • OR and Time-to-response (TTR) by investigator assessment using RECIST v. 1.1 • PD-L1 expression in baseline tumor tissue.
CCI [redacted]	[redacted]

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 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 4.1.

- 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 non 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 Estimands (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 $\tau = 4$ 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) 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.

4. STUDY DESIGN

4.1. Overall Design

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 Japan sites will be allowed to enter the global Phase 2 after Phase 1b meets safety criteria as defined by mTPI design. 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).

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

Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-4 participants during the 28-day or 42-day dose-limiting toxicity (DLT) evaluation period (Cycle 1) for Arms A1 and B1 respectively.

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 steady state.

Phase 2 Design

Participants will be randomized to 2 treatment arms 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 randomization will be stratified by line of therapy (1^{st} line vs 2^{nd} line).

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

The primary objective is to compare PK exposure in terms of area under the curve over the dosing interval (AUCτ) and C_{trough} at Week 12 (at steady state). The objective of the exposure comparison is to demonstrate that the mean PK exposure obtained from 600 mg Q6W regimen is not lower than 20% of the PK exposure obtained from the reference regimen of 300 mg Q4W.

For the primary PK objectives, a sample size of 90 participants (30 and 60 participants for Arms A2 (Reference) and B2 (Test), respectively) will provide at least 80% power that the lower bound for the 90% confidence interval (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%. This estimate is based on the assumption that the true ratio between (Test: PF-06801591 600 mg SC Q6W) and (Reference: PF-06801591 300 mg SC Q4W) treatments for both AUCτ and C_{trough} is 1.0 and also assumes a CV of 26% for AUCτ and a CV of 40% for C_{trough}.

The study will use interactive response technology (IRT) for participant randomization/treatment allocation in Phase 2.

DLT determination

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/mm^3 with a single temperature of >38.3°C (101 °F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour;
    - Grade ≥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 (eg, 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 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 $\leq$ 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.

4.2. Scientific Rationale for Study Design

The primary purpose of the Phase 1b is to assess the safety and tolerability of PF-06801591 in Asian participants. Chinese participants will be enrolled only in the Phase 1b part of this study. Japanese participants may also be enrolled in the Phase 2 part to support potential future schedule optimization.

The Phase 1b escalation part of the study will use the mTPI design to govern dose escalation/de-escalation rules and to evaluate safety of the 300 mg Q4W and 600 mg Q6W PF-06801591 doses in Asian participants. After an acceptable safety profile is established in the escalation part, the expansion part will be conducted to further assess safety and PK of the doses. The mTPI design is selected for Phase 1b escalation part for following reason. Being a model-based design, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated and presented in a 2-way table. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement. The rules in mTPI design are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. As shown by Ji and Wang [12], mTPI design is more efficient and safer than the 3+3 design.

The Phase 2 part of the study will compare 600 mg Q6W regimen to 300 mg Q4W to support a modeling and simulation approach for potentially extending the PF-06801591 dosing interval to Q6W. Phase 2 will use randomization in 1:2 ratio to 300 Q4W and 600 mg Q6W arms, respectively. The 1:2 randomization is selected given that safety and efficacy data are available at 300 mg Q4W but these data are not available at 600 mg Q6W. The randomization will be stratified [13, 14] by line of therapy (1st line vs 2nd line) given the different response rates of anti-PD-1 therapy in 1st line and 2nd line NSCLC participants. The Phase 1b and Phase 2 parts of the study will run in parallel; however Japanese participants will be only enrolled in the Phase 2 part after the Phase 1b part has completed and only if both doses are determined to be tolerable.

CCI [redacted]

4.3. Justification for Dose

PF-06801591 300 mg will be given SC Q4W (Cycles are 28 days in length) in both the Phase 1b and Phase 2 parts of the trial. The 300 mg dose was selected for the Q4W regimen based on data from ongoing Phase 1 Study B8011001 where single- and multiple-dose PK, safety and efficacy of PF-06801591 are being evaluated. The 300 mg Q4W regimen given SC has shown a favorable PK profile, in addition to clinical activity and acceptable safety in participants with advanced or metastatic solid tumors.

PF-06801591 600 mg will be also investigated SC Q6W (Cycles are 42 days in length) in both the Phase 1b and Phase 2 parts of the trial. The 600 mg Q6W regimen was chosen to 1) maintain a comparable exposure to the 300 mg Q4W regimen and 2) to accommodate the SC presentation (as pre-filled syringe) is currently formulated for 300 mg injection increments.

Initial PK modeling suggests that C_{trough} levels can be maintained with longer dosing intervals. AUC_{ss} at 600 mg Q6W have been estimated to be ~30% and C_{trough} ~ 11% higher compared to the 300 mg Q4W dose level, with exposure expected to be well below the highest dose level tested in humans (10 mg/kg Q3W, highest dose level investigated in Study B8011001; no DLTs were observed).

Based on preliminary analyses, relatively flat exposure-response relationships for safety and efficacy were observed for PF-06801591 within the dose range studied. Thus, there is no expectation that the 600 mg Q6W regimen will result in undue safety concerns or a compromise in efficacy.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure and visit shown in the schedule of activities (SoA).

The end of the study is defined as up to 3 years after the last participant is randomized or if the Sponsor determines the study should end earlier.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age

1. Participant must be ≥ 18 years of age inclusive, at the time of signing the informed consent (≥ 20 years of age in Japan; ≥ 19 years of age in South Korea)

Type of Participants and Disease Characteristics

2. Histological or cytological diagnosis of advanced solid tumor (Phase 1b, see details here below) and NSCLC (Phase 2, see details here below).
   For Phase 1b:

   a. Histological or Cytological diagnosis of advanced solid tumor with clinical evidence of response to anti-PD-1 or PD-L1 agent. (No PD-L1 testing required)

   b. Participant must have received at least 1 prior line of therapy for recurrent or metastatic disease, and must have progressed/relapsed, be refractory, or intolerant to standard therapy approved for the specific tumor type. Exception: Participants who actively decline standard therapies.

   For Phase 2:

   a. All participants entering the study must have at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 that has not been previously irradiated (lesions demonstrating definite progression after the radiation is allowed).

   b. Participants must have a documented diagnosis of stage III where participants are not candidates for surgical resection or definitive chemoradiation, or stage IV NSCLC (per 8th International Association for the Study of Lung Cancer [IASLC] classification)[15]

   c. Activating epidermal growth factor receptor (EGFR) mutation (testing is required if status is unknown), known v-raf murine sarcoma viral oncogene homolog B1(BRAF) mutation, and anaplastic lymphoma kinase (ALK) or c-ros oncogene 1

(ROS1) translocation/rearrangement (testing not required if unknown) are not permitted.

d. Participants whose tumor is known to be PD-L1 positive (Tumor Proportion Score [TPS] ≥1%) or unknown are eligible (testing not required if unknown).

e. Up to 1 line of prior therapy in advanced or metastatic disease settings allowed. A neoadjuvant/adjuvant treatment will be counted as a line for advanced or metastatic disease if the development of recurrent or metastatic disease occurs during treatment or within 6 months after last dose.
Based on country-specific regulations, when applicable participants should have actively declined chemotherapy or other standard therapies, including approved anti PD-1 or PD-L1 agents for the treatment of advanced disease (unresectable or metastatic).

f. Participant should not have received prior treatment with anti PD-1/PD-L1 drugs.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
4. Estimated life expectancy of at least 3 months
5. Adequate Bone Marrow Function, including:

   a. ANC ≥1,500/mm^3 or ≥1.5 × 10^9/L;

   b. Platelets ≥75,000/mm^3 or ≥75 × 10^9/L;

   c. Hemoglobin ≥9 g/dL

6. Adequate Renal Function, including:
   a. Estimated creatinine clearance ≥50 mL/min participants as calculated using the method standard for the institution. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

7. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless the participant has documented Gilbert syndrome;

   b. Aspartate and Alanine aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤2.5 × ULN; ≤5.0 × ULN if there is liver involvement by the tumor;

   c. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN in case of bone or liver metastasis).

8. Assessments performed prior to dosing per SoA should also meet all inclusion requirements.

9. Resolved acute effects of any prior therapy to baseline severity or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.

Sex

10. Male or Female

a. Male participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of study intervention.

- Refrain from donating sperm

PLUS either:

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

b. Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, including participants who intend to interrupt breastfeeding, and at least one of the following conditions applies:

Is not a woman of childbearing potential (WOCBP)

OR

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention; and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. As for participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception, as described in Appendix 4. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

Informed Consent

11. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
12. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participants with known symptomatic brain metastases requiring steroids. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 6 weeks (requires magnetic resonance imaging [MRI] confirmation).
2. Participants with Interstitial Lung Disease (ILD) history or complication.
3. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
4. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis)
5. Participants with known active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), sero-positivity to human immunodeficiency virus (HIV) infection.
6. Q-T interval corrected for heart rate QTc > 450 msec for male participants or QTc > 470 msec for female participants or QTc > 480 msec in participants with right bundle branch block.
7. Hypertension that cannot be controlled by medications (eg, systolic > 150 mmHg and diastolic > 90 mmHg) despite optimal medical therapy.
8. Known or suspected hypersensitivity to active ingredient or excipients of the study drug.

9. History of Grade ≥3 immune mediated AE (including AST/ ALT elevations that where considered drug related and cytokine release syndrome [CRS]) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co-stimulatory agents, etc.) and required immunosuppressive therapy (For Phase 1b only).

10. Serum or urine pregnancy test (for females of childbearing potential) positive at screening or C1D1.

Prior/Concomitant Therapy

11. Major surgery within 3 weeks prior to study entry.

12. Radiation therapy within 3 weeks prior to study entry.

13. Monoclonal antibody based anti-cancer therapy within 28 days prior to study entry or small-molecule based anti-cancer therapy (targeted therapy or chemotherapy) within 14 days prior to study entry.

14. Vaccination with live attenuated vaccines within 4 weeks prior to randomization is prohibited; however inactivated vaccines are permitted.

Prior/Concurrent Clinical Study Experience

15. Participation in active treatment with other studies involving investigational drugs within 4 weeks prior to study entry.

Other Exclusions

16. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

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

5.3. Lifestyle Considerations

Contraception: The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partners from the permitted list of contraception methods (see Appendix 4, Section 10.4) and will confirm that the participant has been instructed in its consistent and correct use. **At time points indicated in the SoA,** the investigator or designee will inform the participant of the

need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception; as for female participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception, as described in Appendix 4). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

- **Please refer to the Inclusion Criteria (Section 5.1) under "Sex" for details on contraception timeframes.**
- **Concomitant Therapy**: Refer to Section 6.5
- **Special Precautions for Administration**: Refer to Section 6.1 and Section 6.6.

5.3.1. Meals and Dietary Restrictions

No food restrictions.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06801591
Dose Formulation	Solution for injection
Unit Dose Strengths	150 mg/mL Syringe, 2 mL
Dosage Levels	300 mg Q4W 600 mg Q6W
Route of Administration	SC
Investigational Medicinal Product (IMP) and Non-investigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided as follows: • PF-06801591 150 mg/mL solution for injection (2 mL) pre-filled syringes Each pre-filled syringe (PFS) will be labeled as required per country requirement. Each PFS is for single use only. Additional dosing details will be provided in the IP Manual.

PF-06801591 150 mg/mL solution for injection (2 mL in 2.25 mL PFS) will be provided as a sterile solution for SC administration. Each syringe of PF-06801591 at a nominal concentration of 150 mg/mL, contains a sufficient amount to deliver a dose of 300 mg (2 mL). The investigational product for this study is packaged into a sealed carton containing 1 PFS and is labeled in a way that is consistent with the study design and with the regulatory requirements for each country in which the study is to be performed.

Participants will receive a dose of PF-06801591 on Day 1 of each cycle. Qualified and trained investigator site personnel will administer PF-06801591 at a fixed dose to participants by SC injections to the abdomen.

Two (2) dosing regimens of PF-06801591 will be used in this study which are 300 mg SC Q4W and 600 mg SC Q6W.

For both dose levels, 150 mg/ mL injection (1 injection for 300 mg SC Q4W and 2 injections for 600 mg SC Q6W) will be provided as a sterile solution for SC administration to the abdomen (with preference given to the lower quadrants when possible).

For the 600 mg SC dose, PF-06801591 should be administered to 2 different quadrants of the abdomen.

If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thigh. SC injections in the upper extremities (e.g., deltoid, upper and lower arm) are not permitted. Study staff should refer to the Product Specific Investigational Product (IP) Manual for specific instructions on the handling and administration of study drug.

6.1.1. Medical Devices

- The medical device used to deliver PF-06801591 is a Pre-Filled Syringe (PFS).
- Instructions for medical device use are provided in the IP manual.
- All medical device deficiencies (including malfunctions, use error, and inadequate labeling), shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Investigational Product Manual.
- Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.
- Study intervention should be stored in their original containers and in accordance with the labels.
- Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention

must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

- The sponsor or designee will provide guidance on the destruction of unused study intervention (e.g., at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

PF-06801591

See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

This an open label study. In Phase 2, random allocation of participants between two treatment arms (300 mg Q4W and 600 mg Q6W) will be stratified according to lines of therapies (1L vs. 2L). This stratified randomization will be centrally allocated across all centers via the IRT system. The central randomization will help minimize the risk of participant selection bias between two treatment arms.

Once a participant has signed consent, the site staff will complete registration in interactive response technology (IRT). The IRT will assign a participant identification number and supply this number to the site. The participant identification number will be used on all study-related documentation at the site.

Allocation of participants to treatment groups will proceed using an IRT system (interactive Web-based response [IWR]).
No participant shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

The site personnel (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the protocol number, specific protocol entrance criteria indicated in the system and the screening number. The site personnel will then be provided with, at a minimum, a treatment assignment, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, allocation number and DU or container number assigned. The confirmation report must be stored in the site's file. Investigational product will be administered at the study visits as summarized in the Schedule of Activities (SoA).

The participant must receive the first dose of study treatment within 3 days after randomization.

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

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded.
The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All prior and concomitant treatments, received by participants from screening until the end of study visit including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions) will be recorded on the case report form (CRF). Concomitant medications for AEs and SAEs should follow respective guidance for AE and SAE reporting period.

6.5.1. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment including cancer vaccination therapy is permitted while participants are receiving study treatment.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of investigational product with

radiotherapy, treatment should be interrupted during palliative radiotherapy. Investigational treatment should not be administered within 7 days before starting radiotherapy and resume investigational treatment only after recovery of any radiotherapy associated signs and symptoms to baseline.

6.5.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current American Society of Clinical Oncology (ASCO) guidelines.

6.5.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines[16]. If the secondary prophylactic use of granulocyte-colony stimulating factors is needed it should be discussed with the study clinician before implementation. During screening, Granulocyte Colony-Stimulating Factor (G-CSF) is not permitted to qualify a participant with low ANC counts.
Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

For the countries, including Japan, where the indication and dosage of G-CSF compounds may differ from ASCO guidelines, refer to local package insert or follow clinical practice in their countries. Erythropoietin is not approved in Japan and other countries for anemia caused by cancer treatment.

6.5.4. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis is not required. If required for an individual participant, the decision to incorporate pre-medication will be made following discussions between the sponsor and the investigator.

6.5.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic is allowed as needed.

6.5.6. Corticosteroids

The use of steroids during this trial is restricted as follows:

a) Therapeutic use: for the treatment of injection-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Appendix 12.

b) Physiologic use: replacement for adrenal insufficiency at doses equivalent to $\leqslant$10 mg prednisone daily is acceptable.

c) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) are permitted.

d) Corticosteroids are not prohibited during the Post-Treatment Follow-up Phase.

Any other use of corticosteroids should be discussed with the sponsor before implementation.

6.5.7. Vaccines

Live attenuated vaccines within 4 weeks prior to the first dose of PF 06801591 and through 30 days following the last dose of PF 06801591 are not allowed. Examples of live attenuated vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, and oral typhoid vaccine. Seasonal influenza vaccines for injection are inactivated virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

6.5.8. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and investigational product required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping investigational product is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate investigational product treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.5.9. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with the investigational product; standard medical supportive care must be provided to manage the AEs (Refer to Section 6.6 and 6.8 for dose modification and management of treatment-related adverse events).

6.5.10. Proton-Pump Inhibitors

No restrictions.

6.5.11. Antacids or H2-Receptor Antagonists

No restrictions.

6.6. Dose Modification

Every effort should be made to administer investigational product on the planned dose and schedule. In the event of significant toxicity, dosing may be interrupted/delayed/discontinued as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. Following dose modifications will be allowed as described in Table 4.

Dosing interruption: When participant develops treatment related adverse event meeting "Withhold the treatment" criteria, the treatment administration should be immediately stopped and should not be resumed until the criteria to restart treatment are met.

Dosing Delays: If any treatment related adverse event is not resolved by next scheduled dosing, the dosing should be delayed until the criteria to restart treatment are met.

Permanent Treatment Discontinuation: If participant develops TRAE meeting discontinuation criteria as defined in Section 7.1, the treatment should be permanently discontinued.

General Dose Modification Guidelines:

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting > 4 weeks, treatment resumption will be decided in consultation with the sponsor.

All dosing modifications should be based on recommendations described in Table 4 unless expressly agreed otherwise following discussion between the investigator and the sponsor.

All dosing modifications must be clearly documented in the participant's source notes and CRF.

Depending on when the adverse event resolved, the treatment may lead to delay the initiation of the subsequent cycle. Retreatment is permitted as soon as the criteria to restart treatment are met. The day when treatment is restarted will be counted as Day 1 of the next cycle.

Table 4. Treatment Modification for Related Events**

Severity	PF-06801591
Grade 1	• Continue per schedule.
Grade 2	• First occurrence: continue per schedule. • Follow modifications for G3 event if G2 AE is considered intolerable and recurrent based on medical judgment
Grade 3*	• Withhold until re-treatment criteria are met. (See below) • If re-treatment criteria are not met within 8 weeks of last administration or if based on medical judgment the event is considered critical, permanently discontinue the treatment. • Upon the second occurrence of the same G3 toxicity that does not meet re-treatment criteria within 2 weeks of last administration, treatment must be permanently discontinued. • Exceptions: Laboratory test values out of normal range that do not have any clinical correlation
Grade 4*	• Permanent discontinuation. • Exceptions: Laboratory test values out of normal range that do not have any clinical correlate.

* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
**When applicable AE specific guideline described in Appendix 12 must be followed.

Re-treatment criteria: Retreatment following treatment interruption for treatment-related toxicity may not occur until all of the following parameters have been met:

- ANC $\geq$1,000/mm^3
- Platelets count $\geq$50,000/mm^3
- Non-hematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator's discretion, Grade $\leq$2 if not considered a safety risk for the participant).

No dose reduction is allowed for PF-06801591.

6.7. Intervention after the End of the Study

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

6.8. Management of Treatment Related Adverse Events

Treatment recommendations for the management of irAE are outlined in Appendix 12.

All other AEs should be treated as per standard of care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants who only discontinue study intervention (ie, study treatment) should continue in the study and complete all protocol specified activities after discontinuing study treatment. See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.
Reasons for discontinuing study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death;

Discontinuation of study treatment does not represent withdrawal from the study. Participants who only discontinue study treatment for reasons other than lost to follow-up and death should continue in the study and complete all protocol specified activities even after discontinuing study treatment, in order to provide the data required for the study estimands.

7.1.1. Treatment after Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents, may produce anti-tumor effects by potentiating endogenous cancer specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, participants may continue to receive the investigational product, at the Investigator's discretion after the participant is re-consented via informed consent addendum and informed that, by continuing to receive the investigational product, the participant may be foregoing approved or investigational

therapies with possible clinical benefit(s). The sponsor needs to agree to continuation of the treatment.

The following criteria must be met for continuation of treatment beyond progression:

- Absence of clinical signs and symptoms (including worsening of laboratory test values) of disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If the repeat imaging confirms disease progression, participant should be considered for discontinuation from study treatment. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a participant with evidence of disease progression is still experiencing clinical benefit, the participant may be eligible for continued treatment with PF-06801591. The Investigator's judgment should be based on the overall benefit-risk assessment and the participant's clinical condition, including performance status, clinical symptoms, adverse events, and laboratory data.

7.2. Participant Discontinuation/Withdrawal from the Study

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

- Completed study post-treatment period."
- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are described in Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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

- The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated informed consent document (ICD) before performing any study-specific procedures.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessment

The decision for body areas to be scanned will depend on disease under study and extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum body areas to be scanned at screening include chest, abdomen and brain. Imaging methods may include contrast enhanced computed tomography (CT) or MRI scans for chest, abdomen and brain. For imaging chest, CT scan is preferred. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Bone imaging using bone scan (bone scintigraphy) or 18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) required at baseline only if bone metastases are known or suspected outside the body areas scanned using other techniques, then every 12 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new

bone metastases are suspected. Bone imaging is also required at the time of confirmation of complete response (CR) for participants who have bone metastases.

For participants with known CT contrast allergy, a non-contrast CT of the chest with contrast enhanced abdominal and brain MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. If the imaging technique is changed due to unavoidable circumstances, as assessed by radiologist/investigator, if a comparable measurement of lesion is feasible then the tumor measurement should be reported, otherwise the lesion should be reported as non-evaluable.

When appropriate, clinical evaluation (presence/absence of a superficial lesion or measurement by caliper), X-ray or positron emission tomography (PET) scans can be used. If PET scan is to occur on the same day as the CT scan, it is to be performed prior to the CT due to the sustained levels of the contrast agent.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at following occasions:

- Screening (must be performed within 28 days prior to first dose of study treatment [Phase 1b] or randomization [Phase 2]),
- During treatment as specified in the SoA,
- Whenever disease progression is suspected (eg, symptomatic deterioration),
- After first occurrence of PR or CR is observed according to RECIST version 1.1, repeat imaging at least 4 weeks after initial documentation to confirm the PR or CR.

Assessment of tumor response will be made using RECIST version 1.1 (see Appendix 10).

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

All participants' files and radiologic images must be available for source verification and for potential peer review.

8.1.2. Tumor Markers

No tumor markers will be collected for efficacy assessment.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

The body systems included in the scope of examination will be decided by the treating physician based on the standard of care at the center. The details of the physical examination will not be recorded on a CRF, instead any abnormalities detected during the physical examination will be reported on the medical history or adverse event CRF. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature, pulse rate and blood pressure will be assessed as per the SoA. Temperature and pulse rate need not be recorded in the CRF but if the results represent an AE please record on the AE CRF.
- Blood pressure and pulse rate measurements will be assessed in a sitting or supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones) and prior to administration of study drug.

8.2.3. Electrocardiograms

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs as outlined in the SoA. Triplicate ECG is required at screening. Three consecutive ECGs will be performed at approximately [2-4] minutes apart to determine the mean QTc interval. At C1D1, C2D1 and C3D1, single ECG will be collected at 2 timepoints, first prior to administration of study drug, and then within 1 hour after the administration of study drug. For remaining timepoints, single ECGs will be collected only prior to administration of study drug. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure (BP), and pulse rate. Additional ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.

If participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) single ECGs should be obtained at time of the event.

To ensure safety, if there is finding of corrected QT (QTc) prolongation (≥60 msec from the pre-dose baseline, or >500 msec), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If manual reading verifies the observation, repeat ECGs should be immediately performed at least two times approximately 2 minutes apart. In such cases, while reporting ECG data in CRF, manual reading should be reported. ECG values of potential clinical concern are listed in Appendix 8.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
  Assessments and physician's evaluation of the following labs must be performed, at a minimum, prior to dosing:.
    - Negative pregnancy test (as applicable)
    - Hematology
    - Liver function: AST, ALT, and bilirubin
    - Renal function: Creatinine
    - Any other per protocol lab test(s) to correlate clinical signs or symptoms

    No need to repeat on C1D1 if screening assessment is performed within 72 hours prior to that date. Assessments performed on C2D1 and each subsequent cycle should be performed within 72 hours prior to dosing.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL as required by local regulatory requirements. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA.

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit on C1D1 before the participant may receive the study treatment. Pregnancy tests will also be done as per SoA and whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), at the end of treatment and until Day 30 during the post-treatment period. At Day 90 and Day 180 during the post-treatment period, pregnancy status should be examined (allowed also by telephone call, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.6. ECOG Performance Status

ECOG Performance Status will be evaluated as outlined in the SoA. Refer to Appendix 11 for ECOG Performance Status Criteria.

8.2.7. Local Site Injection Tolerability Assessment

Assessments to monitor local tolerability to PF-06801591 SC injections will be performed for at least 1 hour following study drug administration, as per the SoA. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after study drug dosing. At Cycles > 3, the assessment will only be performed if clinically necessary given participant's previous injection tolerability or if injection site pain or injection site reaction (ISR) characteristics continue to persist. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. If injection site reaction is noted, site tolerability assessments should continue until the symptoms resolve.

8.3. Adverse Events and Serious Adverse Events

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 7. Device deficiencies are covered in Section 8.3.9.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention (see Section 7).

Each participant (or their legally authorized representative) will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 90 calendar days after the last administration of the study intervention.

After completion of the active collection period described above only SAEs will be actively elicited and collected. The SAEs identified after completion of the active collection will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

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

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

Follow up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the clinical trial SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening

treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF. The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory

requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with SRSD for the study and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by different routes of exposure (e.g injection, ingestion, inhalation, or skin contact)
    - A male family member or healthcare provider who has been exposed to the study intervention by different routes of exposure (e.g injection, ingestion, inhalation, or skin contact) then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 180 days after the last dose.

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

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable

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

Not applicable

8.3.8. Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Appendix 12.

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

8.3.8.1. Lack of Efficacy

Lack of efficacy (see Section 10.3.1) is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

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

The definition of a Medical Device deficiency can be found in Appendix 7.
NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Incidents is provided in Appendix 7.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

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

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

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

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength or from inadvertent exposure.
Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, if a participant receives a dose higher than the assigned dose level of PF-06801591, it will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.
In the event of an overdose, the treating physician should:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 6 months after the overdose of PF-06801591.
3. Obtain a plasma sample for PK analysis within 90 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with a SAE**.

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

8.5. Pharmacokinetics

All efforts will be made to obtain the PK samples as required at scheduled visits (see SoA). The exact time of the sample collection will always be noted. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, participant and sponsor. PK sampling schedule may be modified based on emerging PK data.

PK samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

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

Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or further bioanalytical evaluation, CCI CCI unless prohibited by local regulations or ethics committee decision. These data will not be included in the Clinical Study Report (CSR).

Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

8.5.1. Blood for PK Analysis of PF-06801591

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of PF-06801591, as outlined in the SoA. Samples collected on day of dosing with the investigational product should be obtained within 2 hours prior to dosing. Refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.


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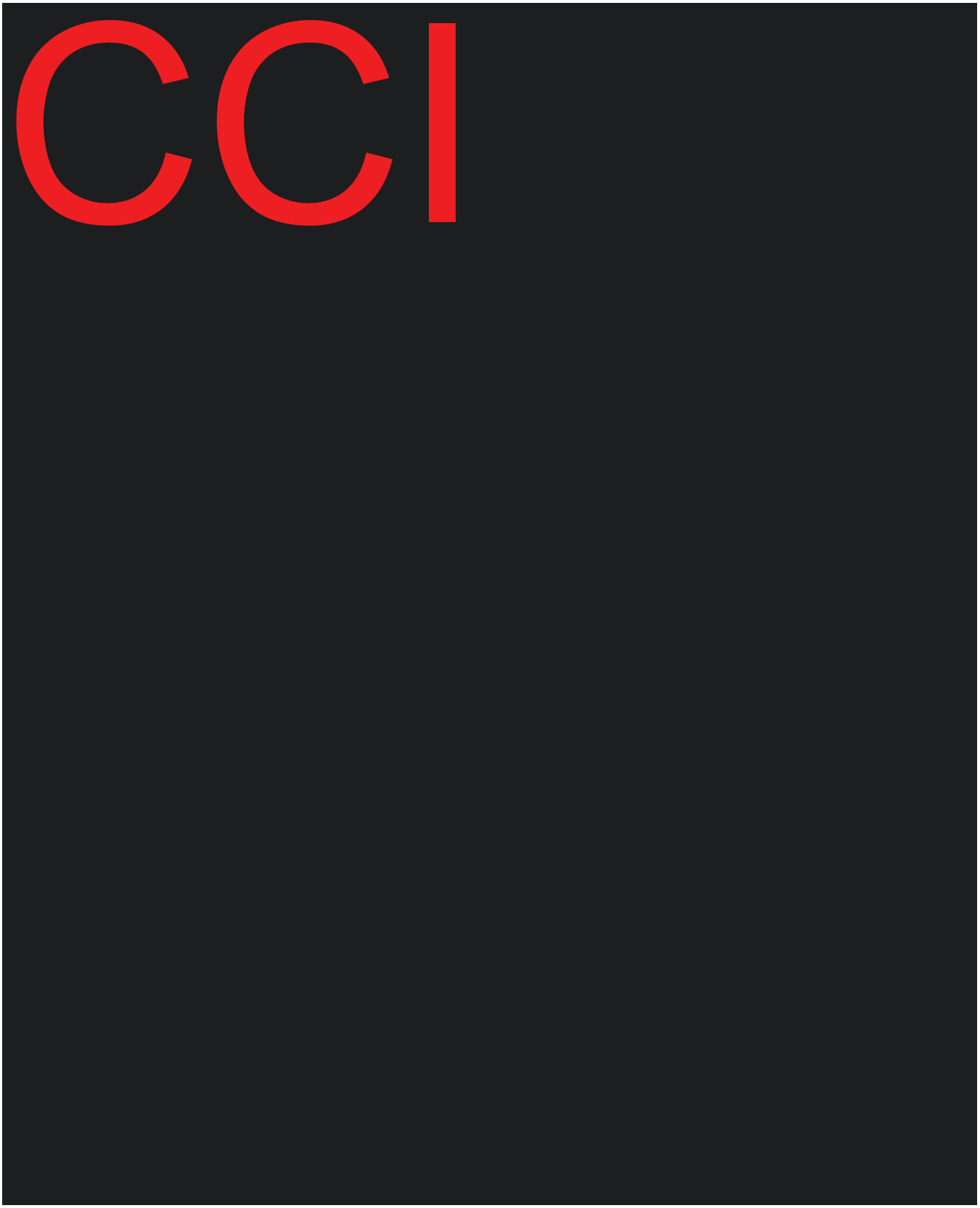
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8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic CCI measurements.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

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 4.1.
- 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 non 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 Estimands (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 1 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) 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.

9.2. 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.

9.2.1. Phase 1b

Approximately 36 participants in total will be enrolled in Phase 1b with 3-6 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. 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-06801591will 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 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 steady state.

9.2.2. Phase 2

The primary objective is to compare PK exposure 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 is not lower than 20% of the PK exposure obtained from the reference regimen of 300 mg SC Q4W.

For the primary PK objectives, a sample size of 90 participants (30 and 60 participants for Arms A2 (Reference) and B2 (Test), respectively) will provide at least 80% power that the lower bound for the 90% confidence interval (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%. This estimate is based on the assumption that the true ratio between (Test: PF-06801591 600 mg SC Q6W) and (Reference: PF-06801591 300 mg SC Q4W) treatments for both AUCτ and C_{trough} is 1.0 and also assumes a CV of 26% for AUCτ and a CV of 40% for C_{trough}.

The randomization will be stratified by line of therapy (1^{st} line vs 2^{nd} line).

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
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. 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 take at least 1 dose of study drug. Participants will be classified according to the study treatment actually received.
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. If there are participants non evaluable for DLT, then additional participants can be enrolled to ensure that target number of DLT evaluable participants is reached.
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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 post-dose concentration measurement above the lower limit of quantitation (LLQ). The PK parameter analysis set is a subset of the safety analysis set and will include participants who have at least 1 C_{trough} at 12 weeks.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The primary analysis will include all data up to a clinical cut-off date corresponding to 12 months after the last participant randomized in Phase 2. The final analysis of the data will be performed after last participant last visit (LPLV).

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. DLT rate assessment

Safety assessment will be performed using the DLT-Evaluable analysis set and the mTPI dosing finding method.

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, including safety data from treated participants who are not DLT evaluable, clinical activity, PK, and PD 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 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.

Refer to Appendix 9 for additional details of the mTPI design.

9.4.2. Efficacy Analyses

All efficacy analyses will be performed by dose levels for Phase 1b and Phase 2 using the full analysis set.

The efficacy endpoints of OR and TTR will be summarized based on investigator assessment using RECIST v1.1.

Objective response (OR) defined as CR, or PR according to RECIST v1.1 based on investigator assessment, from the date of first dose of study treatment (Phase 1b) or

randomization (Phase 2) until the date of the first documentation of progression of 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. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment. ORR, defined as the proportion of participants in the analysis population with OR, will be calculated along with the 2-sided 95% confidence interval (CI) using the Clopper-Pearson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, have PD, or stop tumor assessments 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).

TTR is defined for participants with confirmed objective response (CR or PR) as the time from the date of first dose (Phase 1b) or randomization (Phase 2) to the date of first documentation of objective tumor response which is subsequently confirmed. TTR will be summarized using simple descriptive statistics (eg, median and range). Point estimates will be presented with 95% CIs.

9.4.3. Safety Analyses

9.4.3.1. Primary Safety Analyses

DLT during the DLT evaluation period (Cycle 1) is the primary endpoint of the Phase 1b. Analyses of DLT are based on the DLT-evaluable analysis set.

The occurrence of DLTs and AEs constituting DLTs will be summarized for participants in the Phase 1b as described in Section 9.1.

9.4.3.2. Secondary Safety Analyses

Simple summary statistics (descriptive) will be presented for participants with SAEs, AEs of special interest, laboratory abnormalities, and other secondary safety endpoints during the on-treatment period. The on-treatment period is defined as the period starting with first dose of study treatment through the earliest of (30 days after date of last dose of study treatment) or (start date of new anti-cancer drug – 1).

AEs, ECGs, BP, and safety laboratory data will be reviewed on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory test, ECG, or BP abnormalities of potential clinical concern will be described. Safety data will be summarized descriptively, where appropriate.

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

9.4.3.3. ECG Analyses

Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding values. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's [QTcF; default correction], Bazett's [QT interval corrected by Bazett's formula {QTcB}], and possibly a study specific factor, as appropriate). Data will be summarized and listed for QT interval, HR, RR interval, PR interval, QRS complex, QTcF and QTcB.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTcF and QTcB, and changes from baseline in QTcF and QTcB during the on-treatment period. Categorical analysis will be conducted for the maximum change from baseline in QTcF and QTcB and the maximum post baseline QTcF and QTcB during the on-treatment period.

The effect of drug concentrations on QTcF change from baseline will be explored graphically. Additional concentration QTcF analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.4.3.4. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE data will be reported in tables and listings. Summaries of AE by toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized. Listings of DLTs and deaths will be provided.

9.4.3.5. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay at baseline and during the on-treatment period. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.4.4. Other Analyses

9.4.4.1. PK Analyses

The concentration-time data of PF-06801591 will be summarized by descriptive statistics (n, mean, and standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study.

For participants enrolled in the 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 or if considered appropriate, PK parameters such as $t_{½}$, CL, volume of distribution (V_d)/ volume of distribution at steady state (V_{ss}), and accumulation ratio (R_{ac}, when feasible) will also be estimated for Cycle 1 (both arms), Cycle 4 (for Arm A2) and Cycle 3 (for Arm B2).

The PK parameters will be summarized descriptively by dose level and cycle. 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. These plots will be used to help understand the relationship between PK parameters and dose.

The observed accumulation ratio and the linearity will be summarized descriptively. Individual and median profiles will be presented on both linear-linear and log-linear scales.

Natural log transformed PK parameters (AUCτ or C_{trough} 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 C_{trough} 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. 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.

9.4.4.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/Pharmacodynamic) Modeling

Pharmacokinetic and pharmacodynamic data from this study will 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 will be reported separately.

PK, pharmacodynamic, CCI [redacted] analyses will be described and finalized in the statistical analysis plan before database lock. The population PK analysis and pharmacodynamic analyses, CCI [redacted] will be presented separately from the main clinical study report (CSR).

9.4.4.3. Analysis of Immunogenicity Data

ADA/NAb data will be listed and summarized. The percentage of participants with positive ADA and NAbs will be summarized by treatment arm and, if deemed appropriate, combined across treatments. For participants with positive ADA, the magnitude (titer), time of onset,

and duration of ADA response will also be described, if data permit. The effect of ADA on PF-06801591 pharmacokinetics may be evaluated, if data permit.

9.5. Interim Analyses

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.

9.5.1. Data Monitoring Committee (DMC)

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/(institutional) ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.
- In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The investigator must ensure that each study participant [or his or her legally authorized representative] is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In Japan, participants enrolled in the Phase 1b of the trial will be asked to sign an additional consent document after completion of Cycle 1 for confirmation of the participant's willingness to continue participation in this study before starting Cycle 2.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date. If the rescreening occurs more than 28 days from the previous ICD signature date, a new ICD should be signed.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' personal data will be stored at the study site in encrypted electronic and /or paper form and will be password protected and secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies that are in scope of EU requirements.

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials

24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No

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

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic case report form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the clinical monitoring plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time upon notification to CRO if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

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

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

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

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.
- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.
- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.
- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card

contains, at a minimum, protocol and investigational product identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25mIU/mL as required by local regulatory requirements. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit on C1D1 before the participant may receive the study treatment. Pregnancy tests will also be done as per SoA and whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), at the end of treatment and until Day 30 during the post-treatment period. At Day 90 and Day 180 during the post-treatment period, pregnancy status should be examined (allowed also by telephone call, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

Table 5. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Hemoglobin	White blood cell (WBC) count with Differential: Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils		
Clinical Chemistry[1]	ALT AST Albumin Alk Phos Amylase Lipase	BUN or Urea Chloride Creatinine Glucose (random)	Magnesium Phosphorus/Phosphate Potassium	Sodium Total Bilirubin Total Calcium Total Protein Uric Acid
Pulmonary function	• Sialylated carbohydrate antigen (KL-6) • Arterial oxygen saturation (SpO2)			
Routine Urinalysis[2]	• Protein (qual) and blood (qual) • Microscopy (only if urine dipstick is positive for blood, protein)			
Coagulation	• international normalized ratio (INR) • aPTT			
Endocrinology	• adrenocorticotropic hormone (ACTH) • thyroid-stimulating hormone (TSH)			
Serology	• HBV (only if clinically indicated) • HCV (only if clinically indicated)			
Pregnancy Test	• For female participants of childbearing potential			

NOTES:

1. Details of liver chemistry required actions and follow-up assessments after liver event are given in Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report. The results of each test must be entered in the CRF.

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

10.3.1. Definition of AE

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

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

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

the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

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

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

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

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

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

Assessment of Intensity

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

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Pfizer Safety by telephone.
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SAE Reporting to Pfizer Safety via Paper CRF

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

10.4. Appendix 4: Contraceptive Guidance

Definitions: Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.
Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

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

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT. (The states of high FSH level should be confirmed if there is no other medical cause).
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of study intervention.

- Refrain from donating sperm

PLUS either:

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, including participants who intend to interrupt breastfeeding, and at least one of the following conditions applies:

Is not a woman of childbearing potential (WOCBP)

OR

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in the table below during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention; and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. As for participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception, as described below. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Contraception Methods

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

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation*
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner o *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation o oral o intravaginal* o transdermal* o injectable*
• Progestogen-only hormone contraception associated with inhibition of ovulation o oral o injectable*
• Sexual abstinence o Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
• One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent: o Male or female condom with or without spermicide o Cervical cap, diaphragm, or sponge with spermicide o A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

*Not commercially available in Japan

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision-making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
    - Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.

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

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

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

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

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

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

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

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

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

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

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

10.7. Appendix 7: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.1 for the list of sponsor medical devices).

10.7.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.7.3. Definition of Device Deficiency

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

10.7.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP Manual
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency

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

10.7.5. Reporting of SAEs

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

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

10.7.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

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

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

QTcF prolongation >500 msec.

New ST-T changes suggestive of myocardial ischemia.

New-onset left bundle branch block (QRS complex >120 msec).

New-onset right bundle branch block (QRS complex >120 msec).

Symptomatic bradycardia.

Asystole:

In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.

In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.

Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 beats per minute (bpm).

Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

Type II second-degree (Mobitz II) AV block.

Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

Change in pattern suggestive of new myocardial infarction.

Sustained ventricular tachyarrhythmias (>30 seconds' duration).

Second- or third-degree AV block requiring pacemaker placement.

Asystolic pauses requiring pacemaker placement.

Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.

Ventricular fibrillation/flutter.

At the discretion of the investigator, any arrhythmia classified as an adverse experience.

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

10.9. Appendix 9: Detailed Dose Escalation/De-Escalation Scheme for mTPI design

A safe dose will be determined using the adaptive mTPI design. The mTPI design is flexible and allows dose reduction to doses in between the planned doses.

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing 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. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. As shown by Ji and Wang [12], mTPI design is more efficient and safer than the 3+3 design. They considered 42 scenarios to cover a wide range of practical dose-response shapes, and concluded that the 3 + 3 design was more likely to treat participants at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3 + 3 design exhibited a lower overall toxicity percentage than the mTPI design in only 1 of 42 scenarios.

Being a model-based design, mTPI automatically and appropriately tailors dose re-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a 2-way table. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as [0, pT-e1), the overdosing interval (pT+e2, 1], and the proper-dosing interval [pT- e1, pT+ e2), where e1 and e2 are small fractions. Based on the safety profile of PF-06801591, e1 is selected as 0.05, and e2 is selected as 0.05. Therefore, the target interval for the DLT rate is [0.25, 0.35). The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a participant belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future participants. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next 3-4 participants will be treated at the next higher dose level. Simulations have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The following table defines the dose finding scenarios:

Table 6. Dose finding Rules

		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		

E = Escalate to the next higher dose

S = Stay at the current dose.

D = De-escalate to the next lower dose level.

U = The current dose is unacceptably toxic.

Targeted DLT rate =30%.

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.

10.10. Appendix 10: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al (2009)[17].

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

Lesions with longest diameter at least 20 mm when assessed by chest X-ray.

Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to initiation of study treatment. For an adequate baseline assessment, all required scans must be done within 28 days prior to initiation of study treatment (Phase 1b) or randomization (Phase 2) and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be inevaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INEVALUABLE, PRESENT WITHOUT UNEQUIVOCAL PROGRESSION, UNEQUIVOCAL PROGRESSION. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case should be discussed with the radiologist and the sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target Disease

Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.

Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.

Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

Not evaluable (NE): Progression has not been documented, and

- 1 or more target lesions have not been assessed; or
- Assessment methods used were inconsistent with those used at baseline; or
- 1 or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
- 1 or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.

PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

Not evaluable (NE): Progression has not been determined and

- 1 or more non-target lesion sites have not been assessed; or

- assessment methods used were inconsistent with those used at baseline; or
- 1 or more non-target lesions cannot be assessed (eg, poorly visible or unclear images); or
- 1 or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Participants with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal

Determination of tumor response at each assessment based on non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Participants with Non-Measurable Disease at Baseline

Non-target Lesions	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment (Phase 1b) or randomization (Phase 2) until disease progression/recurrence (taking as reference for progressive disease (PD) the smallest sum on study). For CR and PR, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment (Phase 1b) or randomization (Phase 2) at a minimum interval of 6 weeks.

10.11. Appendix 11: ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: From Oken, NM et al [18]

10.12. Appendix 12 Management of Immune-related Adverse Event (irAEs)

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	-Continue study treatment -Symptomatic treatment (e.g. loperamide)	-Close monitoring for worsening symptoms -Educate participant to report worsening immediately -If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; limiting instrumental ADL Colitis: abdominal pain; blood in stool	-Withhold study treatment - Symptomatic treatment	-If improves to Grade ≤ 1: Resume study treatment -If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	-Withhold for Grade 3. -Permanently discontinue study treatment for Grade 4 or recurrent Grade 3. -1.0 to 2.0 mg/kg/day prednisone IV or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider lower endoscopy	-If improves: -Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). -If worsens, persists > 3 to 5 days, or recurs after improvement: -Add infliximab 5mg/kg (if no contraindication). -Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	-Continue study treatment -Symptomatic therapy (for example, antihistamines, topical steroids)	-If Grade 2 persists > 1 to 2 weeks or recurs: -Withhold study treatment -Consider skin biopsy -Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper. -If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	-Withhold study treatment for Grade 3. -Permanently discontinue for Grade 4 or recurrent Grade 3. -Consider skin biopsy -Dermatology consult -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections	-If improves to Grade ≤ 1: -Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	-Consider withholding study treatment -Monitor for symptoms every 2 to 3 days -Consider Pulmonary and Infectious Disease consults	-Re-assess at least every 3 weeks -If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	-Withhold study treatment -Pulmonary and Infectious Disease consults -Monitor symptoms daily; consider hospitalization -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-Re-assess every 1 to 3 days If improves: -When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume study treatment following steroids taper -If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	-Permanently discontinue study treatment. -Hospitalize. -Pulmonary and Infectious Disease consults. -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-If improves to Grade ≤ 1: -Taper steroids over at least 1 month -If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN if baseline was normal, > 1.5-3.0 x baseline if baseline was abnormal; and/or Total bilirubin > ULN to 1.5 x ULN if baseline was normal, > 1.0-1.5 x baseline if baseline was abnormal	-Continue study treatment	-Continue liver function monitoring -If worsens: Treat as Grade 2 or 3 - 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN if baseline was normal, > 3.0-5.0 x baseline if baseline was abnormal; and/or total bilirubin > 1.5 to ≤ 3 x ULN if baseline was normal, > 1.5-3.0 x baseline if baseline was abnormal	-Withhold study treatment -Increase frequency of monitoring to every 3 days.	-If returns to Grade ≤ 1: -Resume routine monitoring; resume study treatment. -If elevation persists > 5 to 7 days or worsens: -Treat as Grade 3 to 4.

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 3 to 4 AST or ALT > 5 x ULN if baseline was normal, > 5.0 x baseline if baseline was abnormal; and/or total bilirubin > 3 x ULN if baseline was normal, > 3 x baseline if baseline was abnormal	-Permanently discontinue study treatment -Increase frequency of monitoring to every 1 to 2 days -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consult gastroenterologist/ hepatologist -Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	-If returns to Grade ≤ 1: -Taper steroids over at least 1 month -If does not improve in > 3 to 5 days, worsens or rebounds: -Add mycophenolate mofetil 1 gram (g) twice daily -If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	-Continue study treatment	-Continue renal function monitoring -If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	-Withhold study treatment -Increase frequency of monitoring to every 3 days -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections -Consider renal biopsy	-If returns to Grade ≤1: -Taper steroids over at least 1 month, and resume study treatment following steroids taper. -If worsens: -Treat as Grade 4.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 4 Creatinine increased > 6 x ULN	-Permanently discontinue study treatment -Monitor creatinine daily -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections Consider renal biopsy -Nephrology consult	-If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin I, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	-Withhold study treatment. -Hospitalize. -In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. -Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis. -Guideline based supportive treatment as per cardiology consult.* -Consider myocardial biopsy if recommended per cardiology consult.	-If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment. -If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	-Permanently discontinue study treatment. -Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections.	-Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A, abatacept).

*Local guidelines, or eg. ESC or AHA guidelines

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Continue study treatment -Endocrinology consult if needed -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Withhold study treatment -Consider hospitalization ----- Endocrinology consult -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	-If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) -Hormone replacement/suppressive therapy as appropriate -Perform pituitary MRI and visual field examination as indicated **-If hypophysitis is confirmed:** -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month	-Resume study treatment once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). -In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. -Continue hormone replacement/suppression therapy as appropriate.

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
	-Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. -Add prophylactic antibiotics for opportunistic infections.	

10.13. Appendix 13 Japan-specific Requirements

- **Conditions for judging whether the participant can be discharged during the DLT evaluation period (Section 1.1 Synopsis and Section 4.1 Overall design; DLT determination)**

When a participant is discharged from the hospital during the DLT evaluation period, the following conditions/status of the participant should be evaluated on the day of the scheduled discharge by the investigators, and the propriety of discharge should be determined. The tests/medical examinations needed to confirm the participant's status will be conducted per clinical practice at the study site by investigator's judgement as appropriate.

- There are currently no clinically significant adverse events or other medical conditions that require monitoring in a hospital setting.
- If a clinically significant adverse event has occurred or continues to be present, the investigator has determined that the event is manageable by appropriate treatment or prophylaxis in an out of the hospital setting. The investigator will ensure the adverse event is followed up according to the protocol requirement.
- Overall physical condition is stable and acceptable.
- In case of emergency, the participant may return to the clinical study site or other medical institution. If participants go to a medical institution other than the clinical study site, the clinical study site asks that the participants contact the study site and study investigator and the doctor at the medical institution will communicate to discuss appropriate treatments. A study site keeps ready for emergency situations and is available even during nights and holidays, and the sponsor will ensure and the selected study site will thoroughly follow all participants according to study procedures.

CCI

10.13.1. Definitions of serious adverse event, serious adverse event caused by medical device, and unanticipated serious adverse event caused by medical device

Definition of serious adverse event caused by medical device.

A serious adverse event caused by medical device is defined as an adverse event caused by a medical device which led to an outcome characteristic to serious adverse events, or a device-related incident whose recurrence might lead to death or serious deterioration in health.

10.14. Appendix 14. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.
Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

To fulfill the primary and secondary PK endpoints, it is highly recommended that in-clinic study visits are conducted for the following visits (and not substituted with visits/safety assessments listed in Sections 10.14.2 and 10.14.3 below, if feasible):

- For participants receiving Q4W regimen: C1D1, C1D8, C1D15, C1D22, C2D1; and C4D1, C4D8, C4D15, C4D22, C5D1
- For participants receiving Q6W regimen: C1D1, C1D8, C1D15, C1D29, C2D1; and C3D1, C3D8, C3D15, C3D29, C4D1

Sponsor should be contacted prior to implementation of the procedures reported below and discussed with the Medical Monitor case-by-case

10.14.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per

- Exclusion criteria Number 5: Participants with known active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), sero-positivity to human immunodeficiency virus (HIV) infection
- Exclusion criteria Number 16: Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

10.14.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to

communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant treatments or changes in concomitant treatments since the last contact.
- Review and record contraceptive method and results of pregnancy testing, if applicable for the participant. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.10.3.1 of this appendix regarding pregnancy tests.
- Assess ECOG performance status.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.14.3. Alternative Facilities for Safety Assessments

Alternative facilities to the study site may be used as described in this section.

10.14.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. . Note that per protocol, participants may have safety labs completed at a local laboratory even in the absence of a public emergency; however, this section is included to highlight the option to use local labs if needed to facilitate collection of safety laboratory assessments during a public emergency. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

Please refer to the Table 5 for protocol required safety laboratory assessments.

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

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

10.14.3.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. Note that per protocol, participants may have ECGs completed at an alternative facility to the site even in the absence of a public emergency; however, this section is included to highlight the option to use an alternative facility if needed to allow completion of ECGs during a public emergency.

10.14.4. Study Intervention

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

This guidance below is intended to support decision making, but it is not meant to supersede clinical assessment of any individual study participant case.

Regarding the **continued administration of PF-06801591** for ongoing participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection, the following is recommend:

- For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. It is requested that the site inform the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.14.5. Adverse Events and Serious Adverse Events

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

10.15. Appendix 15: Abbreviations

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
ALK	anaplastic lymphoma kinase
AESI	Adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUCτ	area under the concentration-time curve during the dosing interval (τ)
AV	atrioventricular
CCI	[redacted]
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cfDNA	cell-free DNA
C1D1	Cycle 1 Day 1
CI	confidence interval
CK	creatine kinase
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	concentration at the end of the dosing interval
CV	coefficient of variation
D	de-escalation
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid

Abbreviation	Term
DU	dispensable unit
E	escalation
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
18F-FDG-PET	18-fluorodeoxyglucose positron emission tomography
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
G-CSF	Granulocyte Colony-Stimulating Factor
KL-6	sialylated carbohydrate antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IASLC	International Association for the Study of Lung Cancer
IB	investigator's brochure
ICD	informed consent document
ICF	informed consent form
ICH	International Council for Harmonisation
(I)EC	(institutional) ethics committee
IFN-γ	interferon gamma
IL	interleukin
ILD	Interstitial Lung Disease
INR	international normalized ratio
IP manual	investigational product manual
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous(ly)

Abbreviation	Term
IWR	interactive Web-based response
LBBB	left bundle branch block
LPLV	last patient last visit
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTNBC	metastatic triple negative breast cancer
mTPI	modified toxicity probability interval
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NE	not evaluable
(N)IMP	(non-)investigational medicinal product
NSCLC	non-small-cell lung carcinoma
OR	objective response
ORR	objective response rate
PCD	primary completion date
PD	progressive disease
PD-1/L1/L2	programmed death - 1/L1/L2, respectively
PET	positron emission tomography
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PMAP	pharmacometric analysis plan
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
pT	target probability
PT	prothrombin time
PVC	premature ventricular complex
Q3W/Q4W/Q6W	every 3 / 4 / 6 weeks, respectively
QRS	depolarization of the ventricles, between the beginning of the Q wave and the end of S wave
QTc	corrected QT
QTcB	QT interval corrected by Bazett’s formula
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
S	staying at the current dose

Abbreviation	Term
SC	subcutaneous(ly)
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SpO2	arterial oxygen saturation
StoD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCR	T-cell receptor
TMB	tumor mutational burden
TME	tumor microenvironment
TNF	tumor necrosis factor
TPS	Tumor Proportion Score
TRAE	treatment related adverse event
TSH	thyroid-stimulating hormone
TTR	time to response
UC	urothelial carcinoma
ULN	upper limit of normal
UPCR	urinary protein creatinine ratio
UPM	unit probability mass
VBIR	vaccine-based immunotherapy regimen
USADE	unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

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