Protocol C4011001

A PHASE 1 DOSE ESCALATION AND EXPANSION STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMIC, AND ANTI-TUMOR ACTIVITY OF PF-07209960 IN PARTICIPANTS WITH ADVANCED OR METASTATIC SOLID TUMORS

Statistical Analysis Plan (SAP)

Version: **1**

Date: 11 11 2020

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1. VERSION HISTORY

This is the first version.

2. INTRODUCTION

Note: In this document any text taken directly from the protocol is *italicized*.

PF-07209960 is a fusion of a single, potency-reduced, IL-15 mutein and a bivalent high affinity anti- PD-1 full length IgG. This antibody-cytokine fusion molecule is designed to deliver PD-1-mediated avidity-driven IL-2/15 receptor stimulation preferentially to PD-1-positive CD8+ T cells, which are enriched in tumors and can mediate anti-tumor activity, while reducing the natural preference of IL-15 for majority PD-1-negative NK cells, which may mediate toxicity. The exposure of the IL-15 mutein is extended by fusing it to an antibody, which also reduces its potency to prevent systemic activation of PD-1 negative lymphocytes. Pre-clinical data suggest the stimulatory activity of PD-1 targeted IL-15 mutein is enhanced in tumor infiltrating lymphocytes preferentially over peripheral lymphocytes and can lead to anti-tumor activity greater than can be achieved with anti-PD-1 and IL-15 agonist either alone or in combination.

Study C4011001 is a FIH Phase 1 study designed to evaluate the safety, tolerability, PK, PD, and potential clinical benefits of PF-07209960 in participants with selected locally advanced or metastatic solid tumors. Presently, only monotherapy of PF-07209960 is assessed in the study, which is composed to two parts; Part 1: Dose Escalation and Part 2: Dose Expansion.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C4011001. This document provides additional details for the planned analyses that are outlined in the protocol. This SAP was written in reference to Amendment 1 of the protocol dated October 30, 2020 which will be the initial version of the protocol that participants will be enrolled under. The original version of the protocol dated September 15, 2020 will not be used. Any major modifications of the endpoints or analyses will be reflected in amendments to the protocol and/or SAP.

2.1. Study Objectives and Endpoints

2.1.1. Primary Objectives

2.1.1.1. Part 1

- *To assess safety and tolerability at increasing dose levels of PF-07209960 in participants with select locally advanced/metastatic solid tumors in order to estimate the MTD and select the RP2D/schedule.*

2.1.1.2. Part 2

- *To confirm safety and tolerability of PF-07209960 at the RP2D in participants with selected tumor types.*

- *To evaluate preliminary evidence of anti-tumor activity of PF-07209960 in participants with selected tumor types.*

2.1.2. Secondary Objectives

2.1.2.1. Part 1

- *To characterize the single and multiple dose PK of PF-07209960.*
- *To evaluate the immunogenicity of PF-07209960.*
- *To evaluate preliminary anti tumor activity.*

2.1.2.2. Part 2

- *To further evaluate the **PK** of PF-07209960 at the RP2D.*
- *To evaluate the immunogenicity of PF-07209960.*
- *To evaluate the effect of PF-07209960 on immune cells in tumor biopsies.*
- *To evaluate preliminary anti-tumor activity through time to event endpoints.*
- *To assess overall survival of participants treated with PF-07209960.*

2.1.3. Exploratory Objectives

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2.2. Study Design

This is a Phase 1, open label, multicenter, multiple dose, dose escalation, safety, PK and PD study of PF-07209960 in participants with selected locally advanced or metastatic solid tumors (anti-PD-I/PD-LI resistant NSCLC, SCCHN, RCC, UC; or anti-PD 1 naive OvCa and MSS CRC for whom no standard therapy is available, or would not be an appropriate option in the opinion of the participant and their treating physician, or participants who have refused standard therapy.

The study contains 2 parts, single agent dose escalation (Part 1) followed by a dose expansion at the RP2D (Part 2). The overall study design is depicted in the schema (Section 1.2 in the protocoV. *Successive cohorts of participants in Part 1 will receive escalating doses of PF 07209960 as SC or IV administration every 2 weeks. The first and second participant in each dose level must be enrolled > 72 hours apart. BLRM guided by EWOC principle will be used to guide dose escalation process and determine the MTDIRP2D. Part 1 will estimate the MTDIRP2D in sequential dose escalation cohorts for PF-07209960 as single agent in participants with selected solid tumors. After the MTDIRP2D for PF-07209960 single agent is determined, Part 2 expansion will be initiated in participants with selected solid tumors as informed by Part 1.*

Number of Participants: *The total number of participants enrolled to study intervention is estimated to range from approximately 74 to 172. Approximately 14-22 participants are expected to be enrolled in Part 1 dose escalation. Each cohort in Part 2 will enroll 20-30 participants. Approximately 60-90 participants will be initially enrolled in the.first three cohorts, with the option to further enroll approximately 40-60 participants in an additional two cohorts.*

Intervention Groups and Duration: *PF-07209960 will be administered as monotherapy, SC or IV infusion over 1 hours (±10 minutes) on Days 1 and 15 in 28 day cycles as described in Section 4.3.1* in the protocol. *Treatment with study intervention will continue until either disease progression, unacceptable toxicity, participant refusal, or whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments or agree to discontinue treatment or the study is terminated.*

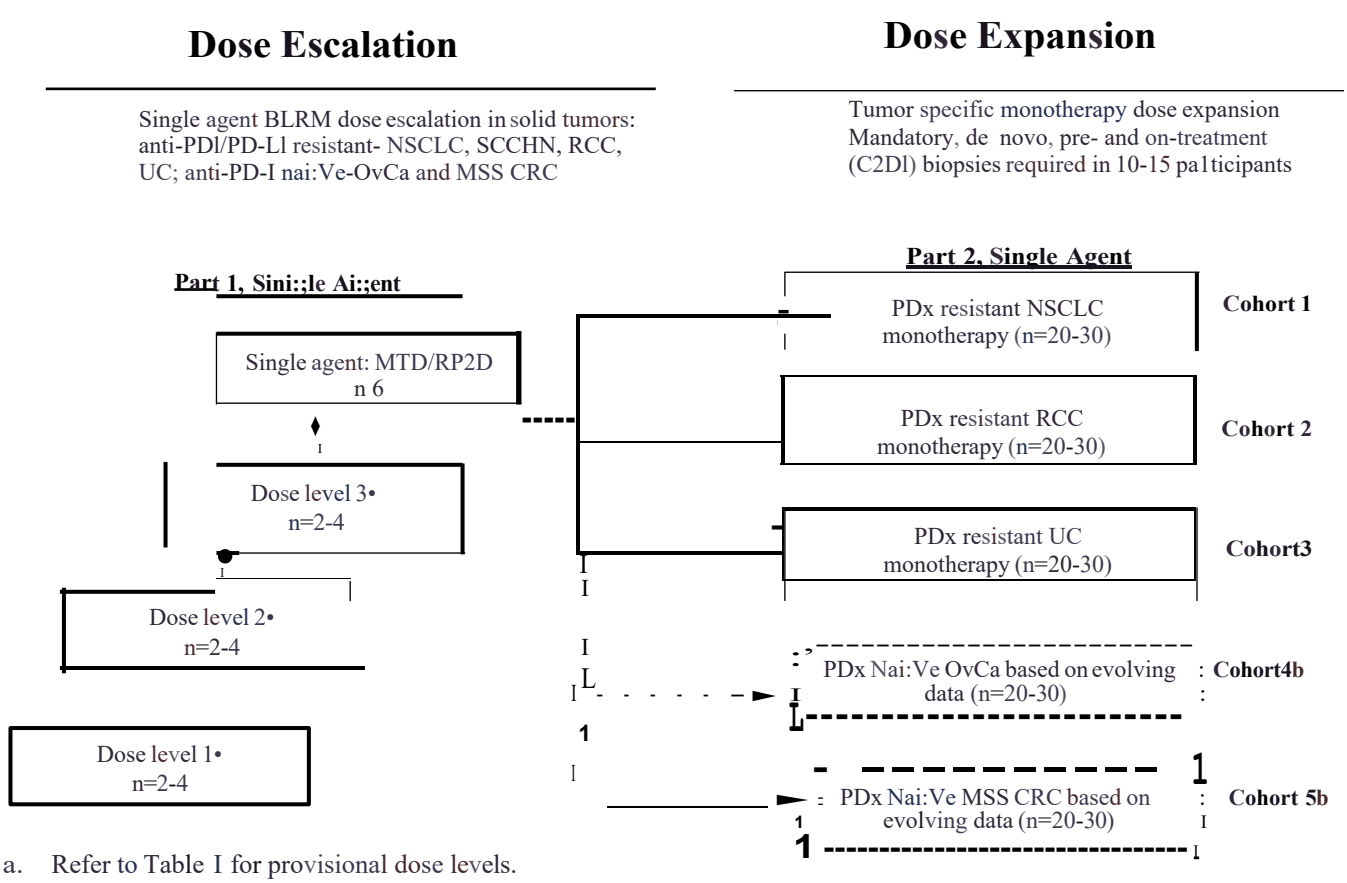
The starting dose for PF-07209960 for this FIH study has been determined to be CCI [redacted]. *The SC route has the potential to reduce the Cmax which is believed to be associated with CRS and inflammatory responses, common AEs for agents that stimulate T cells. If excessive ISR or unexpected low exposure is encountered with SC dosing, an alternative IV infusion Q2W administration may be explored. The IV dose escalation/finding would begin at a starting dose based on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation cohorts with SC Q2W administration. The starting dose for IV infusion is described in Section 4.3.1.2* in the protocol. *All participants will be monitored during and following their first dose (regardless of SC or IV dosing) with a 72-hour inpatient hospitalization period throughout dose escalation. Participants receiving IV dosing on C1D15 will remain at the investigational site for observation for at least 8 hours following IV infusion. Participants may not be released until the investigator has confirmed the participant has not exhibited signs and symptoms of a cytokine reaction. For additional information, refer to Section 4.3.1* in the protocol. *Dose modification information is provided in Section 6.6* in the protocol.

A participant is considered to have completed the study if he/she has completed all phases of the study including the end of treatment visit.

The end of the study will be the date of the last visit of the last participants or 2 years after the last participant receives their first dose (whichever occurs first). The study may also be terminated at any time at the discretion of the sponsor. Any additional treatment beyond 2 years shall be discussed and approved by the sponsor.

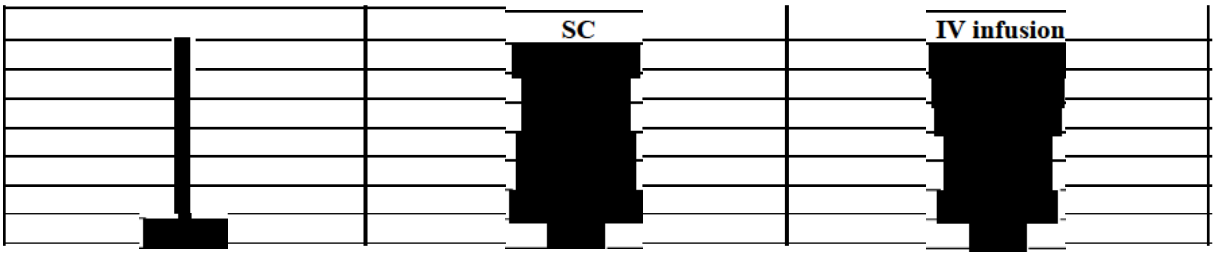
Biomarker Assessments: *The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. The studies may help in the future development of PF-07209960 as a single agent, or in combination with other compounds, and may provide information on tumor sub types that may respond to the study intervention.*

Study Schema: The study schema for dose-escalation and expansion is provided below.



a. Refer to Table I for provisional dose levels.
b. Coho1ts 4 and *5* to be considered for activation only after early signs of efficacy are seen in Coho1ts I, 2 and/or 3.

Table 1. Provisional Dose Levels



a. The IV infusion doses are tentative IV and will be based on emerging data.
b. To be detenuined by BLRM.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Part 1

- *First cycle DLTs.*
- *AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), timing, seriousness, and relationship to study therapy.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*

3.1.2. Part 2

- *AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), timing, seriousness, and relationship to study therapy.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*
- *ORR as determined by RECIST version 1.1.*

3.2. Secondary Endpoint(s)

3.2.1. Part 1

- *Single dose: C_{max}, T_{max}, AUC_{tau}. If data permits, AUC_{inf}, CL/F, $t_{½}$.*
- *Multiple Dose: $C_{max,ss}$, $T_{max,ss}$, $AUC_{tau,ss}$. If data permits, CL_{ss}/F, $t_{½,ss}$, and Rac.*
- *C_{trough} at selected time points.*
- *Incidence, titers and endogenous IL-15 cross reactivity of ADA and NAb against PF-07209960.*
- *ORR, DCR as assessed using the RECIST version 1.1.*
- *Time-to-event endpoints: DOR, PFS, and TTP by RECIST version 1.1.*

3.2.2. Part 2

- *Single dose: C_{max}, T_{max}, AUC_{tau}. If data permits, AUC_{inf}, CL/F, $t_{½}$.*
- *Multiple Dose: $C_{max,ss}$, $T_{max,ss}$, $AUC_{tau,ss}$. If data permits, CL_{ss}/F, $t_{½,ss}$, and Rac.*
- *C_{trough} at selected time points.*

- *Incidence, titers and endogenous IL-15 cross reactivity of ADA and NAb against PF-07209960.*
- *Intra-tumor T cells (such as by CDS IHC) in on-treatment versus baseline tumor biopsy samples.*
- *DCR, DOR, PFS, and TTP by RECISTversion I.I.*
- *Overall survival.*

3.3. Exploratory Endpoint(s)

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3.4. Baseline Variables

Baseline characteristics will be collected according to Schedule of Activities as specified in the protocol. For the primaiy analysis, no baseline vai·iable will be used for strntification or as covariates in the statistical analysis for the primaiy endpoint. Unless othe1wise specified, the baseline value is defined as the value collected at the time closest to, but prior to, staiiing the study intervention administration in the first cycle.

3.5. Safety Endpoints

The on-treatment period will be used for all safety assessments. The on-treatment period is defined as the period that struts with the first dose of study treatment and ends at minimum (last dose of study treatment+ *xx* days, stait of new anti-cancer therapy - 1 day). Two different on-treatment periods will be defined to capture the typical on-treatment period (where 'xx' is 28 days), as well as an extended on-treatment period (where 'xx' is 90 days) in order to identify any late onset AE/SAEs.

3.5.1. Adverse Events

Severity of adverse events will be graded according to Collllllon Tenninology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-emergent AE are defined as AEs with onset date during the on-treatment period.

For the purpose of dose escalation, any of the AEs listed in section 4.3.3 of the protocol that occur during the DLT observation period (i.e., first cycle of treatment) for DLT-evaluable paiiicipants, that are attributable to the study intervention, will be classified as DLTs.

Definitions of an AE and a SAE can be found in Appendix 3 of the protocol.

3.5.2. Vital Signs

Vital signs include temperature, systolic and diastolic blood pressure, and heaii rate. Details on the collection of vital signs can be found in section 8.2.2 of the protocol.

3.5.3. Laboratory Data

Details of the laboratory tests can be found in Appendix 2 of the protocol.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Table 2. Analysis Sets

Population	Description
Full analysis set	*The full analysis set includes all enrolled participants. "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Safety analysis set	*The safety analysis set includes all enrolled participants who receive at least one dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.*
Per protocol analysis set (Evaluable for MTD)	*The per protocol analysis set includes all enrolled participants who had at least one dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period. To be DLT evaluable, a participant must have received at least 75% of their planned doses in each cycle for the first two cycles (i.e., ≥ 11 doses received in each of the first two cycles) and has received all scheduled safety assessments during the DLT window.*
Modified Intent to Treat (mITT)	*The modified intent to treat (mITT) is the analysis population that will follow the ITT principle and include participants receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.*
PK analysis sets	*The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.*

Population	Description
	The PK concentration population is defined as all enrolled participants who are treated and have at least 1 postdose analyte concentration.
Response Evaluable set	*The response evaluable population will include all participants who received at least one dose of study treatment and had measurable disease at baseline and at least one post baseline disease assessment.*
PD/Biomarker analysis set(s)	*The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.*
Immunogenicity analysis set	*The immunogenicity analysis set includes all enrolled participants who receive at least one dose of study treatment and have at least one sample tested for ADA.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There will be no formal hypothesis testing in this study.

Decision Rules for Part 1:

Dosing decisions during dose escalation will be based on the following:

The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07209960. Dose toxicity is modelled using two-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

Assessment of Participant Risk:

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07209960 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing	*[0, 0.16)*
Targeted dosing	*[0.16, 0.33)*
Overdosing	*[0.33, 1]*

The EWOC principle:

Dosing decisions are guided by the escalation with overdose control principal (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the probability of overdosing at that dose is CCI .

Recommendation from the BLRM, along with safety (AEs, SAEs), laboratory, PK, biomarker and other relevant data, will be used at the time of each dose escalation and for MTD/RP2D determination.

Prior distributions:

Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters, see Appendix 8 in the protocol.

Starting dose:

The starting dose is CCI *in Part 1 Dose Escalation. For this dose the prior risk of overdosing satisfies the EWOC criterion.*

Stopping Criteria:

The dose escalation will be stopped when the following criteria are met:

- *At least 6 participants have been treated at the recommended MTD/RP2D.*
- *The dose $d^{\sim}$ satisfies 1 of the following conditions:*
  - *The probability (π) of target toxicity at dose $d^{\sim}$ exceeds 50%, ie, Pr($0.16 \leq rr_{d^{\sim}} < 0.33$) $\geq$50%.*
  - *A minimum of 15 participants have been treated in the trial.*

In case all doses explored appear to be overly toxic and the MTD cannot be determined, the dose escalation will stop.

In case of change of the dosing regimen, DLT data accumulated during the dose escalation with the original regimen might be used to form a MAP prior for further BLRM analysis. MAP priors are derived from hierarchical models, which take into account possible differences between the studies. Details of priors and general description of MAP approach is presented in see Appendix 8 in the protocol *and a statistical technical supplement.*

To mitigate the risk of misclassifying DLTs, a sensitivity that uses weighted DLT/AE data (in equivocal cases) within the BLRM will be performed. If all investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method (see Appendix 8 in the protocol*).*

Decision Rules for Part 2:

The primary objective in dose expansion is to further characterize the safety and preliminary efficacy profile of PF-07209960. There are no formal decision rules and summary statistics will be provided for safety and efficacy endpoints.

5.2. General Methods

Every effort has been made to pre-specify all analyses in this SAP. The SAP will be amended if additional exploratory analyses are deemed necessary that were not initially specified.

The data are summarized by dose level cohort, defined by the initial dose of the study intervention administered to participants. DLT rates at the study dose levels will be presented via mean and medians and a Bayesian credible interval based on the posterior density from the full probability model. This information will also be used for DLRM to guide dose escalation.

For Part 1, unless otherwise specified, all other summaries will be presented by dose level cohort and overall. For Part 2 unless otherwise specified, all other summaries will be presented by expansion cohort. Additionally, summary tables will include the total sample size and number missing/not reported. Lastly, missing data may be imputed according to Section 5.3 and unless otherwise specified missing values that are not imputed will be excluded from the analysis.

5.2.1. Analyses for Binary Endpoints

Binary data will be summarized by number of unique participant incidence and proportion in the analysis set. A 2-sided 95% CI using Clopper-Pearson exact method will be provided if the sample size per cohort permits.

5.2.2. Analyses for Continuous Endpoints

Continuous data will be summarized with the mean, median, minimum, maximum, coefficient of variation, standard deviation, and 2-sided 95% CIs if the sample size permits.

5.2.3. Analyses for Categorical Endpoints

Categorical data will be summarized by number of unique participant incidence and proportion of participants in each category. A 2-sided 95% CI of the proportion if the sample size permits and deemed necessary.

5.2.4. Analyses for Time-to-Event Endpoints

The time-to-event data will be presented for individual participant, by dose level cohort in Part 1, expansion cohort in Part 2, and overall, when applicable. Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time and the number censored. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method, when possible based on the number of observed events. Confidence

intervals for medians and qmuiiles, based on the Brockmeyer-Crowley method, may be presented (Brockmeyer and Crowley, 1982). Confidence intervals for the estimated probability of an event at a particular time point may be generated using the Greenwood fo1mula.

Time to event endpoints include OS, PFS, DOR, and TTP.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard mies for imputation will be applied. See CDISC and PDS Safety Rulebooks for details.

5.3.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in O time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the phannacokinetic and ECG analyses, which will only use the actual date collected or if date not available deem the data missing.

5.3.2. Efficacy Analysis

No imputation will be perfo1med for tumor assessments that will be used for the binaiy efficacy endpoints. Eve1y effo1i will be made to retrieve data in the CRF, however missing data will be left as is. The reasons for missing tumor assessments will be collected.

For the time-to-event endpoints, the missing data handling method will be censoring. Censoring mies for time-to-event endpoints ai·e detailed in Appendix 1.

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5.3.6. QTc

For the co1Tected QT (QTc) analyses, no values will be imputed for missing data.

Further details are given in Section 6.9.4.

5.4. Statistical Considerations of COVID-19 Impacted Data

In March 2020, the World Health Organization (WHO) announced a global pandemic of the vims SARS-CoV-2 and the resulting disease COVID-19. During the conduct of this trial, if any paiiicipant's data is impacted by this pandemic, the following considerations will be given in the data analyses:

a) If a pa1iicipant dropped out of the study during the DLT evaluation window in Pait 1 due to COVID-19, a replacement paiiicipant may be added.

b) Death caused by COVID-19 is still considered as an "event" in the analysis of PFS and OS. If deemed necessaiy, a sensitivity analysis may be perfonned where COVID-19 driven death is censored at the death date.

c) If a scheduled tumor radiographic scan is delayed out of the Schedule of Activity allowable window, or is missing (i.e. pa1iicipant skipped a scheduled tumor radiographic scan) due to any reasons related to the pandemic, this delay or

missingness does not alter the censoring rules for PFS or TTP as described in Appendix 1. A censoring reason of "COVID-19" may be added to the PFS or TTP summary if the specific reason of tumor scan delay or missing can be attributed to COVID-19. If deemed necessary, a sensitivity analysis may be performed where participants would be censored at the date of their last scan prior to their COVID-19 diagnosis.

In the confirmed ORR analysis, as described in Section 6.2.3, if a response can't be confirmed by a subsequent tumor scan because of the pandemic (i.e., the subsequent tumor scan wasn't performed), then the initial response will be considered as unconfirmed. No sensitivity analysis will be performed.

d) Any COVID-19 related symptoms are to be captured as adverse events in the case report form. Those adverse events will be summarized in the same manner as other adverse events. If a label of COVID-19 can be identified in the investigator provided adverse event term, then a separate AE listing may be provided for just the COVID-19 related events.

e) If identifiable, the COVID-19 related data points, including missing data where the reason of missing is identified as COVID-19 related (site closure hence data could not captured; participants skipped a visit because of concern over the pandemic), protocol deviations driven by COVID-19, safety events caused by COVID-19 may be separately listed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints for Part 1

6.1.1. Dose-Limiting Toxicities (DLTs)

- Analysis set: Per protocol analysis set

- Analysis methodology:

  For the purpose of dose escalation, the DLT observation period/window will be the first cycle (defined as 28 days after the start of study treatment), for each participant. Whether an adverse event a participant experienced during the DLT window is determined as a DLT or not is based on the DLT definitions provided in Section 4.3.3 of the protocol.

  The DLT events will be summarized by dose level. A listing of the DLT events will also be provided in which the participant's primary diagnosis (malignancy), dose level the participant was enrolled to, DLT event start day and stop day relative to the C1D1 dose date, the DLT event term, NCI CTCAE grade, relatedness to the investigational product (PF-07209960), outcome of the event, along with other variables deemed important, will be included.

- Missing data: All enrolled participants in Part 1 should have an indicator variable derived to be either 1 (yes) or 0 (no) based on the DLT definitions (provided in

Section 4.3.3 of the protocol) and participant's safety data during the DLT observation window. If a participant fails to have a value on the indicator variable because the participant being non-DLT-evaluable, the participant may be replaced.

6.1.2. Adverse Events (AEs)

- Analysis set: Safety analysis set
- Analysis methodology:

  AEs will be characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria (Lee et al., 2019)) timing, seriousness, and relationship to study therapy. Further description is given in Section 6.9.1. The primary focus will be on TEAEs. TEAEs is defined as any AE that occurs during the on-treatment period, defined in Section 3.5. AEs that occur after the on-treatment period may still be recorded in the clinical database and will be included in the AE listings, but will not be included in the on-treatment emergent AE summaries.

  See Section 6.9.1 for details on the specific AE summaries to be provided.

- Missing data: If an AE start or stop date is missing, imputation will be performed according to Section 5.3.1. The imputed dates will be used to determine whether the AE is to be included in the TEAE summary. The missing AE start or stop dates will be listed as is in AE listings. When the CTCAE grade is missing for an AE, the AE will be excluded from the CTCAE grade summary table.

6.1.3. Laboratory abnormalities

- Analysis set: Safety analysis set
- Analysis methodology:

  Laboratory abnormalities will be presented as tables and characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal high/low, or not done. The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. Shift tables of baseline grade to worst post-baseline grade will be provided. Quantitative summaries for change from baseline and percent change from baseline for the laboratory tests may be provided, if deemed necessary. These summaries will be presented for the entire on-treatment period and for the various subgroups of the study (by dose level for Part 1 and by expansion cohort for Part 2).

Hematology, serology and coagulation lab results can be combined into one summary output. Separate summaries will be created for chemistiy tests. Urinalysis and pregnancy tests will not be summarized and will only be listed.

- Missing data: Missing lab values will not be imputed.

6.2. Secondary Endpoints for Part 1

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6.2.2. Immunogenicity

- Analysis set: Immunogenicity set
- Analysis methodology:

For the immunogenicity data, the percentage of participants with positive ADA and NAb each will be summarized. Listings and summary tabulations of the ADA and NAb data at baseline and post-randomization will be generated. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit. The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data.

6.2.3. Tumor Response

- Analysis set: Response evaluable set

- Analysis methodology:
    - For treatment response, 'start date' is defined as the first date that a participant received the study intervention.
    - Overall Response Rate (ORR)
        - ORR as assessed using RECIST version 1.1. ORR is defined as the proportion of participants who achieved CR or PR per RECIST version 1.1 (details are provided in the protocol, Section 8.1.1 and Appendix). Both confirmed ORR and uORR will be determined based on the confirmed and unconfirmed CR and PR, definitions provided below.
- Disease Control Rate (DCR)
    - A participant with a BOR of CR, PR, non-CR/non-PD or SD is defined as having DC. The DC rate is defined as the percentage of participants with DC in the specified analysis set.
- Best Overall Response (BOR)
    - **Complete Response (CR)**: Two objective assessments of CR a minimum of 4 weeks apart documented before PD.
    - **Partial Response (PR)**: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of 4 weeks apart documented before PD, but not qualifying as CR. Sequences of PR- Stable- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.
    - **Stable Disease (SD)** (applicable only to participants with measurable disease at baseline): At least one objective status of stable disease or better documented at least 6 weeks after 'start date' and before PD but not qualifying as CR or PR.
    - **Non-CR/non-PD** (applicable only to participants with non-measurable disease at baseline): at least one non-CR/non-PD assessment (or better) documented at least 6 weeks after 'start date' and before first documentation of PD (and not qualifying for CR or PR).
    - **Progressive Disease (PD):** Progression documented within 16 weeks after 'start date' and not qualifying as CR, PR or SD.
    - **Not Evaluable (NE):** All other cases. Note that reasons for NE should be summarized and the following reasons could be used:
        - No adequate baseline assessment (defined below).

- No evidence of disease at baseline.
- No post-baseline assessments due to early death, i.e., death prior to 8 weeks after 'start date'.
- No post-baseline assessments due to other reasons (adequate post-baseline assessments defined below).
- All post-baseline assessments have overall response NE.
- New anti-cancer therapy started before first post-baseline assessment.
- SD of insufficient duration (<6 weeks after 'start date' without further evaluable tumor assessments).
- PD too late (>16 weeks after 'start date').
- Special and rare cases where BOR is NE due to both SD of insufficient duration ('too early') and late PD will be classified as 'SD of insufficient duration.

- uCR is defined as one objective status of CR documented before PD.
- uPR is defined as one objective status of PR documented before PD but not qualifying as uCR.

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

- Tumor response will be presented in the form of participants data listings that include, but are not limited to: tumor type, initial actual dose received, tumor response at each assessment, and best overall response. Progression date, death date, date of first response, last assessment date, and date of last contact will also be listed. Additionally, a graphical representation (swimmer plot) will be provided to display tumor response overtime and a waterfall plot displaying the best percentage change in tumor size will be provided.

- Definition of adequate assessments

  - Baseline: The following conditions must be met for a baseline assessment to be adequate,

- Assessment of all lesions (target, and non-target) must be within 28 days prior to and including the 'start date'.
- All lesions (target and non-target) must have non-missing assessments.
- Baseline lesions must be assessed with an acceptable method of tumor assessment as specified in the protocol and could include contrast and non-contrast MRI, contrast and non-contrast CT, and X-ray.

- Post-baseline: An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined.

- Missing data: Missing data will not be imputed.

6.2.4. Time-to-event and duration endpoints

- Analysis set: Response evaluable set
- For treatment response, unless noted otherwise 'start date' is defined as the first date that a participant received the study intervention.
- Duration of Response (DOR)
  - Duration of response is defined as the time from start date (which is the date of first documentation of PR or CR) to date of first documentation of objective progression, death due to any cause, or time of censoring. Both confirmed DOR and uDOR will be determined separately for the subset of participants with a confirmed and unconfirmed objective response of CR or PR (defined above in Section 6.2.3). The outcome, event dates and reasons for censoring for DOR will match those used for the analysis of PFS. However, participants will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only participants with an objective response are included in this analysis of DOR. Censoring and event rules are further outlined in Table 3.
- Progression Free Survival (PFS)
  - PFS is the time from 'start date' to date of first documentation of PD, death due to any cause, or censoring, whichever occurs first. Exceptions to using a PD or death date are outlined in Table 3.
- Time to Progression (TTP)
  - TTP is the time from 'start date' to the date of the first documentation of PD or censoring. TTP is similar to PFS except that death is not treated as an event and is censored. TTP censoring rules are outlined in Table 4.

- Missing data: Missing data will be handled by censoring rnle. Time points where the response is NE, or no assessment was perfonned will not be used for detennining the censoring date.

6.3. Exploratory Endpoints for Part 1

CCI

[redacted]

6.4. Primary Endpoints for Part 2

6.4.1. Adverse Events (AEs)

AEs in Pait 2 will be sUillllllai·ized in the same fashion as Pait 1, which is described in Section 6.1.2.

6.4.2. Laboratory abnormalities

Laborato1y abno1malities in Pait 2 will be sUillllllai·ized in the same fashion as Pait 1, which is described in Section 6.1.3.

6.4.3. Overall Response Rate (ORR)

ORR will be detennined and smnmai·ized in Pait 2 in the same fashion as Pait 1, which is detailed in Section 6.2.3.

6.5. Secondary Endpoints for Part 2

6.5.1. Pharmacokinetic Analysis

Phaimacokinetic analysis for Pait 2 will follow what was done for Pait 1, which is detailed in Section 6.2.1.

6.5.2. Immunogenicity

Immunogenicity will be detennined and smnmarized in Pait 2 in the same fashion as Pait 1, which is detailed in Section 6.2.2.

CCI

[redacted]

I CCI [redacted]

I [redacted]

[redacted]

6.5.4. Tumor Response

DCR, DOR, PFS, and TTP will be detennined and summarized in Pa.ii 2 in the same fashion as Pa.ii 1, which is detailed in Section 6.2.3.

6.5.5. Overall Survival

OS will be detennined and sUilllnai·ized in Pait 2 in the saine fashion as Pa.ii 1, which is detailed in Section 6.2.3.

6.6. Exploratory Endpoints for Part 2

CCI [redacted]

6.7. Subset Analyses

There are no planned subset analyses.

6.8. Baseline and Other Summaries and Analyses

6.8.1. Baseline Summaries

Baseline chai·acteristics such as demographics, prior medication, and primaiy diagnosis will be tabulated and listed. The Safety Analysis Set will be used.

6.8.2. Analysis Sets

Paiiicipant inclusion into the analysis sets in Table 2 will be tabulated. A listing will be also be provided for the analysis sets.

6.8.3. Anti-Cancer Therapies

Prior anti-cancer therapies (diug therapy, radiation, and surge1y) will be tabulated. Similai·ly, follow-up anti-cancer therapies (diug therapy, radiation, and surge1y) will also be tabulated.

6.8.4. Study Conduct and Participant Disposition

Participant discontinuation from treatment and study will be tabulated and listed for each participant separately with their reason for discontinuation. The Safety Analysis Set will be used. Similarly, potentially important protocol deviations will be tabulated and listed for each participant. Participant disposition at baseline, end of treatment, and at long-term follow-up will be tabulated. Participant disposition will be listed for all phases of the trial.

6.8.5. Study Treatment Exposure

The Safety Analysis Set will be used.

The following will be summarized by treatment dose level and overall, for Part 1 and by expansion cohort for Part 2:

- Number of participants;
- Duration of Treatment (DOT): DOT is defined as the last active dose date minus the first active dose date + 1. DOT will be summarized, as a continuous variable and summary statistics including the mean, median, standard deviation and range will be provided. In addition, a DOT will be summarized as a categorical variable in 3 month intervals, e.g., the frequency of participants with a DOT of 3 months, 6 months, 9 months, etc.;
- Dose modifications are described in the protocol. Dose modifications to study intervention due to AEs include the following (ideally presented in one table):
    - Number (%) of dose interruptions (include both known and unknown dates). Dose interruptions is defined as a planned dosing day with 0 mg total dose administered;
    - Number (%) of dose interruptions related to AEs, defined as “Was the Actual Dose adjusted from planned?” = “ADVERSE EVENT(S)” and “Latest Action Taken with Study Treatment:” = “DRUG INTERRUPTED”;
    - Number (%) of participants with dose reductions. A dose reduction is defined as a day when the actual dose is less than the planned dose at enrollment and the actual dose is greater than 0 mg (i.e., missed doses are not counted as a reduction);
    - Number (%) of dose reductions related to AEs, defined as “Was the Actual Dose adjusted from planned?” = “ADVERSE EVENT(S)” and “Latest Action Taken with Study Treatment:” = “DOSE REDUCED”;
    - Number (%) of participants with a dose increase. A dose increase is defined as a day when the actual dose is greater than the planned dose;

- Number (%) of participants with dose reductions or interruptions for each reason (AE vs insufficient clinical response vs Other);

The following will be summarized for cumulative dose by dose level in Part 1 and expansion cohort in Part 2:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and cumulative percent of administered dose (compared to planned dose);
- Actual dose intensity (mg/day): Defined as cumulative actual dose received (mg) divided by the number of doses scheduled per protocol during treatment period;
- Ratio of actual dose intensity to planned dose intensity. Where planned dose intensity is defined as a participant's planned starting dose.

Listings by participant (ordered by dose level): start date and stop date of dosing period within each cycle (including records with 0 mg), total daily dose received for each dosing period, any missed doses with unknown dates (yes/no), number of missed doses with unknown dates, reason for any dosing changes, and cycle number relative to the dosing period.

Listings by participant and cycle (ordered by dose level): cycle length, total planned dose, total actual dose received, percentage of planned dose, dose reduction (yes/no), and dose interruption (yes/no).

6.8.6. Concomitant Medications and Nondrug Treatments

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the WHO medical dictionary. Listings of prior, concomitant, and further therapies will be provided separately.

6.9. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, heart rate, and safety laboratory data will be reviewed on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination, 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 conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Demographic data collected at screening will be reported.

6.9.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA, except CRS, which will be graded by ASTCT criteria (Lee et al, 2019). AE data will be reported in tables and listings. Summaries of TEAEs by primary system organ class and preferred terms, toxicity grade, and seriousness and relationship to study treatment will be presented. In addition, summaries of adverse events leading to death, dose modification, dose interruption, and premature withdrawal from study treatment will be tabulated. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs for the entire on-treatment period, by cycle for Part 1 (Cycle 1 and Cycles beyond 1), and for the various parts of the study (by dose level for Part 1 and by expansion cohort for Part 2). In the summary table for Part 1, a "Total" column, summarizing data across all dose levels, will be presented. Listings of AEs leading to dose modification, dose interruption, permanent discontinuation of the study treatment, and death will be provided. Listings of DLTs, deaths, and SAEs will also be provided. Death and SAE information will be based on the data captured from the CRF.

6.9.2. Physical Examination

Participants will have a physical examination to include weight, assessment of ECOG performance status and height; height will be measured at baseline only.

As noted above, physical examination data collected during the course of the study will be considered source data and will not be required to be reported. However, any untoward findings identified on physical examination conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

6.9.3. Vital Signs

Vital signs will consist of systolic and diastolic blood pressure, and pulse rate measurements. Criteria for clinically relevant abnormal findings are provided in Section 9.2. Measurements that meet these criteria will be listed.

6.9.4. Electrocardiograms

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

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

Safety QTc Assessment

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

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as a Cycle 1 Day 1 pre-dose.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. 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 HR (QTcF) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point.

Categorical data analysis for QRS, pulse rate, and vital signs will follow Section 9.2. Measurements that fulfil these criteria are to be listed.

6.9.5. Clinical Safety Laboratory Assessments

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the various laboratory tests listed in Appendix 2 of the protocol will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

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

7. INTERIM ANALYSES

No fonnal interim anal_sis will be conducted for this stud y. CCI [redacted], facilitating PK modeling, and/or supporting clinical development.

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9. APPENDICES

9.1. Appendix 1

Time to Event Data Analysis Censoring Rules

Table 3. PFS Outcome and Event Dates

Situation	Date of Event/Censoring	Outcome
No adequate baseline assessment	Date of First Dose [a]	Censored [a]
PD or death - ≤ 16 weeks after date of first dose, or - after at most one missing or inadequate post-baseline tumor assessment	Date of PD or death	Event
PD or death - after 2 or more missing or inadequate tumor assessments	Date of last adequate tumor assessment [b] documenting no PD prior to new anti-cancer therapy or missed tumor assessments	Censored
No PD		
New anti-cancer therapy given prior to PD or death		
[a] If the participant dies ≤16 weeks after the date of their first dose and did not initiate new anti-cancer therapy, the death is an event with date on death date. [b] If there are no adequate post-baseline tumor assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of first dose; if the criteria were met the censoring will be on the date of first dose.		

Table 4. TTP Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment	Date of First Dose	Censored
PD - ≤ 16 weeks after date of first dose, or - after at most one missing or inadequate post-baseline tumor assessment	Date of PD	Event
PD - after 2 or more missing or inadequate tumor assessments [a]	Date of last adequate tumor assessment [a] documenting no PD prior to new anti-cancer therapy or missed tumor assessments.	Censored
No PD		
New anti-cancer therapy given prior to PD		
Death due to any cause		
[a] If there are no adequate post-baseline assessments prior to the PD, then the time without adequate assessment should be measured from the date of first dose; if the criteria were met the censoring will be on the date of first dose.		

Table 5. OS Outcome and Event Dates

Situation	Date of Death/Censoring	Outcome
Alive	Date of Last Contact	Censored
Death due to any cause	Date of Death	Event

9.2. Appendix 2

Categorical Classes for ECG and Vital Signs

Clinically Relevant Categories for Pulse Rate and QRS

Pulse Rate (msec)	max. ≥300	
Pulse Rate (msec) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (msec)	max. ≥200	
QRS (msec) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Clinically Relevant Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	≥160 max.
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	≥100 max.
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

9.3. Appendix 3

Abbreviations

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

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
ASTCT	American society for transplantation and cellular therapy
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time versus time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of last measurable concentration
$AUC_{tau,ss}$	area under the steady state dose concentration-time curve over dosing interval tau
BLQ	below the limit of quantification
BLRM	Bayesian logistic regression model
BOR	best overall response
BP	blood pressure
bpm	beats per minute
CCI	[redacted]
C1D1	cycle 1 day 1
C1D15	cycle 1 day 15
C2D15	cycle 2 day 15
CD8+	cluster of differentiation 8 positive
CDISC	clinical data interchange standards consortium
CI	confidence interval
CL	total clearance of drug from eg, plasma
C_{max}	maximum observed concentration
COVID	corona virus disease
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography/clinical trial
CTCAE	common terminology criteria for adverse events
DC	disease control
DCR	disease control rate
DLRM	dose level review meeting
DLT	dose-limiting toxicity
DOR	duration of response
DOT	duration of treatment
ECG	electrocardiogram

Abbreviation	Term
EWOC	escalation with overdose control
FIH	first in human
HR	heart rate
IF	immunofluorescence
IHC	immunohistochemistry
IL	interleukin
ISR	injection site reaction
ITT	intention to treat
IV	intravenous
CCI	[redacted]
MAP	meta-analytic-predictive
MedDRA	medical dictionary for regulatory activities
mg	milligrams
mITT	modified-intent-to-treat
mm	millimeters
MoA	mechanism of action
MRI	magnetic resonance imaging
msec	millisecond
MSS	microsatellite-stable
MTD	maximum tolerated dose
NAb	neutralizing antibodies
CCI	[redacted]
NCI	national Cancer Institute
CCI	[redacted]
NE	not evaluable
NK	natural killer
CCI	[redacted]
NSCLC	non-small cell lung cancer
OR	overall response
ORR	objective response rate
OS	overall survival
OvCa	ovarian cancer
PD	pharmacodynamics(s)/progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDS	Pfizer data standard
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q2W	once every two weeks
QTc	corrected QT
QTcB	QTc corrected QT (Bazett method) using Bazett's formula
QTcF	QTc corrected QT (Fridericia method) using Fridericia's formula
R_{ac}	accumulation ratio based on AUC (observed)

Abbreviation	Term
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCCHN	squamous cell head and neck carcinoma
SD	stable disease
$t_{½}$	terminal phase half-life
TEAE	treatment emergent adverse events
TIL	tumor infiltrating lymphocytes
T_{max}	time to reach C_{max}
TTP	time to progression
UC	urothelial carcinoma
uCR	unconfirmed complete response
uDOR	unconfirmed duration of response
uPR	unconfirmed partial response
uORR	unconfirmed objective response rate
WHO	world health organization

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