A PHASE 1 DOSE ESCALATION AND EXPANSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMIC, AND ANTI-TUMOR ACTIVITY OF PF-07260437 IN ADVANCED OR METASTATIC SOLID TUMORS

Study Intervention Number:	PF-07260437
Study Intervention Name:	N/A
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EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	C4431001
Phase:	1

Brief Title: A Phase 1 Dose Escalation and Expansion Study of PF-07260437 in Advanced or Metastatic Solid Tumors

Document History

Document	Version Date
Amendment 1	09 August 2021
Original protocol	22 June 2021

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs and any protocol administrative clarification letter.

Amendment 1 (09-Aug-2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to incorporate feedback received from the FDA. In addition, clarification, administrative and typographical modifications were made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis; Section 1.2. Schema; Section 2.3. Benefit/Risk Assessment; Section 4.1.1. Dose Escalation (Part 1)	In Part 1, the first cohort of patients at dose level 1 will be staggered by 48 hours between each patient.	To mitigate overall risk to patients enrolled in Part 1.
Section 1.3.1. Part 1 – Schedule of Assessment - Without Priming; Section 1.3.2. Part 1 – Schedule of Assessments – With Priming; Section 1.3.3. Part 2- Schedule of Assessments – With or Without Priming; Section 2.3.1. Risk Assessment; Section 4.1. Overall Design; Section 6.1. Study Intervention(s) Administered;	Participants experiencing ≥ Grade 3 infusion-related AEs (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 subsequent doses (two cycles).	To further ensure patient safety and to reduce any potential risk from CRS.
Section 1.1. Synopsis; Section 5.1 Inclusion Criteria	Eligibility for ER/PR and HER2 status were updated.	To clarify according to respective ASCO/CAP guidelines.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1. Study Schedule of Assessments – Part 1 Without Priming; Section 1.3.2. Study Schedule of Assessments – Part 1 With Priming; Section 2.3.2. Risk Assessment; Section 4.1. Overall Design Section 6.1.1.1. Premedication; Section 6.8.4. Antidiarrheal, Antiemetic Therapy;	Mandatory prophylactic premedication during the first cycle of treatment was removed.	To avoid obscuring the identification of study-drug related toxicity during the first cycle.
Section 1.3.1. Study Schedule of Assessments – Part 1 Without Priming; Section 1.3.2. Study Schedule of Assessments – Part 1 With Priming Section 4.1. Overall Design	Additional monitoring of all participants for approximately 90 days after treatment discontinuation was included.	To monitor possible late immune-related toxicities.
Section 4.3.6.2. Non-Hematologic DLTs	Additional immune-mediated DLTs were included.	To mitigate safety risks to patients.
Section 4.4 End of Study Definition	Stopping rules were incorporated into the protocol.	To mitigate safety risk to additional patients.
Section 1.3.1. Part 1 – Schedule of Assessment – Without Priming; Section 1.3.2. Part 1 – Schedule of Assessment – With Priming	Additional ECG timepoints added.	To correlate with PK timepoints.
Section 6.8. Concomitant Therapy; Appendix 15. Cautionary Use of Concomitant Medications with Narrow Therapeutic Index Due to Drug-Drug Interaction (DDI) Potential.	Added reference to Appendix 15 – a concomitant medication list that has potential DDIs and should be used with caution for concomitant treatment with PF-07260437.	To mitigate risk against potential drug-drug interactions.
Section 4.1. Overall Design; Table 7. Inpatient Observation Stays for SC Administration	Outpatient was added to the 1 hour observation period.	To clarify visit as an outpatient visit.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 1, dose escalation and expansion study to evaluate the safety, tolerability, PK, PD, and antitumor activity of PF-07260437, a B7-H4 x CD3 bispecific mAb, in participants aged ≥18 years of age with advanced or metastatic BrCa, OvCa or endometrial cancer. Adult participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from sponsor.

Brief Title

A Phase 1 Dose Escalation and Expansion Study of PF-07260437 in Advanced or Metastatic Solid Tumors.

Rationale

PF-07260437 is a T cell redirecting B7-H4 x CD3 bispecific mAb with 2 binding domains: a domain that recognizes tumor antigen B7-H4 with high affinity and a domain that recognizes CCI, expressed on T cells, with moderate affinity. Co-engagement of B7-H4 on tumor cells and CCI on T cells leads to a tumor-localized T-cell cytotoxic response and reduces systemic CCI targeting and toxicity. This mechanism circumvents the need for T cells to recognize specific antigenic peptides in the context of CCI on malignant cells. Cytotoxicity is mediated by release and transfer of CCI from the T cell to the B7-H4 expressing target cell. PF-07260437 addresses a significant unmet medical need for BrCa, as its target is expressed in the majority of BrCas across all molecular subtypes.

In Part 1 of this clinical study, PF-07260437 will be evaluated for the treatment of adult participants with advanced or metastatic BrCa, OvCa or endometrial cancer for whom no standard therapy is available with no biomarker selection. The major objectives are to evaluate safety, tolerability, PK and PD and to identify RDE.

In Part 2 dose expansion phase of the study, PF-07260437 will be further evaluated in participants with advanced or metastatic HR+ HER2- BrCa (Part 2A) and TNBC (Part 2C) with high B7-H4 expression to assess early signs of clinical efficacy. In addition, a cohort of 20 participants with advanced or metastatic HR+ HER2- BrCa and TNBC not preselected for B7-H4 expression will be included in Part 2B to further explore biomarker changes in tumor microenvironment and validate the MoA.

De novo paired pre- and on-treatment biopsies are mandatory for 5 participants in Part 2A and Part 2C each, and for 5 HR+ HER2- BrCa and 5 TNBC participants each in Part 2B. If significant TIL infiltrates are observed during PF-07260437 treatment consistent with the preclinical MoA, this could justify further clinical development in combination with endocrine therapy and/or CDK4/6 inhibitors in advanced or metastatic HR+ HER2- BrCa as well as in combination with immune checkpoint inhibitors in TNBC.

Objectives, Endpoints, and Estimands

Dose Escalation (Part 1):

Objectives	Endpoints	Estimands
Primary		
• To assess safety and tolerability at increasing dose levels of PF-07260437 in successive cohorts of participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer. • To estimate the MTD and to select RDE.	• Occurrence of DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5 or CRS grading system) timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (graded by NCI CTCAE v5), and timing.	• DLT rate estimated based on data from DLT-evaluable participants during the DLT evaluation period. • Incidence of AEs estimated in the safety analysis population during the AE evaluation period.
Secondary		
• To assess immune related safety and tolerability at increasing dose levels of PF-07260437 in successive cohorts of participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer.	• irAEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5) timing, seriousness, and relationship to study therapy.	• N/A
• To evaluate the single and multiple dose PK of PF-07260437 as monotherapy.	• Pharmacokinetic parameters of PF-07260437 as monotherapy: SD C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F, and V_z/F. MD (assuming steady state is achieved) $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, $AUC_{ss,\tau}$, and as data permit, CL_{ss}/F, V_z/F, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).	• N/A
• To evaluate immunogenicity of PF-07260437.	• Incidence and titers of ADA and NAb against PF-07260437.	• N/A
• Tertiary/Exploratory		
• To evaluate preliminary antitumor activity of PF-07260437 in participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer.	• ORR, as assessed by investigator based on RECIST v1.1 and irRECIST. • DOR as assessed by investigator based on RECIST v1.1 and irRECIST.	• N/A

Objectives	Endpoints	Estimands
• To explore cytokine and chemokine PD markers in pre and on treatment serum samples.	• Changes in pre- and on-treatment cytokine and chemokine markers in serum samples.	• N/A
• To evaluate T, B, and NK subtypes for immunophenotyping in addition to T cell proliferation and activation markers in whole blood.	• Changes in subtypes of immune cell, activation, and proliferation markers on T cells.	• N/A
• To explore additional biomarkers in tumor biopsies, whole blood, and serum samples to predict response to therapy and to understand resistance mechanisms that may predict escape from therapy.	• Biomarkers from genomic, transcriptomic, and/or protein profiling from tumor, blood, serum or plasma and their relationship to clinical outcome.	• N/A
• To evaluate the effect of PF-07260437 on soluble B7-H4.	• Pre- and post-dose levels of soluble B7-H4 in serum.	• N/A

Dose Expansion (Part 2):

Objectives	Endpoints	Estimands
Primary		
• To assess safety and tolerability of PF-07260437 at the RDE in participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or without biomarker selection.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5 or CRS grading system) timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (graded by NCI CTCAE v5), and timing.	• Incidence of AEs estimated in the safety analysis population during the AE-evaluation period.
Secondary		
• To assess irAEs of PF-07260437 at the RDE in participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or without biomarker selection.	• irAEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5) timing, seriousness, and relationship to study therapy.	• N/A
• To evaluate preliminary antitumor activity of PF-07260437 at the RDE in participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or no biomarker selection.	• ORR, as assessed by investigator based on RECIST v1.1 and irRECIST. • DOR as assessed by investigator based on RECIST v1.1 and irRECIST.	• N/A

Objectives	Endpoints	Estimands
	• PFS as assessed by investigator based on RECIST v1.1 and irRECIST. • TTP as assessed by investigator based on RECIST v1.1 and irRECIST. • OS.	
• To further evaluate the serum PK of PF-07260437 at RDE.	• PK concentration of PF-07260437 at selected timepoints.	• N/A
• To further evaluate immunogenicity of PF-07260437.	• Incidence and titers of ADA and NAb against PF-07260437.	• N/A
• To evaluate immune cells in pre and/or post treatment tumor biopsies.	• Phenotypes, and quantity of TIL before and after PF-07260437 treatment (eg, CD3, CD8, Granzyme B, Ki67 IHC).	• N/A
Tertiary/Exploratory		
• To explore cytokine and chemokine PD markers in pre- and on-treatment serum samples.	• Changes in pre- and on-treatment cytokine and chemokine markers in serum sample.	• N/A
• To evaluate T, B, and NK subtypes for immunophenotyping in addition to T cell proliferation and activation markers in whole blood.	• Changes in subtypes of immune cell, activation, and proliferation markers on T cells.	• N/A
• To explore additional biomarkers in tumor biopsies, whole blood, and serum samples to predict response to therapy and to understand resistance mechanisms that may predict escape from therapy.	• Biomarkers from genomic, transcriptomic, and/or protein profiling from tumor, blood, serum or plasma and their relationship to clinical outcome.	• N/A
• To evaluate the effect of PF-07260437 on soluble B7-H4.	• Pre- and post-dose levels of soluble B7-H4 in serum.	• N/A

Overall Design

This is an open label, multi-center, first-in-human Phase 1 dose escalation and dose expansion study to evaluate the safety, tolerability, PK, PD, and preliminary antitumor activity of PF-07260437, a B7-H4 x CD3 bispecific mAb in advanced or metastatic selected solid tumors (BrCa, OvCa and endometrial cancer). This study contains 2 parts, dose escalation (Part 1) and dose expansion (Part 2).

Part 1 contains dose escalation in participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer that is resistant or intolerant to standard therapy or for whom no standard therapy is available, to determine the MTD and select the RDE. Participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from sponsor.

Once the PF-07260437 monotherapy RDE is selected, either with or without priming, Part 2 dose expansion cohorts may be initiated to further evaluate the safety and preliminary antitumor activity of PF-07260437 monotherapy in advanced or metastatic 2L+ HR+ HER2- BrCa with high B7-H4 expression (Part 2A) and 2L+ TNBC with high B7-H4 expression (Part 2C) as well as unselected HR+ HER2- BrCa or TNBC (Part 2B).

Number of Participants

Total number of participants for Part 1 and Part 2 combined, is estimated to be approximately 100.

Approximately 35 participants are expected to be enrolled into 1 of 5-7 sequential dose levels in Part 1 including at least 6 participants treated at the MTD. The actual number of participants enrolled will depend on the tolerability of PF-07260437 and the number of dose levels that are required to determine MTD/RDE.

Approximately 60 participants are expected to be enrolled into 3 cohorts in Part 2: Part 2A, Part 2B and Part 2C, with approximately n=20 participants in each cohort. Twenty participants for each cohort is clinically sufficient to evaluate safety signals.

Study Population and Specific Inclusion/Exclusion Criteria

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Participants ≥ 18 years of age.
2. Primary disease:
    - **Part 1:** Histological or cytological diagnosis of locally advanced or metastatic BrCa, endometrial cancer and OvCa that is resistant to standard therapy or for which no standard therapy is available. Participants with other advanced or metastatic solid tumors with high B7-H4 expression may be considered after discussion with and approval by sponsor. Similarly, those participants with other advanced or metastatic solid tumors should be resistant to standard therapy or have no available standard therapy.
    - **Part 2A:** 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic HR+ HER2- BrCa showing high B7-H4 expression who have progressed after at least 1 line of SOC CDK4/6 inhibitor and 1 line of SOC endocrine treatment. De novo paired pre- and on-treatment biopsies are mandatory for 5 participants.

- **Part 2B:** 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic HR+ HER2- BrCa who have progressed after at least 1 line of SOC CDK4/6 inhibitor and 1 line of SOC endocrine treatment, or 2L+ TNBC who have progressed after at least 1 line of SOC systemic therapy (eg, chemotherapy in combination with a checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies are mandatory for 5 HR+ HER2- BrCa participants and 5 TNBC participants. No biomarker selection based on B7-H4 expression is needed for Part 2B.
- **Part 2C:** 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic TNBC showing high B7-H4 expression who have progressed after at least 1 line of SOC chemotherapy and 1 line of SOC systemic therapy (eg, chemotherapy in combination with a checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies are mandatory for 5 participants.

3. Participants must be able to provide archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a fresh biopsy during screening. Ten (10) participants enrolling in Part 2B, and 5 participants enrolling in each of Parts 2A and 2C must agree to paired pre- and on-treatment biopsies. Ability of a participant to undergo biopsy safely should be determined during screening. Exceptions that biopsies cannot be obtained due to safety risk should be discussed and approved by the sponsor.
4. Participants with HR+HER2- advanced or metastatic BrCa must have:
   a. Documentation of ER or PR-positive tumor (≥1% positive stained cells) based on most recent tumor tissue utilizing an assay consistent with local standards and ASCO/CAP guidelines (Allison et al, 2020).
   b. Documentation that tumor is HER2-negative as determined with IHC of score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4, consistent with ASCO/CAP guidelines (Wolff et al, 2018).
5. Participants with TNBC must have documentation that tumor tissue is negative (<1% cells with nuclear positivity) for ER and PR as well as negative for HER2 as determined by IHC score 0/1+ or negative by ISH (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4, consistent with ASCO/CAP guidelines (Wolff et al, 2018; Allison et al, 2020).
6. TSH WNL for institution; supplementation is acceptable to achieve a TSH WNL; in patients with abnormal TSH if Free T4 is normal and participant is clinically euthyroid, participant is eligible.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Participants with any other active malignancy within 3 years prior to enrollment. Participants with secondary malignancy that has been adequately treated, or indolent tumors that would not interfere with safety and efficacy assessments might be allowed after discussion with and approval from the sponsor.

2. Participants with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including participants with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement). Note: Participants with indwelling catheter for drainage, or requirement for drainage no more frequently than monthly will be allowed.

3. History of Grade ≥3 immune mediated AE (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co stimulatory agents, etc.) and required immunosuppressive therapy within 1 year of treatment. Participants with Grade 2 hypothyroidism or hypopituitarism resulting from immunotherapy on stable hormone replacement therapy and participants with chronic adrenal insufficiency receiving doses <10 mg/day of prednisone equivalents are eligible.

Intervention Groups and Duration

Part 1

Participants will receive escalating doses of PF-07260437 administered as SC injection with a starting dose level of 100 µg Q2W as monotherapy. Additional dosing frequency such as Q1W or Q3W may be considered if supported by emerging clinical PK, PD, and safety data. BLRM guided by EWOC principle will be used to guide the dose escalation process and determine the MTD/RDE. The maximum allowable PF-07260437 dose increment is 200% (dose tripling from the previous dose level) for cohorts but will be adjusted to no more than 100% (dose doubling from the previous dose level) following the observation of a DLT or if there are two Grade ≥2 clinically significant treatment-related AEs. For monotherapy without priming strategy, DLT will be assessed during the first 28 days. For monotherapy with priming, the DLT assessment period will extend to include priming doses plus 2 full doses (eg, first 42 days). Each dose level group will include approximately 3 participants, with at least 1 DLT evaluable participant per cohort in the first 2 cohorts and at least 2 DLT evaluable participants per dose level group in the remaining cohorts for Part 1. A staggered enrollment strategy will be applied for participants entering Part 1 at dose level 1. Each participant dosed will be observed for 48 hours. If no safety concerns arise during this 48 hour period, then an additional participant may be enrolled at dose level 1. Per BLRM design, expanding additional participants at lower dose levels are allowed to assess safety. Dose escalation cohorts may be switched from SC administration to IV administration if SC administration is not considered as the preferred route due to severe skin toxicities, low PK

exposure or other reasons. IV administration cohorts may initiate at a dose level that is no greater than 20% of the highest SC dose level that is deemed tolerable (eg, starting at 60 µg IV Q2W if 300 µg SC Q2W is deemed tolerable) depending on emerging PK and safety data.

A priming dose approach in the next dose level may be initiated if a dose level induces ≥ Grade 2 CRS (lasting for >24 hours) occurs in >1 participant despite treatment with tocilizumab and/or vasopressors. If the dose escalation has reached the MTD and a priming dose has not been previously incorporated to the dose regimen, a priming dose escalation cohort to minimize C_{max} may be initiated based on clinical safety, PK/PD, and clinical efficacy.

The DLT period for SC or IV dosing without priming will be 28 days. The DLT period with priming will extend to include the duration of the priming doses and 2 full doses after priming (eg, if a priming dose is given on Day 1 and the first full dose on Day 15, the total DLT observation period will be 42 days). A traditional 2-parameter BLRM will be used to model the DLT relationship to the drug and inform dose escalation with or without priming. The maximum dose level increase will be 200% (dose tripling from the previous dose level).

Part 2

The Part 2 dose expansion phase will enroll participants into 3 cohorts detailed as follows:

- **Part 2A (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1 line of standard of care endocrine treatment. De novo paired pre- and on-treatment biopsies are mandatory for 5 participants.
- **Part 2B (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1 line of standard of care endocrine treatment, or 2L+ TNBC who have progressed after at least 1 line of SOC systemic therapy (eg 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1+ or chemotherapy alone if PD-L1 negative/low). Approximately 10 HR+ HER2- BrCa and approximately 10 TNBC participants should be enrolled. De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 HR+ HER2- BrCa participants and 5 TNBC participants. No biomarker selection based on B7-H4 expression.
- **Part 2C (N=20):** PF-07260437 as monotherapy in participants with TNBC showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of SOC systemic therapy (eg, 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies will be mandatory for 5 participants.

Depending on the results of preclinical combination in vivo efficacy data, emerging clinical monotherapy safety and efficacy, PF-07260437 combination cohorts may be added,

including combination with CDK4/6 inhibitor and/or endocrine therapies in HR+ HER2- BrCa and combination with checkpoint inhibitors in TNBC.

All participants will undergo up to 28 days of screening prior to first dose. Eligible participants will then receive study intervention for up to 2 years, or until disease progression defined by irRECIST, unacceptable toxicities, a decision by the participant (withdrawal of consent or no longer willing to participate) or investigator to discontinue treatment, or study termination. Note: If a participant is classified as having PD during an on-treatment tumor assessment, then confirmation of PD by a second scan in the absence of rapid clinical deterioration is required per irRECIST.

Data Monitoring Committee or Other Independent Oversight Committee: No

This study will not use a DMC or independent oversight committees in this study.

Statistical Methods

There is no formal hypothesis testing in this study.

Unless otherwise specified, summaries will be presented by dose group and overall. Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% CIs using an exact method. Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CIs for each time-to-event endpoint will be provided.

The dose escalation in Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07260437. Dose toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07260437 will be evaluated separately for cohorts with and without priming, taking into account the different DLT observation periods (28 days for the regimen without priming; priming doses plus 2 full doses for the regimen with priming). The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

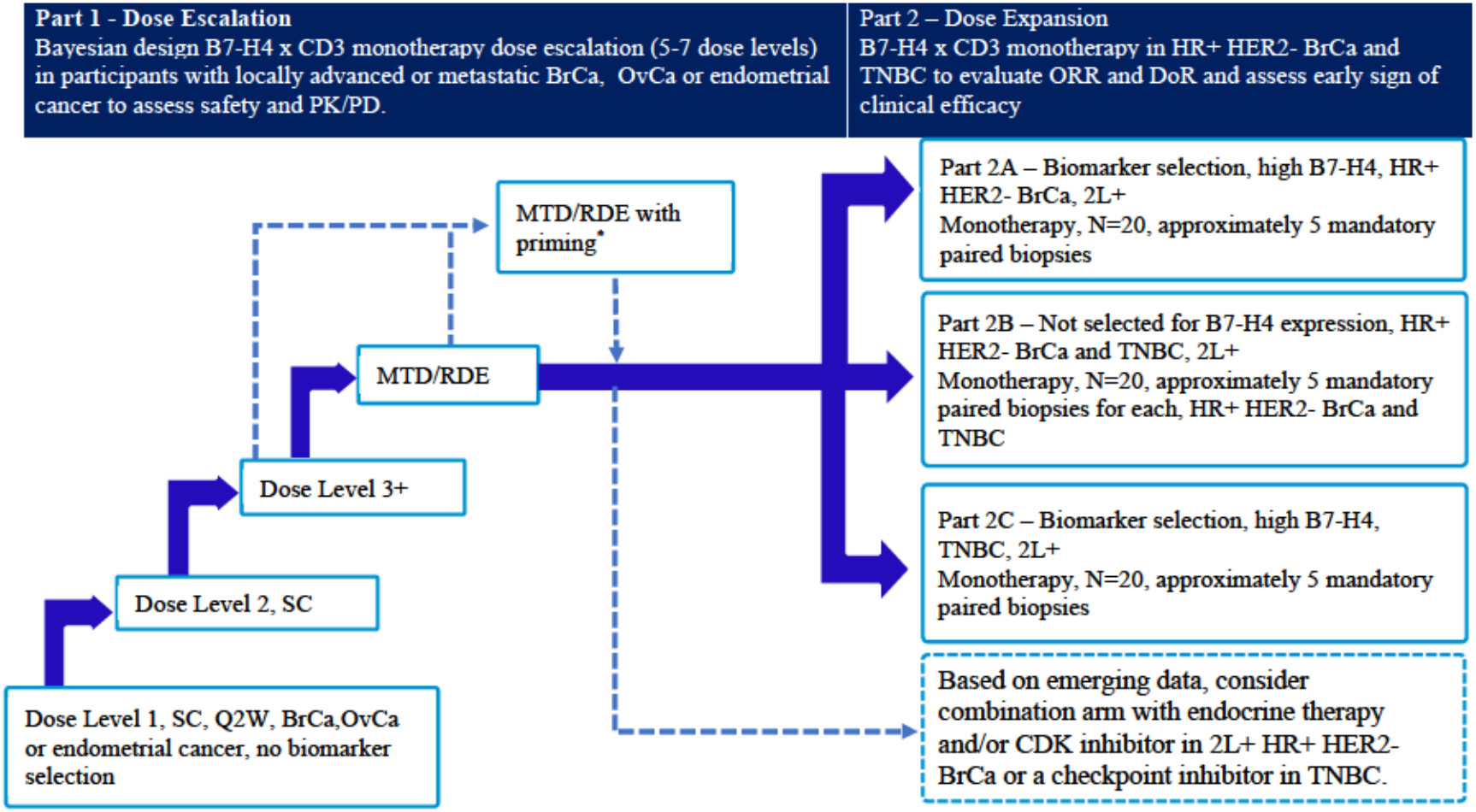
Under-dosing:	[0, 0.16]
Targeted dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

Dosing decisions are guided by the EWOC principal (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the risk of overdosing at that dose is less than 25%.

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/RDE determination.

1.2. Schema

Figure 1 Study Schema



*A priming dose escalation may be initiated if criteria is met.

1.3. Schedule of Activities

The SOA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each 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. Part 1 – Schedule of Assessment - Without Priming

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Informed consent and registration	X													• Informed consent should be obtained prior to any study-specific procedures. • At registration, enrollment (randomization) number and dose level will be assigned by Pfizer.
Screen for inclusion/exclusion criteria	X													• See Section 5.1 and 5.2
Demographics	X													

Table 1. Study Schedule of Assessments – Part 1 Without Priming

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Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Medical history and Physical Examination														• See Section 8.2 for additional information.
Primary cancer diagnosis and prior treatment history	X													• Include date of initial diagnosis and metastatic disease, prior systemic treatments, surgeries, radiotherapy, and recurrence history. • Genomic testing if available.
General medical history	X													• Include any concurrent or resolved illness other than the cancer under study.
Baseline signs and symptoms	X	X												• Signs and symptoms experienced within the 28 days prior to first dose.
Complete physical examination	X										X			• Include height at screening. • See Section 8.2.1 for additional information.
Brief physical examination		X	X		X	X	X	X		X		X		• PE and vital signs should be completed prior to dosing. • See Section 8.2.1 for additional information.
Weight	X	X						X			X			• To be measured prior to dosing.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

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Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Vital signs (BP/pulse rate/RR/temperature)	X	X	X	X	X	X	X	X		X	X	X		• BP and pulse rate should be recorded in the sitting position or semi-recumbent position preceded by at least 5 minutes of rest. • See Section 8.2.2 for additional information.
ECOG performance status	X	X				X	X	X		X	X	X		• See Section 8.2.1.
Contraception check	X	X						X			X	X		• Confirm appropriate selection of contraception for the individual participant and his or her partner(s). • See Section 5.3.1 for additional information.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
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Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
ECG (standard 12-lead)	X	X	X	X	X	X		X	X	X	X	X		• At screening: single 12-lead ECG. • Cycles 1 to 3: triplicate 12-lead ECGs to determine mean QTcF interval. For the days of dose administration, perform ECG up to 60 minutes prior to dosing (SC or IV), and at the end of infusion (IV only). • From Cycle 4 onwards: Triplicate 12-lead ECG up to 60 minutes prior to dosing on Day 1 of every 3 cycles (C4D1, C7D1, etc.). • Refer to Section 8.2.3 for additional information.
Study Intervention														
PF-07260437 administration		X				X		X		X				• Full dose at every dosing timepoint.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Premedication		(X)				(X)		(X)		(X)				• Prophylactic premedication is not allowed during the DLT evaluation period during initial dose escalation. However, if the participant experiences an infusion related reaction (IV), allergic reaction, significant injection site reaction, CRS, fever/chills, allergic reaction, nausea/vomiting, hypotension, or pain, appropriate treatment should initiate and premedication as prophylaxis may be considered for subsequent injections as well as for new participants. See Section 6.1.1.1 for additional information.
Concomitant therapy		◄----------								----------►				• Include medications given to treat AEs, chronic conditions, and supportive medications (except premedication). • See Section 6.8 for additional information.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Inpatient observation		X	X	X		X		(X)		(X)				• Participants will be observed inpatient for at least 48 hours after the first SC dose (or the first IV dose administration, as applicable) on C1D1 and for at least 8 hours after the second SC dose (or the second IV dose administration, as applicable) on C1D15. See Section 4.1. • Participants who experience ≥ Grade 3 infusion-related adverse events (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 doses subsequently (two cycles). See Section 4.1. • See Section 6.1 for additional information.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Injection site tolerability assessment		X	X			X		As clinically indicated						• C1D1: at least 1 hour and 24 hours (±1 hr) after SC injection. • C1D15: at least 1 hour after SC injection. • See Section 8.2.6 for additional information.
Efficacy Assessment														
Tumor response assessment	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.									X			• CT/MRI scans of head, chest, abdomen, pelvis, any clinically indicated sites of disease (see Section 8.1.1).
Bone scan or PET	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.									X			• For bone metastasis (see Section 8.1.1).
Safety Assessment														
Serious and nonserious AE monitoring		◄----------								----------►				• See Sections 8.2 and Section 8.3.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Clinical Safety Laboratory Assessments														• See Section 8.2.4. • See Appendix 2 for a list of Clinical Laboratory tests to be done.
Hematology	X	X	X		X	X	X	X		X	X	X		• No need to repeat on C1D1 if screening was performed within 7 prior days. All samples will be collected prior to dosing.
Blood chemistry	X	X	X		X	X	X	X		X	X	X		
Coagulation	X	Every 8 weeks from C1D1									X			• No need to repeat on C1D1 if screening was performed within 7 prior days.
Lipase and amylase		X						X			X			
TSH and free T4	X													• TSH WNL for institution; in participants with abnormal TSH, if free T4 is WNL and participant is clinically euthyroid, participant is eligible.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Viral disease screen	X													• Include HBsAg, HBcAb, and HCV antibody. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. • See Appendix 2 for additional information.
Urinalysis	X	X									X	X		• Microscopic analyses if dipstick is clinically abnormally indicated. No need to repeat on C1D1 if screening was performed within 7 prior days. Following C1D1, only obtain as clinically indicated until follow-up.
Cytokine (local lab)		Cytokines should be assessed with local laboratory studies in the event of suspected CRS.												• To be collected if CRS is suspected and evaluation of cytokine is required for participant management. • See Appendix 2 for additional information.

Table 1. Study Schedule of Assessments – Part 1 Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow- up	90-day Follow- up for irAEs	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2	3[a]	8	15[a]	22	1	C3D8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a. End of inpatient observation (PK, ECG, vital signs). b. PK/PD and ECG only.
Visit Window (days)		±2			±2	±2	±2	±2	±2	±2		±7	±7	
Pregnancy test	X	X						X			X	X		• Serum or urine pregnancy test for WOCBP. • See Section 8.2.5 for additional information.
Post Treatment														
Late irAE follow-up													X	• Participants will undergo telephone follow-ups at 90 days (±7 days) after the last dose of PF-07260437 to assess potential late irAEs. If any concern arises, the participant should be contacted for an in-person follow-up visit.
Pharmacokinetic Assessments														• See Table 2
Immunogenicity Assessments														
Pharmacodynamic, Biomarker and Biospecimens Assessments														

1.3.1.1. Part 1 - PK, Immunogenicity, PD, Biomarker, and Biospecimen – Without Priming

Table 2. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1 – Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D										EOT	Notes
		Day 1				Day 2	Day 3	Day 8	Day 15			Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	48 hr	168 hr	Pre (0)	4 hr	8 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±4 hr	±24 hr	-6 hr	± 30 min	±1 hr	±24 hr		
PK Assessments														
PK blood sampling		A, B, C, D	A, C (IV only)	A, C	A,C	A	A	A, C	A, C	A	A	A	X	• If CRS is suspected, additional PK sample should be collected at time of AE occurrence if not already scheduled. • IV only: if actual duration of infusion differs from 1 hour, 1-hour point should be adjusted for the sample to be collected at the end of infusion. • See Section 8.4 for additional information.

Table 2. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1 – Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D											EOT	Notes
		Day 1				Day 2	Day 3	Day 8	Day 15			Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	48 hr	168 hr	Pre (0)	4 hr	8 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±4 hr	±24 hr	-6 hr	± 30 min	±1 hr	±24 hr		
Immunogenicity Assessments														
Blood samples for ADA and NAb		A, B, C, D											X	• From Cycle 4 onwards: collection on Day 1 of every 3 cycles. (C4D1, C7D1, etc.) • See Section 8.7 for additional information.
Pharmacodynamic and Biomarker Assessments														
Soluble B7-H4 blood sampling		A, B, C, D		A, C	A, C	A	A	A, C	A, C			A	X	• From Cycle 4 onwards: collection on Day 1 of every 3 cycles. (C4D1, C7D1, etc.) • See Section 8.6.6 for additional information.
Serum for cytokine and circulating markers (central lab)		A, B	A	A	A	A	A	A	A	A	A	A		• See Section 8.6.3.
Blood for Immunophenotyping		A, B				A	A	A	A			A		• Refer to Section 8.6.4.

Table 2. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1 – Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D											EOT	Notes
		Day 1				Day 2	Day 3	Day 8	Day 15			Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	48 hr	168 hr	Pre (0)	4 hr	8 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±4 hr	±24 hr	-6 hr	± 30 min	±1 hr	±24 hr		
Mandatory archival tumor tissue	X													• All participants must provide archival tissue. • Must refer to Section 8.6.1 for specific instruction/acceptable tissue samples.
Optional de novo pre-dose and paired on-treatment biopsy	(X)								(B)				(X)	• (B) (X) = Optional. • Must refer to Section 8.6.1 for specific instruction/acceptable tissue samples.
Plasma for cell free DNA analysis		A											X	• Refer to Section 8.6.3. • A: 10 mL-blood specimens optimized for plasma preparation will be collected.
Blood for germline subtraction		A												• 2 mL whole blood will be collected and sequenced along with tumor samples enabling subtraction of germline variations from somatic mutations.

Table 2. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1 – Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D											EOT	Notes
		Day 1				Day 2	Day 3	Day 8	Day 15			Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	48 hr	168 hr	Pre (0)	4 hr	8 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±4 hr	±24 hr	-6 hr	± 30 min	±1 hr	±24 hr		
Retained Research Sample for Genetics [Prep D1]		A												• A 4 mL whole blood sample optimized for DNA isolation Prep D1 will be collected. See Laboratory Manual - Retained Research Sample collection. • Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.5.2 for additional information.

1.3.2. Part 1 – Schedule of Assessments - With Priming

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Informed consent and registration	X													• Informed consent should be obtained prior to any study-specific procedures. • At registration, enrollment (randomization) number and dose level will be assigned by sponsor.
Screen for inclusion/exclusion criteria	X													• See Section 5.1 and 5.2.
Demographics	X													
Medical history and Physical Examination														See Section 8.2 for additional information
Primary cancer diagnosis and prior treatment history	X													• Include date of initial diagnosis and metastatic disease, prior systemic treatments, surgeries, radiotherapy, and recurrence history. • Genomic testing if available.
General medical history	X													• Include any concurrent or resolved illness other than the cancer under study.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Baseline signs and symptoms	X	X												• Signs and symptoms experienced within the 28 days prior to first dose.
Complete physical examination	X										X			• Include height at screening. See Section 8.2.1 for additional information.
Brief physical examination		X		X	X		X	X	X (C2 only)	X		X		• PE and vital signs should be completed prior to dosing. See Section 8.2.1 for additional information.
Weight	X	X						X			X			To be measured prior to dosing.
Vital signs (BP/pulse rate/RR/temperature)	X	X	X	X	X	X	X	X	X (C2 only)	X	X	X		• BP and pulse rate should be recorded in the sitting or semi-recumbent position preceded by at least 5 minutes of rest. See Section 8.2.2 for additional information.
ECOG performance status	X	X			X		X	X	X (C2 only)	X	X	X		See Section 8.2.1.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Contraception check	X	X						X			X	X		• Confirm appropriate selection of contraception for the individual participant and his or her partner(s). See Section 5.3.1 for additional information.
ECG (standard 12-lead)	X	X	X	X	X	X	X	X	X (C2 & C3 only)	X	X	X		• At screening: single 12-lead ECG. • Cycles 1 to 3: triplicate 12-lead ECGs to determine mean QTcF interval. For the days of dose administration, perform ECG up to 60 minutes prior to dosing (SC or IV), and at the end of infusion (IV only). • From Cycle 4 onwards: Triplicate 12-lead ECG up to 60 minutes prior to dosing on Day 1 of every 3 cycles (C4D1, C7D1, etc.). • Refer to Section 8.2.3 for additional information.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Study Intervention														
PF-07260437		X (priming dose)		(X[c])	X			X		X				• C1D1 is priming dose and C1D15 is full/maintenance dose. • c:A 2-step priming may be considered on C1D1 and C1D8. • See Section 4.1 for additional information.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Premedication		(X)		(X[d])	(X)			(X)		(X)				• Prophylactic premedication is not allowed during the DLT evaluation period during initial dose escalation. However, if the participant experiences an infusion related reaction (IV), allergic reaction, significant injection site reaction, CRS, fever/chills, allergic reaction, nausea/vomiting, hypotension, or pain, appropriate treatment should initiate and premedication as prophylaxis may be considered for subsequent injections as well as for new participants. See Section 6.1.1.1 for additional information. • d: Only applicable to 2-step priming

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Concomitant therapy		◄----------								----------►				• Include medications given to treat AEs, chronic conditions, and supportive medications (except premedication). • See Section 6.8 for additional information.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Inpatient observation		X	X[e]		X	X[e]		(X)		(X)				• e: Participants will be observed inpatient for at least 24 hours after the first priming SC dose (or the first IV priming dose administration, as applicable) on C1D1 and 24 hours after the second (full) SC dose (or the second (full) IV dose administration, as applicable) on C1D15. May not require overnight stay. • Participants who experience ≥ Grade 3 infusion-related adverse events (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 doses subsequently (two cycles). See Section 4.1. • See Section 6.1 for additional information.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Injection site tolerability assessment		X	X		X			As clinically indicated						• C1D1: at least 1 hour and 24 hours (±1 hr) after injection. • C1D15: at least 1 hour after injection. • See Section 8.2.6 for additional information
Efficacy Assessment														
Tumor response assessment	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.									X			• CT/MRI scans of head, chest, abdomen, pelvis, any clinically indicated sites of disease (see Section 8.1.1).
Bone Scan or PET	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.									X			• For bone metastasis (see Section 8.1.1).
Safety Assessment														
Serious and nonserious AE monitoring	◄----------												----------►	• See Sections 8.2 and Section 8.3.
Clinical Safety Laboratory Assessments														• See Section 8.2.4 • See Appendix 2 for a list of Clinical Laboratory tests to be done.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Hematology	X	X		X	X		X	X	X (C2 only)	X	X	X		• No need to repeat on C1D1 if screening was performed within 7 prior days. All samples will be collected prior to dosing.
Blood Chemistry	X	X		X	X		X	X	X (C2 only)		X	X		
Coagulation	X	Every 8 weeks from C1D1									X			• No need to repeat on C1D1 if screening was performed within 7 prior days.
Lipase and amylase		X						X			X			
TSH and free T4	X													• TSH WNL for institution; in participants with abnormal TSH, if free T4 is WNL and participant is clinically euthyroid, participant is eligible.

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Viral disease screen	X													• Include HBsAg, HBcAb, and HCV antibody. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. • See Appendix 2 for additional information.
Urinalysis	X	X									X	X		• Microscopic analyses if dipstick is clinically abnormally indicated. No need to repeat on C1D1 if screening was performed within 7 prior days. Following C1D1, only obtain as clinically indicated until follow-up.
Cytokine (local lab)		Cytokines should be assessed with local laboratory studies in the event of suspected CRS.												• To be collected if CRS is suspected and evaluation of cytokine is required for participant management. • See Appendix 2 for additional information

Table 3. Study Schedule of Assessments – Part 1 With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period									EOT	4-week Follow-up	90-day Follow-up for irAEs	Notes
		Cycle 1 =28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15	16[a]	22	1	8[b]	15				• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). b: This D8 visit is only applicable for Cycles 2 and 3, whereas, C3D8 is applicable for PK/PD and ECG only.
Visit Window (days)		±2		±2	±2		±2	±2	±2	±2		±7	±7	
Pregnancy test	X	X						X			X	X		• Serum or urine pregnancy test for WOCBP. • See Section 8.2.5 for additional information.
Post Treatment														
Late irAE follow up													X	• Participants will undergo telephone follow-ups at 90 days (±7 days) after the last dose of PF-07260437 to assess potential late irAEs. If any concern arises, the participant should be contacted for an in-person follow up visit.
Pharmacokinetic Assessments														• See Table 4
Immunogenicity Assessments														
Pharmacodynamic, Biomarker and Biospecimens Assessments														

1.3.2.1. Part 1 - PK, Immunogenicity, PD, Biomarker, and Biospecimen – With Priming

Table 4. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1- With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D												EOT	Notes
		Day 1				Day 2	Day 8	Day 15				Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 10 min	± 30 min	±1 hr	±3 hr	±24 hr		• Post-dose samples: hours after the most recent scheduled dose
PK Assessments															
PK blood sampling		A, B, C, D	A, C (IV only)	A, C	A, C	A	A, C	A, C	A (IV only)	A	A	A	A	X	• If CRS is suspected, additional PK sample should be collected at time of AE occurrence if not already scheduled • IV only: if actual duration of infusion differs from 1 hour, 1-hour point should be adjusted for the sample to be collected at the end of infusion. • See Section 8.4 for additional information.
Immunogenicity Assessments															
Blood samples for ADA and NAb		A, B, C, D												X	• From Cycle 4 onwards: collection on Day 1 of

Table 4. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1- With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D												EOT	Notes
		Day 1				Day 2	Day 8	Day 15				Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 10 min	± 30 min	±1 hr	±3 hr	±24 hr		
															every 3 cycles. (C4D1, C7D1 etc.) • See Section 8.7 for additional information.
Pharmacodynamic and Biomarker Samples															
Soluble B7-H4 blood sample		A, B, C, D		A, C	A,C	A	A,C	A,C		A	A	A	A	X	• From Cycle 4 onwards: collection on Day 1 of every 3 cycles (C4D1, C7D1, etc.) • See Section 8.6.6 for additional information.
Serum for cytokine and circulating markers (central lab)		A, B	A	A	A	A	A	A	A	A	A	A	A		• Refer to Section 8.6.3.
Blood sample for immunophenotyping		A, B				A	A	A				A	A		• Refer Section 8.6.4.

Table 4. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1- With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D												EOT	Notes
		Day 1				Day 2	Day 8	Day 15				Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 10 min	± 30 min	±1 hr	±3 hr	±24 hr		
Mandatory archival tumor tissue	X														• All participants must provide archival tissue. • Must refer to Section 8.6.1 for specific instruction/acceptable tissues samples.
Optional de novo pre-dose and paired on-treatment biopsy	(X)							(B)						(X)	• (B) and (X) = Optional. • Must refer to Section 8.6.1 for specific instruction/acceptable tissues samples.
Plasma sample for cell free DNA analysis		A												X	• Refer to Section 8.6.3. • A: 10 mL-blood specimens optimized for plasma preparation will be collected.
Blood for germline subtraction		A													• 2 mL whole blood sample will be collected and sequenced along with tumor samples enabling subtraction of germline

Table 4. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – Part 1- With Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D												EOT	Notes
		Day 1				Day 2	Day 8	Day 15				Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 10 min	± 30 min	±1 hr	±3 hr	±24 hr		
															variations from somatic mutations.
Retained Research Sample for Genetics [Prep D1]		A													• A 4 mL whole blood sample optimized for DNA isolation Prep D1 will be collected. See Laboratory Manual - Retained Research Sample collection. • Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.5.2 for additional information.

1.3.3. Part 2 – Schedule of Assessments – With or Without Priming

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
Informed consent	X													• Informed consent should be obtained prior to any study-specific procedures. • Enrolment (randomization) number may be assigned by IRT.
Screen for inclusion/exclusion criteria	X													• See Section 5.1 and 5.2.
Demographics	X													
Medical history and Physical Examination														• See Section 8.2 for additional information.
Primary cancer diagnosis and prior treatment history	X													• Include date of initial diagnosis and metastatic disease, prior systemic treatments, surgeries, radiotherapy, and recurrence history. • Genomic testing if available.

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
General Medical history	X													• Include any concurrent or resolved illness other than the cancer under study.
Baseline signs and symptoms	X	X												• Signs and symptoms experienced within the 28 days prior to first dose.
Complete physical examination	X									X				• Include height at screening. • Section 8.2.1 for additional information.
Brief physical examination		X		X	X		X	X	X		X			• PE and vital signs should be completed prior to dosing. • See Section 8.2.1 for additional information.
Weight	X	X						X		X				• To be measured prior to dosing.
Vital signs (BP/respiratory rate/pulse rate/temperature)	X	X	X	X	X	X	X	X	X	X	X			• BP and pulse rate should be recorded in the sitting or semi-recumbent position preceded by at least 5 minutes of rest. • See Section 8.2.2 for

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														additional information.
ECOG performance status	X	X			X		X	X	X	X	X			• See Section 8.2.1.
Contraception Check	X	X						X		X	X			• Confirm appropriate selection of contraception for the individual participant and his or her partner(s). • See Section 5.3.1 for additional information.
ECG (standard 12-lead)	X	X	X	X	X	X		X	X	X	X			• At screening: single 12-lead ECG. • Cycles 1 to 3: triplicate 12-lead ECGs to determine mean QTcF interval. For the days of dose administration, perform ECG up to 60 minutes prior to dosing (SC or IV), and at the end of infusion (IV only). • From Cycle 4 onwards: Triplicate 12-lead ECG up to

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														60 minutes prior to dosing on Day 1 of every 3 cycles (C4D1, C7D1, etc.). • Refer to Section 8.2.3 for additional information.
Study Intervention														
PF-07260437		X			X			X	X					• Without priming: Full dose at every dosing timepoint. • With priming: Priming dose on C1D1; full dose on C1D15 and beyond. • See Section 4.1 for additional information.
Premedication		(X)			(X)			(X)	(X)					• Premedication is optional (X). • Based on a review of all accumulated safety data (eg, > 50% of participants experienced significant allergic reaction or CRS related symptoms and signs),

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														prophylactic premedication may be considered during the DLT observation period for new participants after agreement between investigators and the sponsor to determine the MTD/RDE with prophylaxis. • See Section 6.1.1.1 for additional information.
Concomitant therapy	◄----------												----------►	• Include medications given to treat AEs, chronic conditions, and supportive medications (except premedication). • See Section 6.8 for additional information.
Inpatient observation		X	X		X	X		(X)	(X)					**Without priming dose**: • participants will be observed inpatient for at least 24 hours after the first dose on C1D1

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														and for at least 8 hours after the second dose on C1D15. **With priming dose:** • Participants will be observed inpatient for at least 24 hours after the priming dose on C1D1 and 24 hours after the second (full) dose on C1D15. • Participants who experience ≥ Grade 3 infusion-related adverse events (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 doses subsequently (two cycles). See Section 4.1. • See Section 6.1 for additional information.
Injection site tolerability assessment		X	X		X			As clinically indicated						• C1D1: 1 hour and 24 hours (±1 hr) after SC injection. • C1D15: 1 hour after SC

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														injection. • See Section 8.2.6 for additional information.
Efficacy Assessments														
Tumor response assessment	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.								X				• CT/MRI scans of head, chest, abdomen, pelvis, any clinically indicated sites of disease (see Section 8.1.1).
Bone scan or PET	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.								X				• For bone metastasis (see Section 8.1.1).
Safety Assessments														
Serious and nonserious AE monitoring		◄----------							----------►					• See Sections 8.2 and Section 8.3.
Clinical Safety Laboratory Assessments														• See Section 8.2.4 • See Appendix 2 for a list of Clinical Laboratory tests to be done.

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
Hematology	X	X	X	X	X		X	X	X	X	X			• No need to repeat on C1D1 if screening was performed within 7 prior days. All samples will be collected prior to dosing.
Blood Chemistry	X	X	X	X	X		X	X	X	X	X			
Coagulation	X		Every 8 weeks from C1D1							X				• No need to repeat on C1D1 if screening was performed within 7 prior days.
Lipase and amylase		X						X		X				
TSH and free T4	X													• TSH WNL for institution; in participants with abnormal TSH, if free T4 is WNL and participant is clinically euthyroid, participant is eligible.
B7-H4 expression (biopsy)	X													• CLIA-validated B7-H4 IHC Laboratory Developed Test on archival tumor biopsies
Viral disease screen	X													• Include HBsAg, HBcAb, and HCV antibody. In the case of apparent ongoing HBV or

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed. • See Appendix 2 for additional information.
Urinalysis	X	X								X	X			• Dipstick is acceptable. Microscopic analyses clinically indicated. No need to repeat on C1D1 if screening was performed within 7 prior days. Following C1D1, only obtain as clinically indicated until follow-up.
Cytokine (local lab)		Cytokines should be assessed with local laboratory studies in the event of suspected CRS.												• To be collected if CRS is suspected and evaluation of cytokine is required for participant management. • See Appendix 2 for additional information.

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
Pregnancy test	X	X						X		X	X			• Serum or urine pregnancy test for WOCBP. • See Section 8.2.5 for additional information.
Pharmacokinetic Assessments														• See Table 6.
Immunogenicity Assessments														
Pharmacodynamic, Biomarker and Biospecimens Assessments														
Post-Treatment														
Late irAE follow-up												X		• Participants will undergo telephone follow-ups at 90 days (±7 days) after the last dose of PF-07260437 to assess potential late irAEs. If any concern arises, the participant should be contacted for an in-person follow-up visit.
Survival follow-up													X	• Survival status will be collected by telephone every

Table 5. Part 2 – Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 17	Screening	Treatment Period								EOT	4-week Follow- up	90-day Follow-up for irAEs	Survival Follow- up	Notes
		Cycle 1 = 28 days						Cycle ≥2 (28 days)						
Study Day	-28 to -1	1	2[a]	8	15[a]	16[a]	22	1	15					• Additional visit window may be allowed after discussion and agreement between investigator and sponsor. a: End of inpatient observation (PK, ECG, vital signs). Day 2 for all participants; Day 16 for priming dose schedule only.
Visit Window (days)		±2		±2	±2		±2	±2	±2		±7	±7	±14	
														3 months until death, or up to 24 months after first dose of the last participant.

1.3.3.1. Part 2- PK, Immunogenicity, PD, Biomarker, and Biospecimen – With or Without Priming

Table 6. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D										EOT	Notes
		Day 1				Day 2	Day 8	Day 15			Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 30 min	±1 hr	±3 hr	±24 hr		
PK Assessments														

Table 6. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D											EOT	Notes
		Day 1				Day 2	Day 8	Day 15			Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 30 min	±1 hr	±3 hr	±24 hr		
PK blood sampling		A, B, C, D	A,C (IV only)	A, C	A, C	A	A	A, C	A	A	A (Priming only)	A	X	• If CRS is suspected, additional PK sample should be collected at time of AE occurrence if not already scheduled • IV only: if actual duration of infusion differs from 1 hour, 1-hour point should be adjusted for the sample to be collected at the end of infusion. • See Section 8.4 for additional information.
Immunogenicity Assessments														
Blood samples for ADA and NAb		A, B, C, D											X	• From Cycle 4 onwards: collection on Day 1 of every 3 cycles. (C4D1, C7D1, etc.) • See Section 8.7 for additional information.
Pharmacodynamic and Biomarker Samples														

Table 6. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D										EOT	Notes
		Day 1				Day 2	Day 8	Day 15			Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 30 min	±1 hr	±3 hr	±24 hr		
Soluble B7-H4 blood sample		A, B, C, D					A	A					X	• From Cycle 4 onwards: collection on Day 1 of every 3 cycles. (C4D1, C7D1, etc.) • See Section 8.6.6 for additional information.
Serum for cytokine and circulating markers (central lab)		A, B	A	A	A	A	A	A	A	A	A (Priming only)	A		• Refer to Section 8.6.3.
Blood sample for immunophenotyping		A, B				A	A	A			A (Priming only)	A		• Refer to Section 8.6.4.
Optional or mandatory archival tissue	X													• Optional if de novo tissue sample is provided. • Mandatory if a de novo tissue sample is not provided. • Refer to Section 8.6.2 for details.
Mandatory or optional de novo	X							B					(X)	• (x) = Optional

Table 6. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D										EOT	Notes
		Day 1				Day 2	Day 8	Day 15			Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 30 min	±1 hr	±3 hr	±24 hr		
pre-dose and paired on-treatment biopsy														• Mandatory for 5 participants in Part 2A and Part 2C each, and for 5 HR+ HER2- BrCa and 5 TNBC participants in Part 2B. • Optional for the rest of the participants. • EOT sample is optional for all participants • See Section 8.6.2.
Plasma sample for cell free DNA analysis		A											X	• Refer to Section 8.6.3. • A 10 mL-blood specimen optimized for plasma preparation will be collected.
Blood for germline subtraction		A												• 2 mL whole blood sample will be collected and sequenced along with tumor samples enabling subtraction of germline variations from somatic mutations.

Table 6. PK, Immunogenicity, PD, Biomarker, and Biospecimen Schedule of Assessments – With or Without Priming

Visit Identifier Abbreviations used in this table may be found in Appendix 16	Screening	CYCLE 1 - A CYCLE 2 - B CYCLE 3 - C CYCLE ≥4 - D										EOT	Notes
		Day 1				Day 2	Day 8	Day 15			Day 16	Day 22		
Hours Before/After Dose		Pre (0)	1 hr	4 hr	8 hr	24 hr	168 hr	Pre (0)	4 hr	8 hr	24 hr	168 hr		• Pre-dose samples: hours before the immediate dose • Post-dose samples: hours after the most recent scheduled dose
Visit Window		-6 hr	+ 10 min	± 30 min	±1 hr	±3 hr	±24 hr	-6 hr	± 30 min	±1 hr	±3 hr	±24 hr		
Retained Research Sample for Genetics [Prep D1]		A												• A 4 mL whole blood sample optimized for DNA isolation Prep D1 will be collected. See Laboratory Manual - Retained Research Sample collection. • Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.5.2 for additional information.

2. INTRODUCTION

This is a Phase 1, dose escalation and expansion study to evaluate the safety, tolerability, PK, PD, and antitumor activity of PF-07260437, a B7-H4 x CD3 bi-specific mAb, in participants aged ≥18 years of age with advanced or metastatic BrCa, OvCa or endometrial cancer. Adult participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from sponsor.

B7-H4, a member of the B7 family of proteins encoded by gene [CCI], has been shown to have wide expression in BrCa along with other gynecologic malignancies (ovarian, endometrial). In addition, its limited expression in normal tissues makes B7-H4 an appealing tumor-associated antigen for targeting BrCas with CD3 bispecific molecules. PF-07260437 is a first in class bispecific mAb with 2 binding domains: a domain that recognizes tumor antigen B7-H4 with high affinity, a novel target in breast, OvCa and uterine cancer, and a domain that recognizes [CCI], expressed on T-cells, with moderate affinity. Bispecific antibodies are able to simultaneously bind to CD3 and the tumor antigen, thereby initiating a MHC-independent cytotoxic response towards the bound tumor cell. By directly targeting cytotoxic T-cells to tumors, bispecific antibodies offer a novel immunotherapeutic approach for cancer and is currently being investigated in participants with advanced or metastatic BrCa, OvCa and endometrial cancer.

2.1. Study Rationale

PF-07260437 is a T cell redirecting B7-H4 x CD3 bispecific mAb with 2 binding domains: a domain that recognizes tumor antigen B7-H4 with high affinity and a domain that recognizes [CCI], expressed on T cells, with moderate affinity. Co-engagement of B7-H4 on tumor cells and [CCI] on T cells leads to a tumor-localized T-cell cytotoxic response and reduces systemic [CCI] targeting and toxicity. This mechanism circumvents the need for T cells to recognize ific antigenic peptides in the context of [CCI] on malignant cells. Cytotoxicity is mediated by release and transfer of [CCI] from the T cell to the B7-H4 expressing target cell. PF-07260437 addresses a significant unmet medical need for BrCa, as its target is expressed in the majority of BrCas across all molecular subtypes.

Preclinically PF-07260437 demonstrated B7-H4 expression-dependent antitumor activity against a panel of cell line xenograft and patient derived xenograft breast tumors grown in immune-compromised mice that were implanted with human T cells.

The purpose of this FIH study is to evaluate the safety, tolerability, PK, PD, and potential clinical activity of escalating doses of PF-07260437 in advanced or metastatic solid tumors including BrCa, OvCa and endometrial cancer.

In Part 1 of this clinical study, PF-07260437 will be evaluated for the treatment of adult participants with advanced or metastatic BrCa, OvCa or endometrial cancer for whom no standard therapy is available with no biomarker selection. Adult participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from the sponsor.

The major objectives are to evaluate safety, tolerability PK and PD and to identify RDE, see Section 4.3.9.

In Part 2 dose expansion phase of the study, PF-07260437 will be further evaluated in participants with advanced or metastatic HR+ HER2- BrCa (Part 2A) and TNBC (Part 2C) with high B7-H4 expression to assess early signs of clinical efficacy. In addition, a cohort of 20 participants with advanced or metastatic HR+ HER2- BrCa and TNBC not preselected for B7-H4 expression will be included in Part 2B to further explore biomarker changes in tumor microenvironment and validate the MoA.

De novo paired pre- and on-treatment biopsies are mandatory for 5 participants in Part 2A and Part 2C each, and for 5 HR+ HER2- BrCa and 5 TNBC participants each in Part 2B. If significant TIL infiltrates are observed during PF-07260437 treatment consistent with the preclinical MoA, this could justify further clinical development in combination with endocrine therapy and/or CDK4/6 inhibitors in advanced or metastatic HR+ HER2- BrCa as well as in combination with immune checkpoint inhibitors in TNBC.

2.2. Background

B7-H4 is a novel molecular target that overexpressed in breast, ovarian, endometrial and a significant percentage of other solid tumors. Despite the advancement of chemotherapy, hormonal therapies, targeted therapies and immunotherapies, metastatic solid tumors have high unmet medical need. Effective therapies are needed to improve patient outcomes. PF-07260437 is a first in class CD3 bispecific mAb targeting B7-H4. Preclinical research has demonstrated potent monotherapy antitumor activities in multiple in vivo animal models and good therapeutic index, which justifies further clinical development.

2.2.1. Nonclinical Pharmacology

PF-07260437 is a CCI [redacted] molecule comprised of 2 recombinant humanized IgG chains, one against B7-H4 and the other against CD3 CCI [redacted] (B7-H4 x CD3 bispecific), with CCI [redacted]. PF-07260437 demonstrated binding to a panel of tumor cell lines that express B7-H4 protein and human T lymphocytes that express CD3. The bispecific molecule exhibited concentration-dependent binding across a panel of cancer cell lines with varying levels of endogenous B7-H4 expression, as well as concentration-dependent binding on a panel of human donor T cells. In the presence of T cells, PF-07260437 elicited CTL responses against a panel of cancer cell lines expressing B7-H4. In the absence of T cells PF-07260437 did not affect tumor cell growth. In vivo, PF-07260437 demonstrated B7-H4 expression-dependent antitumor activity against a panel of cell line xenograft and patient derived xenograft breast tumors grown in immune-compromised mice that were implanted with human T cells. Tumor growth inhibition following PF-07260437 treatment was dose dependent.

2.2.1.1. In Vitro Pharmacodynamics

PF-07260437 was shown to bind to a panel of cell lines expressing B7-H4 CCI [redacted]

CCI [redacted]

The B7-H4 binding specificity of PF-07260437 translated to T cell-dependent in vitro cytotoxic activity. CTL activity was observed CCI [redacted] in cell lines expressing B7-H4. The potency of PF-07260437 directly correlated with the level of B7-H4 expression on each cell line. No CTL activity was observed in a B7-H4 negative cell line. Additionally, CTL activity in all B7-H4 positive cell lines was associated with a concomitant increase in cytokines released in supernatants.

PF-07260437 was further characterized in a cell proliferation assay in the absence of T cells and shown not to affect cell growth in BrCa cell lines of HR+ HER2-, HER2+, and TNBC molecular subtypes.

2.2.1.2. In Vivo Pharmacodynamics

PF-07260437 demonstrated B7-H4 expression-dependent antitumor efficacy CCI [redacted] PF-07260437 showed efficacy in models of HR+HER2-, HER2+, and TNBC molecular subtypes. Efficacy observed with PF-07260437 was dose dependent. PF-07260437 treatment showed antitumor efficacy in models CCI [redacted]

The efficacy observed with PF-07260437 was the result of the induction of accumulation and activation of T cells in B7-H4 expressing tumors. PF-07260437 bound B7-H4 on tumor cells and CD3 on T cells, induced formation of immune synapses, and resulted in T cell activation. CCI [redacted] T cell activation, proliferation, and recruitment resulted in T-cell accumulation in the tumor. Accumulated T cells, among other potential mechanisms, produce functional cytotoxic molecule granzyme B to kill tumor cells.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

After single IV administration of PF-07260437, linear PK was observed with CL of approximately 0.3 mL/h/kg and low V_{ss} of 47.9 – 86.2 mL/kg. Following a single SC dose, the bioavailability was approximately 76%.

In the GLP toxicity study, mean systemic exposure increased with increasing dose following SC administration. Based on mean AUC168 values, minimum accumulation (<2x) occurred

between Days 1 and 22. No consistent sex-related differences in systemic exposure were observed. The overall incidence of ADA induction to PF-07260437 was approximately 89% across all dose groups.

In human, the PK of PF-07260437 is projected to be linear with CL and V_{ss} values of 0.2 mL/h/kg and 84 mL/kg, respectively. The terminal $t_{½}$ is projected to be 15 days. SC bioavailability of PF-07260437 in humans is expected to be similar to that in monkeys, which is approximately 70%. The projected clinical dose of PF-07260437 that is expected to achieve the minimal C_{eff} is 200 µg SC (Q2W).

2.2.3. Nonclinical Safety

PF-07260437 was characterized in toxicity studies up to 1 month in duration in cynomolgus monkeys (ie, the only pharmacologically relevant species). The highest doses tested in the 1-month study (0.3 mg/kg/week SC and 0.1 mg/kg/week IV) are the HNSTDs and NOAELs. A more conservative MABEL approach was used instead of the 1/6 HNSTD calculation to select the clinical starting dose. For more information about the clinical starting dose, see Section 4.3.1.

Based on the nonclinical toxicity studies, the organs of potential clinical importance are the immune system and pancreas. The key findings were immune-mediated effects from the primary pharmacology of PF-07260437 (ie, cytokine induction and T cell activation). CRS-like clinical observations included emesis, hypoactivity, and reduced appetite. Mild to moderate increases of circulating cytokines were mostly observed after the first dose, typically peaked by 7 hours, and returned to baseline values within 48 hours. Immune-related toxicities (eg, mononuclear cell infiltration, vacuolation, and degeneration) in tissues with B7-H4 expression were typically minimal to mild in severity and fully or partially resolved after a recovery period. There were no findings in the pancreas; however, expression of B7-H4 in human pancreas may result in inflammation not observed in cynomolgus monkeys due to lack of expression of B7-H4 in the latter. Given this, the pancreas has been included as a potential target organ.

Overall, the nonclinical toxicity of PF-07260437 caused pharmacology-based, exposure-responsive findings expected to be reversible and clinically monitorable.

More details of the nonclinical safety program are provided in the IB.

2.2.4. Clinical Overview

This is a first in human study and no clinical data are available.

2.2.5. Bispecific Redirected T-cell Engaging Therapies

The potential of redirected T-cell therapeutics in cancer treatment has been demonstrated by the US FDA's approval of the bispecific T-cell engager, blinatumomab, for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (Solit et al, 2006).

Bispecifics with a redirected T-cell engaging modality have also shown promise for the treatment of solid tumors.

CTLs conventionally recognize cell protein antigens presented in complex with MHC Class I molecules on the cell surface via their TCRs. CD3 bispecifics circumvent the need for TCR engagement through MHC Class I in complex with antigenic peptide, and instead recruit T cells to target cells expressing cell surface target protein (antigen). One arm of the bispecific binds to a tumor associated cell surface antigen, and the other arm binds to the CD3ε protein, which is a part of the TCR complex on T cells. Co-engagement of CD3ε on T cells and target antigen on tumor cells via a bispecific molecule leads to a cytotoxic response. Cytotoxicity is mediated by release and transfer of CCI [redacted] and perforin from the T cell to the target cell. Using this CD3 bispecific mechanism of action, PF-07260437 redirects T cells to target B7-H4 expressing tumor cells through co-engagement of CD3ε on the T cell, and B7-H4 on the tumor cell surface, thereby broadening the repertoire of T cells that can recognize tumors and act as effector cells.

2.3. Benefit/Risk Assessment

For this study, the investigational product is PF-07260437.

There continues to be significant unmet medical need for more effective therapies for advanced or metastatic BrCa or other solid tumors. Currently available therapies have limited clinical benefit both in terms of response and duration of response. No human studies have been conducted to date evaluating PF-07260437. In preclinical pharmacology studies with PF-07260437, B7-H4 expression-dependent antitumor efficacy was observed CCI [redacted] PF-07260437 showed efficacy in models of HR+ HER2-, HER2+, and TNBC molecular subtypes.

The safety of PF-07260437 has been characterized in toxicity studies up to 1 month in duration in cynomolgus monkeys (ie, the only pharmacologically relevant species). The highest doses tested in the 1-month study (0.3 mg/kg/week SC and 0.1 mg/kg/week IV) are the HNSTDs and NOAELs. A more conservative MABEL approach was used instead of the 1/6 HNSTD calculation to select the clinical starting dose.

It is anticipated that CRS and irAEs may occur in the clinical study potentially at higher doses. Close medical monitoring, including a staggered enrollment strategy will be applied for participants entering Part 1 at dose level 1. Each participant dosed will be observed inpatient for at least 48 hours and for at least 8 hours following the second PF-07260437 SC dose will be required, along with safety assessments throughout the study. If no safety concerns arise during this 48-hour period, then an additional participant may be enrolled at dose level 1. Supportive care measures as described in Section 6.8.2 are available that may be considered in the management of CRS and irAEs (Benson et al, 2004; Lee et al, 2014; Lee et al, 2019).

At this stage of development, the anticipated benefit-risk for PF-07260437 is considered acceptable in patients with advanced or metastatic BrCa or other solid tumors who do not have access to curative treatment options.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07260437 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07260437		
CRS (on-target off-tumor effect)	The potential risks are based on pre-clinical toxicology data for PF-07260437	• A staggered enrollment strategy will be applied for participants entering Part 1 at dose level 1. • All Part 1 participants, regardless of dose level, will be hospitalized for at least 24-48 hours on C1D1 and 8-24 hours on C1D15 to closely monitor and manage acute toxicities. See SOA and Section 4.1. • Participants who experience Grade ≥3 infusion-related AE (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 subsequent doses (two cycles). See SOA and Section 4.1. • A priming dose approach in the next dose level may be initiated if a dose level induces ≥Grade 2 CRS (lasting for >24 hours) occurs in >1 participant despite SOC. See SOA and Section 4.1. • MABEL starting dose with strong confidence in high expression in tumors vs normal tissues. • Frequent safety lab tests, closely monitor for AEs and manage AEs per protocol/clinical guidance. • Premedication will be considered based on safety profile.
B7-H4 expression in normal human tissues (ie, kidney)	B7-H4 expression in normal human tissues	• Frequent clinical laboratory assessments including hematology (complete blood counts and differentials), coagulation, and clinical chemistry. See SOA. • AEs will be monitored on an ongoing basis. • PF-07260437 doses may be interrupted or reduced based on toxicities observed. • Effective contraception methods will be used in all participants
Pancreatitis (based on B7-H4 expressing in human Pancreas, like other B7-H4 positive health tissues/organs)		• Routine amylase and lipase monitoring. Supporting imaging (abdominal ultrasound, CT/MRI) will be conducted to confirm the diagnosis of acute pancreatitis. Dose modifications and discontinuation criteria are incorporated in the protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related toxicity		• Careful monitoring of potential immune related toxicity. Guidelines on the management of irAEs are provided in Appendix 3, Section 10.3.5. • Premedication will be considered based on safety profile.
Study Procedures		
De novo (fresh) tumor biopsy Bleeding, swelling, scarring, soreness, or bruising, nerve damage, infection of wound, contamination of cancer cells to unaffected tissue.		• Local anesthetic will be administered. • Sterile techniques will be used. • Procedures will be performed by qualified medical practitioners. • Participants should not be subjected to a significant risk procedure to obtain the biopsies (ie, the absolute risk of mortality or major morbidity in the participant's clinical setting and at the institution completing the procedure should be <2%).
SC ISR.		• ISRs will be monitored at each injection.
CT or MRI procedures for tumor assessments Increased radiation exposure (CT scans) Contrast agent allergy Worsening of kidney function. (CT scans)	Participants in this study will have more frequent (every 8 weeks) CT/MRI scans than per SOC (every 12 weeks) for the first 6 months of the study for a total of 1 additional scan assessment.	• Only experienced professionals will conduct the CT or MRI procedures. • The participant will be asked about allergies to the contrast dye. • Medical history will be reviewed for kidney disease, and information will be provided to minimize dehydration.
COVID-19	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility	• Inclusion of COVID-19 specific precautions (See Appendix 8).

2.3.2. Benefit Assessment

This is a FIH study to evaluate PF-07260437. The study intervention should be used with appropriate caution typical for an investigational drug. Participant benefits include contributing to the process of developing new therapies in oncology areas of unmet need, receiving study intervention that may have clinical utility, and receiving medical evaluations and assessments associated with the study procedures.

2.3.3. Overall Benefit/Risk Conclusion

Preclinically, PF-07260437 has demonstrated B7-H4 expression-dependent antitumor efficacy [redacted]. PF-07260437 showed efficacy in models of HR+ HER2-, HER2+, and TNBC molecular subtypes. Efficacy observed with PF-07260437 was dose dependent. The efficacy observed with PF-07260437 was the result of the induction of accumulation and activation of T cells in B7-H4 expressing tumors. PF-07260437 has displayed a tolerable safety profile and promising therapeutic index.

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07260437 are justified by the anticipated benefits that may be afforded to participants with advanced or metastatic B7-H4 expressing solid tumors including HR+ HER2- BrCa, HR+ HER2+ BrCa, TNBC, OvCa, and endometrial cancer.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Dose Escalation (Part 1):

Objectives	Endpoints	Estimands
Primary		
• To assess safety and tolerability at increasing dose levels of PF-07260437 in successive cohorts of participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer. • To estimate the MTD and to select RDE.	• Occurrence of DLTs (Section 4.3.6). • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5 or CRS grading system) timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (graded by NCI CTCAE v5), and timing.	• DLT rate estimated based on data from DLT-evaluable participants during the DLT evaluation period. • Incidence of AEs estimated in the safety analysis population during the AE evaluation period.
Secondary		
• To assess immune related safety and tolerability at increasing dose levels of PF-07260437 in successive cohorts of participants with locally	• irAEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5) timing, seriousness, and relationship to study therapy.	• N/A

Objectives	Endpoints	Estimands
advanced or metastatic BrCa, OvCa or endometrial cancer.		
• To evaluate the single and multiple dose PK of PF-07260437 as monotherapy.	• Pharmacokinetic parameters of PF-07260437 as monotherapy: SD C_{max}, T_{max}, AUC_{last}, and as data permit, $t½$, AUC_{inf}, CL/F, and V_z/F. MD (assuming steady state is achieved) $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, $AUC_{ss,\tau}$, and as data permit, CL_{ss}/F, V_z/F, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).	• N/A
• To evaluate immunogenicity of PF-07260437.	• Incidence and titers of ADA and NAb against PF-07260437.	• N/A
• Tertiary/Exploratory		
• To evaluate preliminary antitumor activity of PF-07260437 in participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer	• ORR, as assessed by investigator based on RECIST v1.1 and irRECIST. • DOR as assessed by investigator based on RECIST v1.1 and irRECIST.	• N/A
• To explore cytokine and chemokine PD markers in pre and on treatment serum samples.	• Changes in pre- and on-treatment cytokine and chemokine markers in serum samples.	• N/A
• To evaluate T, B, and NK subtypes for immunophenotyping in addition to T cell proliferation and activation markers in whole blood.	• Changes in subtypes of immune cell, activation, and proliferation markers on T cells.	• N/A
• To explore additional biomarkers in tumor biopsies, whole blood, and serum samples to predict response to therapy and to understand resistance mechanisms that may predict escape from therapy.	• Biomarkers from genomic, transcriptomic, and/or protein profiling from tumor, blood, serum or plasma and their relationship to clinical outcome.	• N/A
• To evaluate the effect of PF-07260437 on soluble B7-H4.	• Pre- and post-dose levels of soluble B7-H4 in serum.	• N/A

Dose Expansion (Part 2)

Objectives	Endpoints	Estimands
Primary		
• To assess safety and tolerability of PF-07260437 at the RDE in	• AEs as characterized by type, frequency, severity (as graded by	• Incidence of AEs estimated in the

Objectives	Endpoints	Estimands
participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or without biomarker selection.	NCI CTCAE v5 or CRS grading system) timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (graded by NCI CTCAE v5), and timing.	safety analysis population during the AE-evaluation period.
Secondary		
• To assess irAEs of PF-07260437 at the RDE in participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or without biomarker selection.	• irAEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5) timing, seriousness, and relationship to study therapy.	• N/A
• To evaluate preliminary antitumor activity of PF-07260437 at the RDE in participants with advanced or metastatic HR+ HER2- BrCa and TNBC with high B7-H4 expression or no biomarker selection.	• ORR, as assessed by investigator based on RECIST v1.1 and irRECIST. • DOR as assessed by investigator based on RECIST v1.1 and irRECIST. • PFS as assessed by investigator based on RECIST v1.1 and irRECIST. • TTP as assessed by investigator based on RECIST v1.1 and irRECIST. • OS.	• N/A
• To further evaluate the serum PK of PF-07260437 at RDE.	• PK concentration of PF-07260437 at selected time points.	• N/A
• To further evaluate immunogenicity of PF-07260437.	• Incidence and titers of ADA and NAb against PF-07260437.	• N/A
• To evaluate immune cells in pre and/or post treatment tumor biopsies.	• Phenotypes, and quantity of TIL before and after PF-07260437 treatment (eg, CD3, CD8, Granzyme B, Ki67 IHC).	• N/A
Tertiary/Exploratory		
• To explore cytokine and chemokine PD markers in pre- and on-treatment serum samples.	• Changes in pre- and on-treatment cytokine and chemokine markers in serum sample.	• N/A
• To evaluate T, B, and NK subtypes for immunophenotyping in addition to T cell proliferation and activation markers in whole blood.	• Changes in subtypes of immune cell, activation, and proliferation markers on T cells.	• N/A
• To explore additional biomarkers in tumor biopsies, whole blood, and serum samples to predict response to therapy and to understand resistance mechanisms that may predict escape from therapy.	• Biomarkers from genomic, transcriptomic, and/or protein profiling from tumor, blood, serum or plasma and their relationship to clinical outcome.	• N/A
• To evaluate the effect of PF-07260437 on soluble B7-H4.	• Pre- and post-dose levels of soluble B7-H4 in serum.	• N/A

4. STUDY DESIGN

4.1. Overall Design

This is an open label, multi-center, first-in-human Phase 1 dose escalation and dose expansion study to evaluate the safety, tolerability, PK, PD, and preliminary antitumor activity of PF-07260437, a B7-H4 x CD3 bispecific mAb, in advanced or metastatic selected solid tumors (BrCa, OvCa, and endometrial cancer). This study contains 2 parts, dose escalation (Part 1) and dose expansion (Part 2). The overall study design is depicted in the Schema.

Part 1 contains dose escalation in participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer that is resistant or intolerant to standard therapy or for whom no standard therapy is available, to determine the MTD and select the RDE. Participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from sponsor.

Participants will receive escalating doses of PF-07260437 administered as SC injection with a starting dose level of 100 µg Q2W as monotherapy. Additional dosing frequency such as Q1W or Q3W may be considered if supported by emerging clinical PK, PD, and safety data. BLRM guided by EWOC principle will be used to guide the dose escalation process and determine the MTD/RDE. The maximum allowable PF-07260437 dose increment is 200% (dose tripling from the previous dose level) for cohorts but will be adjusted to no more than 100% (dose doubling from the previous dose level) following the observation of a DLT or if there are two Grade $\geq$2 clinically significant treatment-related AEs. For monotherapy without priming strategy, DLT will be assessed during the first 28 days. For monotherapy with priming, the DLT assessment period will extend to include priming doses plus 2 full doses (eg, first 42 days). Each dose level group will include approximately 3 participants, with at least 1 DLT evaluable participant per cohort in the first 2 cohorts and at least 2 DLT evaluable participants per dose level group in the remaining cohorts for Part 1. Per BLRM design, expanding additional participants at lower dose levels are allowed to assess safety.

The SC route has the potential to reduce the C_{max} which is believed to be associated with CRS and inflammatory responses, a common AE for bispecific antibodies. Depending on emerging PK and safety data, IV administration may be investigated during dose escalation after the discussion between investigators and sponsor and approval from sponsor.

Based on the MoA and preclinical toxicology studies, PF-07260437 has the potential to cause CRS and irAEs. The following measures will be taken in order to minimize the risk in study participants:

- A staggered enrollment strategy will be applied for participants entering Part 1 cohort 1. Each participant dosed will be observed for at least 48 hours to ensure no acute safety concerns before dosing the next participant in cohort 1.
- Prophylactic premedication is not allowed during the DLT evaluation period during initial dose escalation. However, if the participant experiences an infusion related

reaction (IV), allergic reaction, significant injection site reaction, CRS, fever/chills, allergic reaction, nausea/vomiting, hypotension, or pain, appropriate treatment should initiate and premedication as prophylaxis may be considered for subsequent injections as well as for new participants. (See Section 6.1.1.1).

- Dose escalation cohorts may be switched from SC administration to IV administration if SC administration is not considered as the preferred route due to severe skin toxicities, low PK exposure or other reasons. IV administration cohorts may initiate at a dose level that is no greater than 20% of the highest SC dose level that is deemed tolerable (eg, starting at 60 µg IV Q2W if 300 µg SC Q2W is deemed tolerable) depending on emerging PK and safety data.
- **Priming Dose:** A priming dose approach in the next dose level may be initiated if a dose level induces ≥ Grade 2 CRS (lasting for >24 hours) occurs in >1 participant despite treatment with tocilizumab and/or vasopressors. Initially, a single priming dose may be administered on C1D1 at 1 dose level below the dose level in which the recurrent ≥ Grade 2 CRS event was observed. The first full dose will be administered on C1D15 with a starting full dose that is not higher than the full dose at which the recurrent ≥ Grade 2 CRS event occurred. Depending on the observed safety and tolerability profile, dose escalation of the full dose may proceed with full dose increased by a maximum of 200%. If ≥ Grade 2 CRS is observed after the administration of full doses, a 2 (or more) step-up priming dose approach may also be implemented (for example, 2 priming doses administered on C1D1 and C1D8, respectively); the initial priming dose will be at a dose level where predicted probability of ≥ Grade 2 CRS is <20%. In addition, dose finding without priming may still continue in parallel if MTD without priming has not been reached and RDE without priming has not been determined. Finally, additional priming dose strategies (eg, additional doses, different dosing levels and intervals) may be investigated based on emerging data.

  All Part 1 participants in cohorts without a priming dose will be observed inpatient for at least 48 hours after the first SC dose (or the first IV dose, as applicable) on C1D1 and for at least 8 hours after the second SC dose (or the second IV dose, as applicable) on C1D15. Participants in cohorts with a priming dose will be observed inpatient for at least 24 hours after the first SC priming dose (or the first IV priming dose administration, as applicable) on C1D1 and 24 hours after the second (full) dose on C1D15 (Table 7). Modification of inpatient observation period might be allowed based on emerging safety data and will require discussion and agreement between investigator and sponsor.

- Participants who experience Grade ≥3 infusion-related adverse events (IV administration) or clinically significant cytokine release syndrome must be hospitalized for at least 24 hours for at least 4 doses subsequently (two cycles). If subsequent doses are tolerated without recurrence of Grade ≥3 infusion-related adverse events or clinically significant cytokine release syndrome, outpatient PF-

07260437 administration during clinical visits may be resumed after agreement between investigator and sponsor.

- Participants should be observed for at least 1 hour post dose for all outpatient visits starting with C2D1 in both cohorts until the investigator has confirmed the participant has not exhibited signs of CRS (Table 7).

- Participants will undergo a telephone follow-up at 90 days (±7 days) after the last dose of PF-07260437 to assess potential late irAEs. If any concern arises, the participant should be contacted for an in-person follow-up visit.

Dose escalation will continue until MTD has been reached (if an MTD is identified) and the RDE has been determined. At that time, if the dose escalation has reached the MTD and a priming dose has not been previously incorporated to the dose regimen, a priming dose escalation cohort to minimize C_{max} may be initiated based on clinical safety, PK/PD, and clinical efficacy. The same approach to priming as described above will be utilized. Priming dose escalation cohorts will continue until MTD with priming has been reached (if an MTD is identified) and the RDE with priming has been determined. Depending on emerging safety data, a 2 (or more) step-up priming dose approach may also be implemented as described above.

The DLT period for SC or IV dosing without priming will be 28 days. The DLT period with priming will extend to include the duration of the priming doses and 2 full doses after priming. (eg, if a priming dose is given on Day 1 and the first full dose on Day 15, the total DLT observation period will be 42 days). A traditional 2-parameter BLRM will be used to model the DLT relationship to the drug and inform dose escalation with or without priming. The maximum dose level increase will be 200% (dose tripling from the previous dose level).

Approximately 35 participants are expected to be enrolled into 1 of 5-7 sequential dose levels in Part 1 including at least 6 participants treated at the MTD. The actual number of participants enrolled will depend on the tolerability of PF-07260437 and the number of dose levels that are required to determine MTD/RDE.

Once the PF-07260437 monotherapy RDE is selected, either with or without priming, Part 2 dose expansion cohorts may be initiated to further evaluate the safety and preliminary antitumor activity of PF-07260437 monotherapy in advanced or metastatic 2L+ HR+ HER2- BrCa with high B7-H4 expression (Part 2A) and 2L+ TNBC with high B7-H4 expression (Part 2C) as well as unselected HR+ HER2- BrCa or TNBC (Part 2B).

Approximately 60 participants are expected to be enrolled into Part 2.

The Part 2 dose expansion phase will enroll participants into 3 cohorts detailed as follows:

- **Part 2A (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1 line of standard of care endocrine

treatment. De novo paired pre- and on-treatment biopsies are mandatory for 5 participants.

- **Part 2B (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1L of standard of care endocrine treatment, or 2L+ TNBC who have progressed after at least 1 line of SOC systemic therapy (eg 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1+ or chemotherapy alone if PD-L1 negative/low). Approximately 10 HR+ HER2- BrCa and approximately 10 TNBC participants should be enrolled. De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 HR+ HER2- BrCa and 5 TNBC participants. No biomarker selection based on B7-H4 expression.
- **Part 2C (N=20):** PF-07260437 as monotherapy in participants with TNBC showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of SOC systemic therapy (eg 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies will be mandatory for 5 participants.

Depending on the results of preclinical combination in vivo efficacy, emerging clinical monotherapy safety and efficacy data, PF-07260437 combination cohorts may be added, including combination with CDK4/6 inhibitor and/or endocrine therapies in HR+ HER2- BrCa and combination with immune checkpoint inhibitors in TNBC.

Participants in Part 2 will receive PF-07260437 at the RDE (with or without priming, based on results from Part 1). Depending on the evaluation of safety and PK data of the priming dose cohorts, Part 2 participants may be switched to a priming dose schedule determined from Part 1 dose escalation with priming. All Part 2 participants will be observed inpatient for at least 24 hours after the first SC dose on C1D1, and if a priming dose approach is used, participants will be observed for up to 24 hours after the first full dose on C1D15 (observation after additional priming doses if given will be based on emerging data). Participants may only be released after the investigator has confirmed the participant has not exhibited signs of CRS (Table 7).

Table 7. Inpatient Observation Stays for SC Administration

Part	Schedule	C1D1	C1D15	All other outpatient visits
1	Without Priming	Up to 48 hours	8 hours	1 hour
	With Priming	24 hours	24 hours	1 hour
2	With or Without Priming	24 hours	24 hours if priming is used; 8 hours without priming	At investigator's discretion

*The length and number of inpatient observation stays may be modified based on emerging data but in any case, participants may only be released after confirmation of the absence of clinically significant CRS.

If the 2 (or more) step-up priming doses approach is implemented, the observation period after the second priming SC dose on C1D8 will be determined based on emerging safety data and clinical investigator's assessment.

Please refer to Section 6.1 for general recommendation on inpatient observation stays for SC and IV administration as applicable.

Modification of inpatient observation period might be allowed based on emerging safety data and will require discussion and agreement between investigator and sponsor.

All participants will be required to provide archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a fresh biopsy during screening for both Part 1 dose escalation and Part 2 dose expansion. For 5 participants in each of Part 2A and 2C and for 5 HR+ HER2- BrCa participants and 5 TNBC participants in Part 2B, paired pre- and on-treatment biopsy samples will be mandatory. These biopsies will be to confirm the MoA, understand tumor-based pharmacodynamics and evaluate potential resistance mechanism during treatment.

All participants will undergo up to 28 days of screening prior to first dose. Eligible participants will then receive study intervention for up to 2 years, or until disease progression defined by irRECIST, unacceptable toxicities, a decision by the participant (withdrawal of consent or no longer willing to participate) or investigator to discontinue treatment, or study termination. Note: If a participant is classified as having PD during an on-treatment tumor assessment, then confirmation of PD by a second scan in the absence of rapid clinical deterioration is required per irRECIST (Appendix 13).

Any additional treatment beyond 2 years shall be discussed and approved by the sponsor. After EOT, all participants will complete a 28-day post-treatment follow-up visit for AEs. All participants will be contacted by telephone approximately 90 days post treatment to assess late irAEs. Participants in Part 2 dose expansion cohorts will be contacted by telephone approximately every 3 months for survival data collection until end of trial (2 years from last participant first dose), unless otherwise notified by the sponsor.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SOA including OS, if applicable. OS follow-up should not continue after end of the study (Section 4.4).

During treatment with study intervention, all cycles will be 28 days in length. Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicities, dosing may be interrupted, modified, or discontinued as described in Section 6.5 and 7.1.

4.2. Scientific Rationale for Study Design

PF-07260437 will be evaluated for the treatment of BrCa (and other malignancies, including uterine and OvCas). PF-07260437 addresses a significant unmet medical need for BrCa, as

its target B7-H4 is expressed in the majority of BrCas across all molecular subtypes (Leong et al, 2015). B7-H4, a member of the B7 family of proteins encoded by gene [redacted], has been shown to have wide expression in BrCa along with other gynecologic malignancies. In addition, its limited expression in normal tissues makes B7-H4 an appealing tumor-associated antigen for targeting BrCas with CD3 bispecific molecules.

PF-07260437 demonstrated binding to a panel of tumor cell lines that express B7-H4 protein and human T lymphocytes that express CD3. The bispecific molecule exhibited concentration-dependent binding across a panel of cancer cell lines with varying levels of endogenous B7-H4 expression, as well as concentration-dependent binding on a panel of human donor T cells. In the presence of T cells, PF-07260437 elicited CTL responses against a panel of cancer cell lines expressing B7-H4. In the absence of T cells, PF-07260437 did not affect tumor cell growth. In vivo, PF-07260437 demonstrated B7-H4 expression-dependent antitumor activity against a panel of cell line xenograft and patient derived xenograft breast tumors grown in immune-compromised mice that were implanted with human T cells. Tumor growth inhibition following PF-07260437 treatment was dose dependent.

The objective of the biomarker assessments in this study is to provide insight into the pharmacological effects of PF-07260437 on the tumor and immune system. The assessments will contribute to confirming target engagement and measuring T-cell activation. Evaluation of target expression and modulation of immune signatures associated with the mechanism of PF-07260437 will require the collection of recent archival and/or de novo pre-treatment and on-treatment biopsies to establish the association between B7-H4 expression, biomarkers, and response parameters to PF-07260437 as described in the SOA and the Laboratory Manual. Biomarker assessments are intended to elucidate potential resistance mechanisms to PF-07260437 and identify participants who are most likely to benefit from treatment

Banked biospecimens will be collected for exploratory/pharmacogenomic/genomic/ biomarker analyses and retained in the BBS, which makes it possible to better understand the in vivo MoA and potential mechanisms of resistance of the investigational product and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study. These studies may help in the future development of PF-07260437 as a single agent and may provide information on tumor subtypes that may respond to the study intervention.

The PK analyses would serve to characterize the PK of PF-07260437 in human and its relationship with various factors (eg, body weight). Further identification of the PK-PD and exposure-response relationship for efficacy, safety, and the relevant biomarkers would guide the dose selection in subsequent trials.

4.2.1. Hormone Receptor (ER and/or PR) Positive BrCa

BrCa is the most common noncutaneous cancer in women with over 275,000 new cases expected to be diagnosed in the US in 2020. Approximately 70%-80% of new BrCas express the estrogen and/or progesterone receptor. Patients with advanced or metastatic HR-positive tumors benefit from hormonal therapy and CDK4/6 inhibitors. In addition, recently Alpelisib

was approved by FDA in treating advanced or metastatic HR+ HER2-, PIK3CA-mutant BrCa after an endocrine-based regimen. However, most patients develop resistance to these therapies, and all are associated with significant toxicities. Therefore, there remains an urgent need to identify new treatments.

4.2.2. Triple Negative BrCa

TNBC accounts for 15% of BrCas and is associated with poor long-term outcomes. Compared with other BrCa subtypes, TNBC affects younger women, is more frequent in black and Hispanic women and shows higher prevalence of germline BrCa mutation. TNBC is usually high grade, shows shorter time to relapse and higher risk for visceral metastases (Sharma, 2016).

The lack of ER, PR and HER2 expression precludes the use of targeted therapies in TNBC (Costa et al, 2019). Systemic therapy regimens for advanced or metastatic TNBC include taxanes as single agents or in combination with anthracyclines, platinum, or gemcitabine. A pooled analysis of Phase 3 trials in the first-line setting showed ORR of 23%, median PFS of 5.4 months and median OS of 17.5 months. Recently, FDA has granted accelerated approval to combine checkpoint inhibitors (Pembrolizumab and Atezolizumab) with chemotherapy as first-line therapy in PD-L1 positive advanced or metastatic TNBC. Most recently, FDA has granted regular approval to sacituzumab govitecan for patients with unresectable locally advanced or metastatic TNBC who have received 2 or more prior systemic therapies, at least one of them for metastatic disease. In addition, talazoparib and olaparib have been approved by FDA in treating germline BrCa mutant HER2-negative advanced or metastatic BrCa. However, none of these therapies is curative, and all are associated with significant toxicities. Therefore, new therapies for mTNBC are urgently needed.

Preclinically, PF-07260437 has demonstrated B7-H4 expression-dependent antitumor activity against HR+ HER2-, HER2+, and TNBC molecular subtype cell line xenograft and patient-derived xenograft breast tumors grown in immune-compromised mice that were implanted with human T cells. PF-07260437 treatment did not show antitumor efficacy in a model that does not express B7-H4.

These data provide rationale for exploring potential use of PF-07260437 in HR+ HER2- BrCa and TNBC.

4.2.3. Diversity of Study Population

Part 1 of the study will enroll adult participants with locally advanced or metastatic solid tumors including BrCa, OvCa and endometrial cancer. Adult participants with other B7-H4 expressing tumors may be included after discussion with and approval from sponsor. Part 2 will enroll participants with HR+ HER2- BrCa and TNBC with high B7-H4 expression and a cohort of 20 participants with HR+ HER2- BrCa or TNBC not selected for B7-H4 expression.

4.2.4. Dose Level Review

The determination of safety for each dose level with or without priming will be based on the discussion by the safety review team, comprised of the investigators and the sponsor. In addition, Pfizer will conduct unblinded data reviews during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling or supporting clinical development.

4.2.5. Choice of Contraception/Barrier Requirements

Studies to evaluate the development toxicity of PF-07260437 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.6. Collection of Retained Research Samples

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

4.3. Justification for Dose

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Starting Dose

4.3.1.1. Subcutaneous Administration

The starting dose will be 100 µg SC Q2W in 28-day cycles. The selection of the starting dose for this study was based on the MABEL in accordance with the ICH S9 Guidance, given that PF-07260437 is a bispecific T cell-engaging agent with immune agonistic properties. The 100 µg Q2W SC starting dose is predicted to result in minimal biological effect considering in vitro cytokine release and cytotoxicity experiments.

The in vitro biological activities for PF-07260437 were determined via cytotoxicity and cytokine release assays. The EC_{50} value from the most sensitive in vitro assay was 0.062 nM. With a starting dose of 100 µg Q2W, the predicted PF-07260437 C_{max} after single dose, assuming 70% bioavailability from the SC route, is 9.2 ng/mL (0.063 nM), which is similar to the EC_{50} (0.062 nM) of the most sensitive in vitro assay. Since C_{max} is believed to be associated with CRS and inflammatory responses, the blunted C_{max} offered by SC route is expected to increase the patient tolerability.

In addition, the proposed MABEL starting dose is lower compared to the 1/6 of HNSTD (1100 µg assuming 70 kg body weight) determined in the GLP 1-month toxicology study (0.3 mg/kg/week SC) in cynomolgus monkeys.

In summary, the proposed MABEL starting dose of 100 µg Q2W via the SC route is expected to result in minimal biological effect and to provide an adequate safety margin.

4.3.1.2. Alternative Intravenous Administration

If PK and safety data suggest that SC route is not a viable approach (eg, very low SC bioavailability or intolerable ISR), IV administration may also be evaluated in subsequent dose cohorts. To provide sufficient safety margin, the IV starting dose will be 20% of the highest safe/tolerable SC dose with assumption of 2.5 L of plasma volume for IV administration. For example, if the 300 µg SC dose level is deemed tolerable, the IV starting dose will be 60 µg. Notably, in the absence of any clinical safety data from SC dosing, the MABEL approach would yield an IV starting dose of 23 µg as the predicted C_{max} is similar to the EC_{50} value from the most sensitive in vitro assay (0.062 nM). While it is not feasible to administer this IV dose of 23 µg based on the current formulation (with a lowest feasible IV dose of 45 µg), the IV route will not be potentially implemented until a SC dose level of ≥300 µg. Therefore, the lowest possible IV dose is 60 µg, which is expected to provide similar exposure coverage with 300 µg at SC dose level 2 (see Table 8).

In addition, the HNSTD was 0.1 mg/kg/week from the IV arm of the GLP 1-month toxicity study in cynomolgus monkeys. This yielded an IV starting dose of 376 µg (1/6 HNSTD assuming 70 kg body weight in humans), which is higher than our provisional IV starting dose of 60 µg.

If IV route is evaluated, inpatient monitoring in a hospital for at least 48 hours after the first dose in Cycle 1 in dose escalation will be implemented as described in Section 6.1. Additional inpatient observation for subsequent cycles beyond Cycle 1 may be considered based on the investigator's discretion and should be discussed with the sponsor.

4.3.2. Justification for Priming Dose Regimen

Priming dose approaches are commonly applied for T-cell engager bispecific modalities to initially sensitize the immune system at lower doses to reduce rate and grade of CRS (Costa et al, 2019; Garfall, 2020; Madduri et al, 2020; BLINCYTO (blinatumomab), 2021). A priming dose approach may be initiated if a dose level induces ≥ Grade 2 CRS (lasting for >24 hours) occurs in >1 participant despite treatment with tocilizumab and/or vasopressors. Initially, a single priming dose will be administered on C1D1 at 1 dose level below the dose level whereby the ≥ Grade 2 CRS event was observed. The first full dose will be administered on C1D15 with a starting full dose that is 100% higher than the priming dose. Depending on the observed safety and tolerability profile, dose escalation on the full dose may still proceed with up to 3-fold increment from current full dose level. If ≥ Grade 2 CRS is observed after the administration of full doses, a 2 step-up priming doses approach may also be implemented with the 2 priming doses administered on C1D1 and C1D8, respectively; both priming doses will be at dose levels where predicted probability of ≥ Grade 2 CRS is <20%.

4.3.3. Fixed Dosing Approach

A fixed-dose approach will be applied for the FIH study of PF-07260437 given that fixed dosing approach was shown to provide similar PK variability compared to a body-weight adjusted dosing for monoclonal antibodies, therapeutic peptides, and proteins (Wang et al,

2009; Zhang et al, 2012; Hendrikx et al, 2017). In addition, fixed dosing offers ease of preparation and less chance of dosing errors.

4.3.4. Dosing Interval (Q2W)

The Q2W dosing frequency of PF-07260437 in this study was selected based on the projected $t_{½}$ of 15 days in humans. Based on emerging PK, PD, and safety data, regimens with alternative dosing frequencies (eg, weekly administration, or Q4W) may also be considered.

4.3.5. Criteria for Dose Escalation

BLRM guided by the EWOC principle will be used in dose escalation. See Table 8 and Appendix 9 for more details on the model. Using DLT data at all tested dose levels and prespecified prior distribution of model parameters, posterior probabilities of probability of having a DLT falling into 3 dosing intervals (underdosing, target dosing, overdosing) will be calculated for all dose levels. A dose may only be used for newly enrolled participants if the risk of excessive toxicity, ie, toxicity higher than 0.33 at that dose is less than 25%.

Typically, participants will be enrolled in cohorts of approximately 3 participants with at least 1 DLT evaluable participant in the first dose level in Part 1 without a priming dose and 2 DLT evaluable participants at all other dose levels in Part 1 with or without a priming dose. The maximum dose increases from the previous dose levels for regimen will be up to 200% (dose tripling from the previous dose level) but will be adjusted to no more than 100% (dose doubling from the previous dose level) following the observation of a DLT or if there are two Grade ≥2 clinically significant treatment-related AEs.

The provisional dose levels to be evaluated are listed in Table 8.

Table 8. Provisional Dose Levels in Dose-Escalation (SC Administration)

Dose Level[a]	Dose (µg)
-1 (if applicable)	60
1[b]	100
2	300
3	900
≥4	Escalation to continue to MTD or desired pharmacologic activity

a. Intermediate doses may be evaluated based on clinical findings. Maximum 3-fold increment (dose tripling) at each dose level.

b. If the 100 µg SC Q2W dose is not tolerated, then a lower dose of 60 µg Q2W via SC route will be evaluated.

Dose escalation will stop when stopping criteria are met (see Appendix 9). According to the stopping criteria, at least 6 participants will be evaluated at the MTD.

Intra-participant dose escalation to the next dose level may be considered in consultation with the sponsor for participants(s) enrolled in the first dose level with the following conditions: 1) have cleared the DLT period in the dose escalation phase, 2) the next immediate higher dose level is safe in all participants with no DLTs, and 3) a period of a minimum of 2 cycles after the DLT observation period with the next immediate higher dose level has confirmed there are no clinically significant toxicities.

Stopping criteria:

The sponsor estimates that the maximum number of participants in the Part 1 dose escalation portion of the trial is 40 participants. However, the actual number may be more or less based on observed PK and safety. The dose escalation will stop when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD or RDE.
- The dose d for PF-07260437 satisfies 1 of the following conditions for the mono-escalation part:
    - The probability of target toxicity at dose d exceeds 50%, ie, Pr (0.16 $\leq \pi d < 0.33) \geq 50\%$, or
    - A minimum of 15 participants have been treated in Part 1.

4.3.6. Dose Limiting Toxicity (DLT) Definition

A participant is classified as DLT evaluable if they either 1) receive all the planned doses of the study intervention and have received all scheduled safety assessments during the DLT observation period or 2) have experienced a DLT. If a participant fails to meet these criteria, they may be replaced. The sole exception to criterion 1) is if the participant has missed a minority of safety assessments due to emergency situations (eg, site accessibility issues, inability to go to an external lab, etc). In such cases, the Dose Level Review Committee may judge the participant evaluable, depending on the abundance of the available data.

DLT observation period: For the purpose of dose escalation, the DLT observation period for SC or IV dosing without priming will be 28 days including laboratory results obtained on the morning of Day 29 in each participant. The DLT period for dosing with priming will extend to include the duration of priming doses and 2 full doses (eg, if a single priming dose is administered 2 weeks prior to the first full dose, the DLT evaluation period will be 42 days (14 days plus 28 days) including laboratory results obtained on the morning of Day 43 (C2D15).

Any of the following treatment-related AEs occurring during the DLT observation period that in the opinion of the investigator cannot be reasonably attributed to the participant's underlying disease, concomitant medications or preexisting conditions are considered DLTs. Severity of AEs will be graded according to CTCAE version 5.0, with the exception of CRS, which will be graded according to the ASTCT CRS Consensus Grading for CRS (Appendix 11). For those events involving a worsening of a baseline abnormality, a DLT must represent a clinically significant (in the opinion of the Investigator after discussion with the sponsor) shift from baseline.

4.3.6.1. Hematological DLTs

- Grade 4 neutropenia
- Febrile neutropenia, defined as ANC <1.0 x 10^9/L [<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 neutropenia lasting >7 days;
- Grade 3 neutropenia with infection;
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion
- Grade 4 anemia
- Grade 3 anemia requiring blood transfusion.

4.3.6.2. Non-Hematologic DLTs

Any treatment-related Grade ≥3 non-hematologic toxicity (see below for specifications applying to special circumstances):

- Hepatic toxicity:
  - Clinical events consistent with Hy's Law, ie,
    - ≥3-fold elevations above the ULN of ALT or AST AND;
    - >2x ULN elevation of serum total bilirubin without alternative explanation (eg, cholestasis or Gilbert's syndrome) AND;
    - Absence of initial findings of cholestasis (eg, elevated serum ALP) AND;
    - Absence of other reason(s) to explain the combination of increased AT and TBili, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.
  - For participants with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level >10 times the ULN.
- Grade ≥3 fatigue lasting ≥5 days.
- Grade ≥3 nausea/vomiting or diarrhea lasting ≥3 days despite adequate antiemetic and other supportive care.
- Grade ≥3 CRS of any duration.
- Grade ≥3 QTcF prolongation (Repeat testing, re-evaluate by a qualified person, and correct reversible causes (such as electrolyte abnormalities or hypoxia). If, after

correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event should be considered a DLT).

- A treatment-related AE inducing a delay by >2 weeks in receiving the next scheduled cycle.
- Grade ≥3 anaphylaxis.
- Any Grade 5 AE (death) not clearly due to either the underlying disease or other etiologies.

In addition, irAEs that meet the following criteria will be considered as DLTs:

- Any Grade 4 irAE regardless of duration, any ≥ Grade 4 colitis regardless of duration;
- Any Grade 3 or Grade 4 non-infectious pneumonitis regardless of duration;
- Any Grade 3 irAE, excluding colitis and pneumonitis, that does not start downgrading to ≤ Grade 2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or dose not downgrade to ≤ Grade 1 or baseline within 14 days;
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.

4.3.6.3. Other DLTs

Clinically important, persistent (eg, responsible for significant dose delay) toxicities that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor. All DLTs need to represent a clinically significant shift from baseline.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade 3 amylase or lipase elevation not associated with clinical symptoms or clinical manifestations of pancreatitis. Grade 3 endocrinopathy not controlled by hormonal replacement.

4.3.7. Late Toxicity Definition and Management

Significant AEs considered to be related to the study intervention or treatment under investigation that occur after the DLT observation period will be reviewed in the context of all available safety data.

The details of the potential late onset toxicity will be reviewed during dose level review meetings to inform decisions about enrollment and dosing (eg, dose level increments, determination of the dose(s) used beyond dose escalation, regimen). Late onset toxicities that meet the definition of DLT will be considered in the evaluation of the MTD, Phase 1 RDE and/or RP2D, as appropriate.

The option for dose reduction will be discussed with any given participant that is on-treatment at dose levels that are subsequently considered to be above the MTD. If a participant tolerated the above-MTD dose level well and is benefiting from therapy, continuation of treatment at the above-MTD dose level will require re-consenting.

4.3.8. Maximum Tolerated Dose (MTD) Definition

MTD is defined as the highest dose with true DLT rate within the target toxicity interval. The target interval for the DLT rate is defined as 0.16, 0.33.

The safety of each cohort will be assessed by a Dose Level Review Committee, which is composed of sponsor representatives and the Investigators. The Committee will consider all relevant clinical data, including safety, PK, efficacy, and PD in making decisions such as whether to dose escalate, dose de-escalate, dose level increments, expand cohorts, and declare MTD.

4.3.9. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further investigation based on Phase 1 study results. The RDE is the dose chosen for further investigation based on Part 1 dose escalation results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of participants, then this dose becomes the RDE. However, RDE might be lower than the MTD. Safety, efficacy, and PK data as well as potential exposure-response relationships will be considered in identifying the RDE. After expansion cohorts with larger sample size and sufficient data, the final "Study" RP2D will be determined by the sponsor based on the recommendation from investigators and study team. The determination of "Study" RP2D will be based on safety, tolerability and early signs of clinical efficacy and benefit from both Part 1 dose escalation and Part 2 expansion.

The dose(s) selected for use in the expansion cohorts will be referred to as the Phase 1 Expansion Dose(s).

4.4. End of Study Definition

The end of the study is defined as 2 years from the last participant's first dose unless otherwise notified by the sponsor.

Accrual may be halted and a thorough safety analysis will be conducted and submitted to FDA in the event of significant safety concerns (eg, one Grade 5 SAE or two Grade 4 events considered at least possibly related to PF-07260437).

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last scheduled procedure shown in the SOA which for Part 1 is the 4-week follow-up visit and for Part 2 is the OS follow-up.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants ≥18 years.
    a. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Primary disease:

    Part 1: Histological or cytological diagnosis of locally advanced or metastatic BrCa, endometrial cancer and OvCa that is resistant to standard therapy or for which no standard therapy is available. Participants with other advanced or metastatic solid tumors with high B7-H4 expression may be considered after discussion with and approval by sponsor. Similarly, those participants with other advanced or metastatic solid tumors should be resistant to standard therapy or have no available standard therapy.

    Part 2A: 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic HR+ HER2- BrCa showing high B7-H4 expression (see Section 8.6.2.1) who have progressed after at least 1 line of SOC CDK4/6 inhibitor and 1 line of SOC endocrine treatment. De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 participants.

    Part 2B: 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic HR+ HER2- BrCa who have progressed after at least 1 line of SOC CDK4/6 inhibitor and 1L of SOC endocrine treatment, or 2L+ TNBC who have progressed after at least 1L of SOC systemic therapy (eg, 1L chemotherapy in

combination with a checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 HR+ HER2- BrCa and 5 TNBC participants. No biomarker selection based on B7-H4 expression is needed for Part 2B.

Part 2C: 2L+ participants with histological or cytological diagnosis of locally advanced or metastatic TNBC showing high B7-H4 expression (see Section 8.6.2.1) who have progressed after at least 1L of SOC chemotherapy and 1 line of SOC systemic therapy (eg, chemotherapy in combination with a checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 participants.

4. Participants have at least 1 measurable lesion as defined by RECIST version 1.1 that has not been previously irradiated. For Part 1 dose escalation, participants with metastatic HR+ HER2- breast cancer with non-measurable but evaluable disease may be eligible after discussion with and approval from the sponsor.
5. Participants must be able to provide archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a fresh biopsy during screening. 10 participants enrolling in Part 2B, and 5 participants enrolling in each of Parts 2A and 2C must agree to paired pre- and on-treatment biopsies. Ability of a participant to undergo biopsy safely should be determined during screening. Exceptions that biopsies cannot be obtained due to safety risk should be discussed and approved by the sponsor.
6. Participants with HR+ HER2- advanced or metastatic BrCa must have:
   a. Documentation of ER or PR-positive tumor (≥1% positive stained cells) based on most recent tumor tissue utilizing an assay consistent with local standards and ASCO/CAP guidelines (Allison et al, 2020)
   b. Documentation that tumor is HER2-negative as determined by IHC score of 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4, consistent with ASCO/CAP guidelines (Wolff et al, 2018).
7. Participants with TNBC must have documentation that tumor tissue is negative (<1% cells with nuclear positivity) for ER and PR as well as negative for HER2 as determined by IHC score of 0/1+ or negative by ISH (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4, consistent with ASCO/CAP guidelines (Wolff et al, 2018; Allison et al, 2020).

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion criteria:

9. ECOG PS 0 or 1.

10. Adequate Bone Marrow Function, defined as:

    a. ANC $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L;

    b. Platelets $\geq$100,000/mm^3 or 100 x 10^9/L;

    c. Hemoglobin $\geq$9 g/dL.

11. Adequate Renal Function, as follows:

    a. Serum creatinine $\leq$1.5 x ULN) or estimated CrCl $\geq$50 mL/min as measured or calculated using the Cockcroft Gault formula below:

       - Female CrCl = [(140 - age in years) x weight in kg x 0.85]/ [72 x serum creatinine in mg/dL];
       - Male CrCl = [(140 - age in years) x weight in kg x 1.00]/ [72 x serum creatinine in mg/dL];

    b. If an estimated CrCl is believed to be inaccurate for a participant, 24-hour urine collection with actual assessment of CrCl is allowed.

12. Adequate Liver Function, defined as:

    a. Total bilirubin $\leq$1.5 x ULN unless the participant has documented Gilbert's syndrome;

    b. AST and ALT $\leq$2.5 x ULN; $\leq$5.0 x ULN if there is liver involvement by the tumor;

    c. Alkaline phosphatase $\leq$2.5 x ULN ($\leq$5 x ULN in case of bone or liver metastasis).

13. Participants with brain metastases must meet all the following conditions:

    a. Have completed their planned course of treatment;

    b. Have recovered from the acute effects of radiation therapy or surgery prior to first dose;

    c. Have discontinued corticosteroid treatment for these metastases for at least 4 weeks;

    d. Have been on stable doses of anti-seizure medications (if applicable) for at least 3 months. Antiseizure medications must meet any eligibility criteria outlined for concomitant medications.

    e. Are neurologically stable for 3 months since the conclusion of therapy, as documented by both neurologic and MRI examinations.

f. Participants who are diagnosed with a CNS metastasis during the screening period must also meet these criteria.

14. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE Grade ≥1 (except for AEs not constituting a safety risk in the investigator's judgment).

15. TSH WNL for institution; supplementation is acceptable to achieve a TSH WNL; in participants with abnormal TSH if Free T4 is WNL and participant is clinically euthyroid, participant is eligible.

16. Negative serum or urine pregnancy test for women of childbearing potential at screening and at C1D1 (before the patient may receive the investigational product).

17. Male patients who are able to father children, and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 5 months after the last dose of assigned treatment.

18. Female patients who are not of childbearing potential as defined below, are eligible to be included (ie, meet at least 1 of the following criteria):
    a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    b. Have medically confirmed ovarian failure; or
    c. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; a serum FSH level within the laboratory's reference range for postmenopausal women.
    d. 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 any other active malignancy within 3 years prior to enrollment. Participants with secondary malignancy that had been adequately treated, or indolent tumors that would not interfere with safety and efficacy assessments might be allowed after discussion with and approval from the sponsor.

2. Participants with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including participants with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement). Note: Participants with indwelling

catheter for drainage, or requirement for drainage no more frequently than monthly will be allowed.

3. Clinically important (eg, 150/90 mmHg) hypertension despite optimal medical therapy.

4. Known or suspected hypersensitivity to PF-07260437 or excipients.

5. History of Grade ≥3 immune mediated AE (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co stimulatory agents, etc.) and required immunosuppressive therapy within 1 year of treatment. Participants with Grade 2 hypothyroidism or hypopituitarism resulting from immunotherapy on stable hormone replacement therapy and participants with chronic adrenal insufficiency receiving doses <10 mg/day of prednisone equivalents are eligible.

6. Prior irradiation to >25% of the bone marrow (see Appendix 10, Bone Marrow Reserve in Adults).

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

Prior/Concomitant Therapy:

8. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8, Concomitant Therapy.
9. Therapeutic anticoagulation with high bleeding risk or active bleeding.
10. Systemic anti-cancer therapy chemotherapy or endocrine therapy within 4 weeks or 5 half-lives (whichever is shorter) prior to first dose (6 weeks for mitomycin C or nitrosoureas). If the last immediate anticancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 3 weeks or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required.

11. Requirement for systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)]. Inhaled, intranasal, intraocular, intraarticular, and topical corticosteroids are allowed.

12. Major surgery within 3 weeks prior to first dose or during the study. Minor surgery may be allowed after consultation with and approval from sponsor.

13. Radiation therapy within 3 weeks prior to first dose or during the study. Palliative radiation to a limited field may be allowed after consultation with and approval from sponsor.

Blood product support:

14. Requirement for periodic blood product transfusions for a chronic condition. Blood product transfusions for transient and reversible cytopenias that are secondary to prior anti-cancer treatment are allowed after discussion with the sponsor.

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving investigational drug(s) within 3 weeks or 5 half-lives (whichever is shorter) prior to first dose. A participant may be eligible even if they are in the follow-up phase of an investigational study as long as they haven't received treatment in the study for 4 weeks of 5 half-lives prior to first dose.

Diagnostic Assessments:

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

17. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, COVID-19/SARS-CoV2, and known HIV or AIDS-related illness. Comments regarding specific circumstances follow:
    a. COVID-19/SARS-CoV2: This protocol excludes patients with active infections, as noted above. While SARS-CoV2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a patient has a positive test result not from prior COVID vaccination but from SARS-CoV2 active infection (not from prior vaccination but from active infection), is known to have asymptomatic infection or is suspected of having SARS-CoV2, he/she is excluded. COVID-19 vaccine administration relative to the dosing of study drug on planned C1D1 is at the discretion of the investigator although it may be best to avoid administration the 7 days prior to C1D1 and consider the potential for vaccine-related adverse events.
    b. HIV: In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes could be considered eligible. Potential eligibility for a specific HIV positive protocol candidate should be evaluated and discussed with the sponsor prior to any screening, based on current and past CD4 and T cell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. Healthy HIV positive participants who are included should be treated using the same standards as trial participants with other comorbidities.

c. HBV/HCV: Relevant laboratory tests should be performed at screening, see table in Appendix 2. Refer to CDC website (https://www.cdc.gov/hepatitis/index.htm) for further details.

d. HBV:

- This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis).
- However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.
- Patients with positive anti-HBcAb but negative HBsAg and anti-HBsAb profile may, depending on clinical circumstances, be eligible. Discussion with the sponsor is indicated. Patients whose clinical history and profile suggest either low level chronic infection or resolving acute infection should not be considered eligible.

e. HCV:

- Positive HCV antibody is indicative of infection but may not necessarily render a potential candidate ineligible, depending on clinical circumstances. Discussion with the sponsor is indicated. If exposure to HCV is recent, HCV antibody may not have yet turned positive. In this circumstance it is recommended to test for HCV RNA. Refer to CDC website for further details (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).

18. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF>470 ms, complete LBBB, signs of an acute or indeterminate age- myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second or -third-degree AV block, or serious brady arrhythmias or tachyarrhythmias). If the baseline uncorrected QTcF is >470 ms, this interval should be rate corrected using the Fridericia method and the resulting QTcF- should be used for decision making and reporting. QTcF exceeds 470 ms, or QRS complex exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS complex values should be used to determine the participant's eligibility. Computer interpreted-ECGs should be over-read by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with the sponsor to judge eligibility.

19. Any of the following in the previous 6 months: myocardial infarction, long QT syndrome, Torsade de Pointes, clinically important atrial or ventricular arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, bifascicular block [defined as right bundle branch and left anterior or posterior hemiblock], 3rd degree AV block), unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, New York Heart Association Class III or IV, cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of

thrombo-embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE ≥ Grade 2, atrial fibrillation of any grade (≥ Grade 2 in the case of asymptomatic lone atrial fibrillation). If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible. Participants with cardiac rhythm device/pacemaker must be discussed in detail with the sponsor to judge eligibility.

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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, up to a limit of 1 time.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to investigational product.

6.1. Study Intervention(s) Administered

Intervention Name	PF-07260437	
Arm Name (group of participants receiving a specific treatment (or no treatment)	All	
Type	Biologic	
Dose Formulation	Powder for solution for injection	Solution for injection
Unit Dose Strength(s)	15 mg/vial	15 mg/mL, 1 mL per vial
Dosage Level(s)	Dose amount and frequency – reference the study scheme/figure or text below as appropriate	
Route of Administration	SC or IV	
Use	Experimental	
IMP or NIMP	IMP	
Sourcing	Provided centrally by the sponsor. Reference IP manual for supply distribution process details.	
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. Study intervention will be provided as open-label product.	
Current/Former Name(s) or Alias(es)	PF-07260437, B7-H4 bispecific antibody	

Each single-use vial of liquid formulation contains 1 mL of PF-07260437 15 mg/mL. The vial is sealed with a coated stopper and an overseal and is labeled according to local regulatory requirements.

Inpatient Observation

For PF-07260437 administration without a priming dose, all participants will be observed inpatient for at least 48 hours after the first SC dose (or the first IV dose, as applicable) on C1D1 and for at least 8 hours after the second SC dose (or the second IV dose, as applicable) on C1D15 and for at least 1 hour post dose for all subsequent outpatient visits to closely manage and monitor acute toxicities.

For PF-07260437 administration with a priming dose, all participants will be observed inpatient for at least 24 hours after the first SC injection (or the first IV dose administration, as applicable) on C1D1 and for at least 24 hours after the second (full) SC dose (or the second [full] IV dose, as applicable) on C1D15 to closely manage and monitor acute toxicities. Participants should be observed for at least 1 hour post SC dose for all outpatient visits starting with C2D1 in both cohorts until the investigator has confirmed the participant has not exhibited signs of CRS (Table 7). Additional inpatient observation for subsequent cycles of IV dosing beyond Cycle 1 may be considered based on the investigator's discretion and should be discussed with the sponsor.

In addition, participants who experience ≥ Grade 3 infusion-related adverse events (IV administration) or clinically significant CRS must be hospitalized for at least 24 hours for at least 4 subsequent doses (two cycles).

Modification of inpatient observation period might be allowed based on emerging safety data and will require discussion and agreement between investigator and sponsor.

6.1.1. Administration

6.1.1.1. Premedication

Prophylactic premedication for infusion related reaction, allergic reaction or CRS is not allowed during the DLT evaluation period during initial dose escalation. However, if the participant experiences an infusion related reaction (IV), significant injection site reaction, CRS, fever/chills, nausea/vomiting, hypotension, or pain, appropriate treatment should initiate and premedication as prophylaxis may be considered for subsequent cycles as follows:

- Acetaminophen 650 mg (or equivalent), oral
- Diphenhydramine 25 mg, oral or IV
- Dexamethasone 10 mg (or equivalent), oral or IV

Modifications to the premedication regimen (eg, frequency of premedication, doses of individual agents, removal, or addition of agents) may be allowed per hospital or local clinical practice after discussion and agreement between the sponsor and investigator.

Based on a review of all accumulated safety data (eg, $\geq$ 50% of participants experienced significant allergic reaction or CRS related symptoms and signs), prophylactic premedication may be considered for new participants after agreement between investigators and the sponsor to determine the MTD/RDE with prophylaxis.

In addition, depending on accumulated safety data, prophylactic premedication during cycle 1 after identification of the maximum tolerated dose (MTD)/recommended dose for expansion (RDE) may be allowed.

The pre-treatment medication will not be supplied by sponsor.

6.1.1.2. SC Administration

Qualified and trained investigational site personnel will administer PF-07260437 to participants by SC injection. PF-07260437 will be administered at a flat dose via SC injection Q2W at 28-day cycles (on Day 1 and Day 15) until the participant meets one of the study intervention discontinuation criteria (See Section 7.1). Participants should have SC injections in the abdomen with preference to the lower quadrants when possible. For participants receiving 2 or more SC injections, PF-07260437 should be administered in 2 or more different quadrants of the abdomen (with preference given to the lower quadrant when possible); 1 or 2 injections per quadrant. The injection can be rotated with each administration for participant comfort. Refer to Appendix 14, for details on administration of multiple injections to the abdomen.

Each injection volume may be up to 2 ml in volume. If an institutional policy sets a maximum volume <2 ml, the number of injections may be increased to ensure that the correct volume is administered. Refer to the IP Manual for specific instructions on the handling and preparation of study treatment.

Refer to Table 7 for required inpatient observation stays following PF-07260437 administration.

6.1.1.3. IV Administration

If IV route is evaluated. Qualified and trained investigational site personnel will administer PF-07260437 to participants by IV infusion. PF-07260437 will be administered at a flat dose intravenously over approximately 60 minutes (±15 minutes) Q2W at 28-day cycles (on Day 1 and Day 15) until the participant meets one of the study intervention discontinuation criteria (see Section 7.1).

If IV route is evaluated, a 1-hour infusion and inpatient monitoring in a hospital for at least 48 hours after the first dose in Cycle 1 in dose escalation will be implemented. Additional inpatient observation for subsequent cycles beyond Cycle 1 may be considered based on the investigator's discretion and should be discussed with the sponsor as described in Section 6.1.

Details for preparation of PF-07260437 infusion are provided in the IP Manual.

6.2. Preparation, Handling, Storage and Accountability

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

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

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

and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

6. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted. Specific details of the dilution are provided in the IP Manual.

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

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the vials provided, in quantities appropriate according to the participant's dose. A second staff member will verify the dispensing.

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Vials are single use.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of PF-07260437.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

For Part 1:

Study intervention will be dispensed at the study visits summarized in the SOA.

Returned study intervention must not be redispensed to the participants.

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

Dose level allocation in Part 1 will be performed by the sponsor after participants have given their written informed consent and have completed the necessary screening assessments. The site staff will fax/email a complete Participant Registration Form to the designated sponsor study team member or designee. The sponsor 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.

No participant shall receive investigational product/study intervention 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.

In Part 1, sites will use the IRT for drug supply and inventory management.

For Part 2:

Allocation of participants in Part 2 of the study to treatment groups may proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the SOA.

Returned study intervention must not be redispensed to the participants.

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

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the

time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the 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. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, which may include a DLT, dosing may be delayed, reduced, or 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. In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Toxicities potentially related to PF-07260437 should be managed according to the dose modifications described in Table 10 and Table 11.

Selected toxicities that do not resolve or worsen following supportive care and dose modifications and with a clinical presentation consistent with a potential irAE without a clear alternative explanation, may require treatment with corticosteroids or other immunosuppressants and should be managed according to the management of irAEs as described in Section 10.3.5.

CRS should be managed according to the CRS Mitigation and Management guidance as described in Appendix 11.

6.5.1. Dosing Interruptions

With respect to study intervention, participants experiencing Grade 3 or 4 potentially treatment-related toxicity or intolerable Grade 2 toxicity despite supportive treatment should have their treatment interrupted as indicated in Table 10 and Table 11.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 6.5.2.

Doses may be held up to 4 weeks until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the participant missing subsequent planned doses within that same cycle or to delay the initiation of the subsequent cycle as follows:

- If the planned Day 1 dose (of any cycle) cannot be administered due to an AE, then Day 1 dose will be delayed until the AE has resolved and the study drug can be administered.
- If the planned Day 15 dose (of any cycle) is delayed for ≤7 days, then the planned day 15 dose can be administered as the delayed Day 15 dose. Day 1 of the subsequent cycle will be administered 2 weeks after the delayed Day 15 dose.
- If the planned Day 15 dose (of any cycle) is delayed for >7 days, then Day 15 will be skipped. The next dose will be administered when the AE has resolved and will be considered the Day 1 dose of the subsequent cycle.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

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.

See Appendix 8, Section 10.8.4 for COVID-19 related dose interruption.

6.5.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3.
- Platelets count ≥50,000/mm^3.

Nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the participant).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 4 weeks of treatment interruption, PF-07260437 may be resumed. Refer to the Dose Reductions Section 6.5.3 for AEs requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of PF-07260437 for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor. In this situation, if a treatment interruption continues for more than 4 weeks, the day when treatment is restarted will be counted as Day 1 of the next cycle.

6.5.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-07260437 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1 or 2 treatment-related toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Dose reduction of PF-07260437 by 1 and, if needed, 2 dose levels (See Table 9) will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions will be discontinued from the treatment and entered into the Follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intraparticipant dose re-escalation is not allowed.

Table 9. Available Dose Reduction Levels From Starting Dose

Dose Level	PF-07260437 SC	PF-07260437 IV
Starting dose	100 µg Q2W	60 µg Q2W
-1	60 ug Q2W (one dose level below starting dose)	N/A

Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and sponsor, the participant is benefiting from therapy.

In some cases, participants experiencing recurrent and intolerable Grade 2 toxicity may reduce the dose to the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Recommended dose modifications of PF-07260437 for non-immune related toxicity are described in Table 10.

Table 10. Dose Modifications for Study for Non-Immune-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic (except pancreatitis)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade <1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.*	Withhold dose until toxicity is Grade <1, or has returned to baseline, then reduce the dose by 1 level or 2 levels, or permanently discontinue at the discretion of the investigator.*

Table 10. Dose Modifications for Study for Non-Immune-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Pancreatitis	Continue at the same dose level.	Withhold dose until toxicity is resolved, then reduce the dose by 1 level.	Consider discontinuation (continuation requires sponsor approval).	Permanent discontinuation of study drug for related Grade 4 adverse events of any duration.
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade <2, or has returned to baseline, then reduce the dose by 1 level.	Withhold dose until toxicity is Grade <2, or has returned to baseline, then reduce the dose by 1 level or 2 levels or permanently discontinue at the discretion of the investigator.*

* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.

Recommended dose modifications of study intervention for immune related toxicity are described in Table 11. Please refer to Section 10.3.5 for detailed dose modification and comprehensive management of irAEs.

Table 11. Dose Modifications for Immune-Related Toxicity

Organ System	Grade 1	Grade 2	Grade 3	Grade 4
GI (Diarrhea)	Continue investigational treatment.	Withhold investigational treatment. If improves to Grade 1, resume treatment. If persists >5-7 days or recur treat as Grade 3 or 4.	Withhold investigational treatment. If improves to Grade 1 after treatment, resume investigational therapy at the same dose level or reduce the PF-07260437 dose by 1 level at the discretion of the investigator.	Discontinue Investigational treatment.
Skin (Dermatitis)	Continue investigational treatmen.t If persists >1-2 weeks, withhold. If improves after treatment with corticosteroids, then resume investigational treatment.	Continue investigational treatment. If persists >1-2 weeks, withhold. If improves after treatment with corticosteroids, then resume investigational treatment.	Withhold investigational treatment. If improves to Grade 1 after treatment, resume investigational therapy.	Withhold or discontinue investigational treatment. If improves to Grade 1 after treatment, resume investigational therapy.
Lung (pneumonitis)	Consider delay of investigational treatment.	Withhold investigational treatment; re-image.	Discontinue	Discontinue

Table 11. Dose Modifications for Immune-Related Toxicity

Organ System	Grade 1	Grade 2	Grade 3	Grade 4
	Monitor	If symptoms return to baseline, then resume investigational treatment.		
Liver (hepatitis)	Continue investigational treatment.	Withhold investigational. treatment; increase monitoring of LFTs; resume investigational therapeutic if labs return to baseline. If elevations persist ≥5 to 7 days or worsen, treat with corticosteroids, resume investigational treatment if labs return to Grade 1 or baseline.	Discontinue	Discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus)	Continue investigational treatment.	Continue investigational treatment.	Withhold investigational treatment. If improves to Grade 1 after treatment, resume investigational therapy.	Discontinue

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

No intervention will be provided per protocol to study participants beyond the end of the study.

6.7. Treatment of Overdose

For this study, any dose of PF-07260437 greater than the intended dose level at any study intervention administration time point will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07260437 (whichever is longer).

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

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

5. Obtain a blood sample for PK analysis within 2 weeks from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by case-basis).

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.

6.8. Concomitant Therapy

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from screening until the end of treatment visit will be recorded on the CRF.

Authorized or approved COVID-19 vaccines are considered allowed concomitant medications and standard AE collection and reporting processes should be followed. The timing of vaccine dosing relative to the dosing of study drug(s) is at the discretion of the investigator, although it may best to avoid the 7 days prior to C1D1 and the DLT observation period, to consider the potential for vaccine-related adverse events, and to administer the vaccine during scheduled dosing holidays, if applicable. Discussions between the investigator and the sponsor regarding individual cases may occur if further clarification is required.

PF-07260437 transiently increased serum cytokine levels (eg, IL-6) in monkeys in vivo and likely in patients (also demonstrated via in vitro human and monkey PBMC assays) which is expected with CD3-targeted bispecifics. Cytokines have been shown to result in down-regulation of some CYP450 enzymes. Therefore, treatment with PF-07260437 has a theoretical potential to increase the exposure of concomitant medications that are substrates for these enzymes. Caution should be used upon concomitant use of sensitive substrates of CYP450 enzymes with narrow therapeutic index (eg, CYP3A4: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus; CYP2C9: phenytoin, warfarin) especially during the initial treatment cycle. Refer to Appendix 15 for details on the list of drugs which may result in a drug-drug interaction.

6.8.1. Prohibited and/or Limited use of Anti-tumor/Anti-Cancer or Experimental Drugs, or Procedures

No additional antitumor treatment will be permitted while participants are receiving study treatment.

In view of the current lack of data about the interaction of PF-07260437 with radiotherapy, 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. PF-07260437 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after recovery to baseline.

6.8.2. 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 ASCO guidelines.

6.8.2.1. Supportive Care for Cytokine Release Syndrome

Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash, and shortness of breath. The severity of symptoms can be mild to life threatening and thus there should be a high suspicion for CRS if these symptoms occur. The severity of CRS will be assessed according to the modified grading described by Lee et al (Lee et al, 2019). A suggested treatment algorithm for the management of CRS is also provided in Appendix 11; however, if local standard of care is a different regimen this should be utilized.

The decision to incorporate pre-medication (ie, corticosteroids) for CRS prophylaxis in all participants will be made following discussions between the sponsor and the investigators. The pre-treatment medication will not be supplied by the sponsor.

6.8.2.2. Supportive Care for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS is defined as disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. It has been observed following administration of some CAR T cells and bispecific antibodies and can occur independently of CRS. The severity of ICANS should be graded according to the ASTCT consensus criteria (Lee et al, 2019). General management guidelines can be found in Neelapu et al (Neelapu et al, 2018; Neelapu, 2019) or per local standard of care practice. These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute. Management guidelines are provided in Appendix 11, Section 10.11.2.

6.8.2.3. Supportive Care for Infusion Related Reactions (IV infusion only)

IRR is characterized by fever and chills, and less commonly hypotension, either experienced by a particular participant or if seen in other participants, pretreatment medication should be administered to reduce the incidence and severity. In the event of IRRs, investigators should institute treatment measures according to best medical and nursing practice. A local standard of care for the management of IRR should be utilized.

6.8.2.4. Supportive Care for Injection Site Reactions (ISR)

ISR is a type of hypersensitivity reaction that may be immediate, although it usually appears within 24-48 hours after injection. ISR, by definition, includes the following erythema, pruritus, pain, inflammation, rash, induration, itching and edema at the injection site. To evaluate ISRs, site tolerability assessments will be performed per the Schedule of Activities. ISR will not be considered DLTs but may be a reason for discontinuation of SC dosing.

Topical corticosteroids and topical or systemic antihistamines may be applied to treat any rash or pruritis at the injection site depending on the severity and per investigator's assessment.

6.8.2.5. Supportive Care for Hypersensitivity Reactions Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving study intervention and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the participant will be treated symptomatically with supportive care, further monitoring, and treatment with antihistamines and/or corticosteroids. Study infusions may be stopped, and the participant will be followed until the end of the study.

Detailed guidance on treatment, dose interruptions and potential re-treatment is provided Section 6.5.

6.8.2.6. Supportive Care for Immune-Related Adverse Events

For immunotherapeutic agents, treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade version 5.0 (latest version as applicable). In general, Grade 1 or 2 irAEs are treated symptomatically with persistent Grade 2, Grade 3, or Grade 4 irAEs managed with moderate to high dose corticosteroids.

Guidelines on the treatment of irAEs are provided in Appendix3, Section 10.3.5.

A more detailed summary of Management of Immune Related AEs is described in Brahmer et al (Brahmer et al, 2018).

6.8.3. Hematopoietic Growth Factors

Primary prophylactic use of colony stimulating factors is not permitted during the DLT assessment period in Part 1, but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines (Smith et al, 2006). During the screening window (ie, 14 days prior to Day 1), Granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

If the local indication and dosage of G-CSF compounds differs from ASCO guidelines, refer to the local product label or follow the country's clinical practice.

6.8.4. Antidiarrheal, Antiemetic Therapy

Primary prophylaxis is not recommended during the initial dose escalation. However, if the participant experiences nausea, vomiting or diarrhea, appropriate treatment and supportive care should be initiated. Prophylaxis may be considered for subsequent injections as well as for new participants at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included Section 6.8, Concomitant Therapy.

Diarrhea is a possible adverse event. As there is no prior clinical experience with PF-07260437, the exact nature of treatment related diarrhea in humans is unknown. In general, management of cancer treatment-induced diarrhea have been described (Benson et al, 2004). Initial management for mild to moderate diarrhea may include dietary modifications (eliminating lactose and other high-osmolar dietary supplements), loperamide or diphenoxylate/atropine, along with oral antibiotics if persistent with concern for infection. Management of higher severity or more complicated diarrhea may also include consideration of intravenous fluids for hydration, electrolyte replacement, octreotide, stool workup along with hospitalization for observation and treatment if indicated in the investigator's medical judgement. In addition, management of diarrhea as described in supportive care for irAEs for diarrhea (Section 10.3.5) may also be considered if the clinical impression of the etiology of diarrhea is associated with immune dysfunction

6.8.5. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.8.6. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included Section 6.8, Concomitant Therapy.

6.8.7. Surgery

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07260437 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07260437 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-07260437 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. Postoperatively, the decision to reinitiate PF-07260437 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. Palliative radiotherapy to specific sites of disease will be permitted if considered medically necessary by the treating physician. All attempts will be made to rule out progressive disease in the event of increased localized pain.

6.8.8. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07260437; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following:

- 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;

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety follow-up and survival follow-up (Part 2). See the SOA for data to be

collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

Safety Follow-Up:

At least 28 calendar days, and no more than 35 calendar days after discontinuation of study intervention, participants will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment related AEs. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the participant will be asked to return for drug concentration and ADA blood sampling at up to 3-month intervals, until the last follow-up of the AE.

For part 2 of the study, survival status will be collected by telephone every 3 months until death, or up to 24 months after first dose of the last participant.

7.1.1. ECG Changes

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec and QTcF > 450 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include:

- Refused further study procedures;
- 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.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to 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. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD 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 Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced head, chest, abdomen, and pelvis computed tomography or MRI scans; brain computed tomography or MRI scan for participants with known or suspected brain metastases; bone scan and/or PET scan for all participants to monitor potential bone metastases. For participants with known computed tomography contrast allergy, a non-

contrast computed tomography of the chest with contrast enhanced abdominal and pelvic 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.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter as specified in the SOA, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). Assessment of response will be made using RECIST version 1.1 (see Appendix 12) and irRECIST (See Appendix 13). Confirmation of response (CR/PR) with a second consecutive scan at least 4 weeks later is preferred.

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

Antitumor activity will be assessed at baseline, during treatment as specified in the SOA, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks).

If imaging is used in disease assessment, the same imaging technique used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments.

8.2. Safety Assessments

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

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

8.2.1. Physical Examinations

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only. Refer to Appendix 16 for ECOG performance status grading.

A complete physical examination will include more comprehensive assessments of the cardiovascular, respiratory, GI, genitourinary (if needed, musculoskeletal and neurological systems in addition to the assessments for the brief physical exam listed below.

A brief physical examination will include, at a minimum, assessments of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

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

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

When should it be done:

Physical examination should be completed prior to dosing.

8.2.2. Vital Signs

Oral temperature, pulse rate, respiratory rate, and BP will be assessed. BP and pulse rate measurements will be assessed in a sitting or semi-recumbent position (the same position should be maintained throughout the study) with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP 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).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 2 BP measurements (2 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 2 BP readings will be recorded on the CRF.

When should it be done:

Vital sign assessments should be completed prior to dosing.

8.2.3. Electrocardiograms

A single 12-lead ECG will be utilized as screening. A triplicate 12-lead ECGs will be utilized for Cycles 1 to 3 to determine mean QTcF interval. For the days of dose administration, perform ECG up to 60 minutes prior to dosing (SC or IV), and at the end of infusion (IV only).

From Cycle 4 onwards: Triplicate 12-lead ECG up to 60 minutes prior to dosing on Day 1 of every 3 cycles (C4D1, C7D1, etc.).

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SOA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline and is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTcF values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia, and concomitant medications for drugs with the potential to prolong the QTcF interval should be performed.

If the QTcF interval reverts to less than the threshold criteria listed above, and in the judgment of the investigator(s) and sponsor, it is determined that the cause(s) of QTcF prolongation is something other than study intervention, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above the threshold values, the study intervention will be held until the QTcF interval decreases to below the threshold values. Participants will then restart the study intervention at the next lowest dose level. If the QTcF interval has still not decreased to <480 msec after 2 weeks, or if at any time a participant has a QTcF interval >515 msec or becomes symptomatic, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

When should it be done:

- ECG assessments should precede blood collection for clinical laboratory tests if possible.

- **At screening:** single 12-lead ECG.
- **Cycles 1 to 3:** triplicate 12-lead ECGs to determine mean QTcF interval. For the days of dose administration, perform ECG up to 60 minutes prior to dosing (SC or IV), and at the end of infusion (IV only).
- **From Cycle 4 onwards:** Triplicate 12-lead ECG up to 60 minutes prior to dosing on Day 1 of every 3rd cycle.
- If a participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at or close to the time of the event.
- **End of Treatment and 4-week follow-up:** triplicate 12-lead ECG.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

No need to repeat a clinical laboratory assessment on Cycle 1 Day 1 if the baseline assessment was performed within 7 days prior to that date.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SOA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit

prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

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

8.2.6. Injection Site Tolerability Assessments

Assessments of the injection sites in the abdominal fat fold to monitor local tolerability to PF-07260437 SC injections will be performed for at least 1 hour following study drug administration in Cycle 1 (Days 1 and 15), as per the Schedule of Activities. An assessment should also be performed 24 hours (±1 hour) after the C1D1 dose. Injection site tolerability assessments for at least 1 hour post the PF-07260437 injection should continue after each dosing day visit in Cycle 2 and beyond, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after PF-07260437 administration. The diameter of the affected area will be measured, and the condition of the injection site will be recorded on the CRF. Any observed abnormality at the injection site will be judged by the investigator to determine if the event should also be reported as an adverse event. ISRs should be immediately photographed in color, with scaled ruler placed by the reaction, and these photographs should be included in the participant's source documentation. 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 severe ISR or unexpected low exposure is encountered with SC dosing, alternative IV infusion administration cohorts may be considered after discussion between investigators and sponsor and approval from sponsor.

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

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue

and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/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 study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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 purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

If a participant begins a new anticancer therapy, the recording period for nonserious 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 AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-Up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention 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 10 weeks 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 preprocedural 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), 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 any unplanned direct contact with the product.

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

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

8.3.6. Cardiovascular and Death Events

Not applicable

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

The following DREs are common in participants with advanced or metastatic BrCa, OvCa or endometrial cancer and can be serious/life threatening:

- Disease or neoplasm progression
- Brain metastases
- Malignant pleural or peritoneal effusion

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the AE page in the participant's CRF within the appropriate time frame. These DREs will be monitored by a safety review committee, safety review team on a routine basis.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This Phase 1 study is not designed to investigate the definitive clinical efficacy of PF-07260437.

8.3.9. Medical Device Deficiencies

Not applicable.

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.

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.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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

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

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

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

8.4. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of 1 mL serum, will be collected for measurement of serum concentrations of PF-07260437 as specified in the SOA. If CRS is suspected, and if a PK sample is not already scheduled to be taken, a PK sample should also be taken. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in the Pharmacokinetic and

Biomarker Sampling table (see Section 1.3) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

Samples will be used to evaluate the PK of PF-07260437. Samples collected for analyses of PF-07260437 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of PF-07260437 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

A 4 mL whole blood sample optimized for DNA isolation Prep D1 will be collected according to the SOA, as local regulations and IRBs/ECs allow..

Retained Research Samples may be used for research related to study intervention(s) and cancer study. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.6. Biomarkers

A key element of this study is the evaluation of potential cellular and molecular signatures that could be modified by PF-07260437. The biomarker studies will be used to evaluate the in vivo MoA of PF-07260437, as monotherapy, and potential in combination with other agents, as well as evaluate potential mechanisms of resistance.

Table 12 below summarizes the biomarker assays that include, but are not limited to, those which will be used and the source of the samples. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses. Refer to the SOA for details pertaining to specific days of sample collection and to the study manual for details of sample preparation. The biomarker sampling schedule may be modified based on emerging PK and PD data.

Table 12. Biomarker Collections and Analyses

Assay	Sample Type
Measurement of B7-H4 expression levels and other tumor and immune biomarkers	Archival and de novo pre-treatment tumor biopsies
Immunophenotyping of blood immune cell subtypes frequency and activation modulation	Whole blood
Measurement of peripheral cytokines and other circulating markers	Serum
Modulation of intra-tumoral target pathway modulation (ie, gene expression signature, cellular and protein changes)	De novo pre-, on-, post-treatment tumor biopsies
Measurement of tumor mutational changes	Plasma pre- and post-treatment
Germline DNA	Whole Blood

Biospecimens collected for PD and other biomarker assessments may include but are not limited to peripheral blood and tumor tissues and may be used to analyze DNA, RNA, proteins, or metabolic biomarkers, for achieving planned biomarker objectives. Refer to the schedule of activities for sample collection time points and Laboratory Manual for sample processing and shipping. The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses.

Tumor biospecimens from archival and/de novo biopsies will be used to analyze candidate nucleic acid and protein and cellular biomarkers for their ability to inform those participants who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the TME. Optional, and/or de novo tumor biopsies obtained during therapy and upon disease progression may be used to help confirm pharmacodynamic effects of treatment and investigate potential acquired mechanisms of resistance (ie, presence of but not

limited to regulatory T cells or myeloid-derived suppressor cells and other immune suppressive cells or proteins).

8.6.1. Tumor Sample Collection for Part 1

All participants in Part 1 must provide an archival FFPE tumor tissue sample (block preferred) at screening. Samples provided should be taken from the most recently conducted available biopsy, preferably within 6 months of start of study treatment, containing sufficient tumor tissue of diagnostic quality and representative of the diagnosed malignancy. Tissue blocks are preferable, but freshly cut paraffin sections are acceptable. Sites should contact sponsor for approval to submit slides and refer to Laboratory manual for instructions on submitting slides. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) and bone biopsy specimens are not adequate and should not be submitted.

If the archived sample is older than 12 months, the investigator must contact the sponsor's Medical Monitor to discuss eligibility prior to enrollment.

If an appropriate archival FFPE tumor sample is not available, a de novo fresh FFPE tumor sample should be collected. Each de novo collections (pre-treatment and on-treatment) should attempt to obtain 6 core biopsies, with a minimum of preferably 3 cores. Samples should be obtained in accordance with local institutional practice for tumor biopsies. If a biopsy cannot be performed safely or insufficient tumor biopsy material due to safety risk, the participant may still be eligible. However, such exceptions should be discussed with and approved by the sponsor.

In Part 1, optional de novo pre- and on-treatment tumor biopsies are encouraged for all participants on the trial when participants have accessible lesions. Optional on-treatment tumor biopsies are preferentially collected after the third dose, within 7 days of Cycle 2 Day 15 (C2D15 ±7 days). Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

8.6.2. Tumor Sample Collection for Part 2

In Part 2, archival biopsies should be requested from all participants, in order to establish relationship between target expression and efficacy observations. Archival biopsies should meet the criteria outlined in Section 8.6.1.

De novo pre-treatment biopsies are also requested from all participants, unless not medically feasible, to further establish the relationship between target expression and efficacy observations. If a de novo pre-treatment biopsy is not medically feasible, the sponsor should be contacted for approval before initiating screening activities. For a subset of participants in all cohorts (approximately 5 participants in Part 2A and 2C, and approximately 5 HR+ HER2- BrCa and 5 TNBC participants in Part 2B), mandatory pre-treatment and on-treatment biopsy samples will also be collected in order to confirm the MoA and evaluate potential resistance mechanism during treatment. For all other participants, on-treatment biopsies are optional but encouraged. In Part 2, 20 participants will be enrolled in each

cohort. If 15 participants have been enrolled in Part 2A or Part 2C and <5 paired pre- and on-treatment biopsies have been collected, collections may be made mandatory for the remaining participants and the cohort may be expanded by up to 5 participants to obtain sufficient numbers of paired pre- and on-treatment biopsies. If 5 participants with HR+ HER2- BrCa or TNBC have been enrolled in Part 2B and <5 paired pre- and on-treatment biopsies have been collected, collections may be made mandatory for the remaining participants in each histology and the cohort may be expanded to obtain sufficient numbers of paired pre- and on-treatment biopsies. If a de novo pre-treatment biopsy is not medically feasible, the sponsor should be contacted for approval before initiating screening activities.

For participants with a pre-treatment biopsy, an additional optional biopsy is also encouraged at disease progression to evaluate suspected acquired resistance to therapy. Mandatory de novo tumor collections (pre-treatment and on-treatment) should attempt to obtain 6 core biopsies, with a minimum of preferably 3 cores. Samples should be obtained in accordance with local institutional practice for tumor biopsies. Additional information on tissue collection procedures can be found in the Laboratory Manual.

Mandatory pre-treatment de novo tumor biopsies are to be collected within 28 days of first study treatment dose. On-treatment tumor biopsies are preferably collected after the second dose, within 7 days of Cycle 2 Day 15 (C2D15 ±7 days). If on-treatment tumor collection takes place greater than ±3 days from C2D15, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T-cell immunophenotyping sample should be collected to match the day of biopsy collection.

8.6.2.1. B7-H4 expression for Part 2 eligibility

Part 2 dose will evaluate PF-07260437 in participants with advanced or metastatic HR+ HER2- BrCa (Part 2A) and TNBC (Part 2C) with high B7-H4 expression to assess early signs of clinical efficacy. Reference sets will be immunostained at a CLIA-certified central laboratory with a B7-H4 LDT and the resulting H-scores will be ranked from low to high and divided into 3 equal tertiles. Patient samples with H-scores that fall within the highest tertile of the reference set will be deemed as high B7-H4 expressors. The arbitrary threshold for high B7-H4 expression may be modified based on emerging clinical data. An additional cohort of 20 participants with advanced or metastatic HR+ HER2- BrCa and TNBC will be enrolled in Part 2B. These patients will not be enrolled based on B7-H4 expression. Samples will be immunostained and evaluated retrospectively to further explore B7-H4 expression levels and clinical efficacy.

8.6.3. Peripheral Blood Sample Collection and Assessments

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure soluble proteins, and analyze nucleic acids to support study objectives. Examples may include but are not limited to cytokines, cell free DNA, and germline DNA.

For cytokine and circulating markers to be analyzed at a central laboratory, one 5 mL blood sample will be collected to isolate serum for cytokine and circulating marker measurement. Baseline collection is required pre-dose on Cycle 1 Day 1. On-treatment samples for cytokine

and circulating markers measurement will be collected as described in the SOA. These samples will be used to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected to match clinically indicated safety cytokine samples.

The cytokines to be measured may include, but not limited to IFN-γ, TNF-a, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, and IL-10. Additional exploratory circulating markers may also be evaluated to measure changes in immune activation after therapy.

For analysis of cell-free DNA, plasma will be isolated from 10 ml blood at C1D1 and upon disease progression. Analysis of circulating tumor DNA in these samples may be correlated with participant response to therapy.

A 2 ml whole blood sample will be collected at C1D1 for isolation of baseline germline DNA. This sample may be used to enable subtraction of germline DNA variants from somatic mutations that may be identified in tumor or cell-free DNA samples.

Instructions for sample collection, processing, storage, and shipment will be provided in the Laboratory manual.

8.6.4. T Cell Immunophenotyping

Blood samples of approximately 5 mL of whole blood samples will be collected for evaluation of T, B, and NK cell immunophenotyping as well as characterization of T cells for markers such as but not limited to Ki67, PD-1, HLA-DR and other indicators of proliferation, activation, and exhaustion after therapy. Samples will be collected at the times specified in the Schedule of Activities. Instructions for sample collection, processing, storage, and shipment will be provided in the Laboratory manual.

Samples may also be used for flow cytometry assay development. Samples used for this purpose will be retained in accordance with local regulations and if not used within this time frame, will be destroyed.

8.6.5. Retained Research Samples for Biomarkers

Not applicable as Retained Research Samples for Biomarkers are not collected in this study.

8.6.6. Soluble B7-H4 Assessment

Whole blood samples (approximately 3 mL) to provide a minimum of 1 mL serum for soluble B7-H4 assessment will be collected at the times specified in the SOA. An additional soluble B7-H4/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, from Cycle 4 onwards). Instructions for sample collection, processing, storage, and shipment will be provided in the laboratory manual. Soluble B7-H4 levels will be determined by a ligand binding assay, and samples may be used for further evaluation of the bioanalytical method, as well as for other internal exploratory

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

8.7. Immunogenicity Assessments

Blood samples of approximately 5 mL, to provide a minimum of 2 mL serum, will be collected for determination of ADA and NAb as specified in the SOA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity 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 changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There will be no formal hypothesis testing in this study.

9.1.1. Estimands

9.1.1.1. Primary Estimand/Co-Primary Estimands

Primary Estimand (DLT) for Part 1:

DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (28 days for regimen without priming; priming doses plus 2 full doses for regimen with priming) in Part 1.

Variable: Occurrence of DLTs. DLTs are defined in Section 4.3.6

Analysis population:

For the dose escalation without priming, DLT-evaluable participants defined as participants:

- who receive at least 1 dose of study treatment and experience DLT during the DLT-evaluation period (28 days),

OR

- who complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least 2 full doses of study drug for reasons other than treatment-related toxicity are not evaluable for DLT.

For the dose escalation with priming, DLT-evaluable participants defined as participants:

- who receive at least 1 dose of study treatment and experience DLT during the DLT-evaluation period (priming doses plus 2 full doses, eg, 42 days),

OR

- who complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least the priming dose and 2 full doses of study drug for reasons other than treatment-related toxicity are not evaluable for DLT.

Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

Primary Estimand for Parts 1 and 2:

Incidence of AEs estimated in the analysis population during the AE-evaluation period, defined as the time from the first dose to earliest of 28 days post last dosing date and day of new anti-cancer therapy-1 day.

Variable: Occurrence of AEs. AEs are defined in Section 8.3.

Analysis population: Safety analysis set defined as participants who receive at least 1 dose of study treatment without regard to tolerability or duration of treatment.

Population-level summary measure: Incidence of AEs defined as the number of participants with AEs in the AE-evaluation period divided by the number of participants in the analysis population. AEs will be summarized by type, frequency, severity (as graded by NCI CTCAE version 5), timing, seriousness, and relationship to treatment.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set (FAS)	All enrolled participants.
Safety Analysis Set (SAS)	All enrolled participants who receive at least 1 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	All enrolled participants who do not have major protocol deviations during the course of the study
DLT Evaluable Set	All enrolled participants who had at least 1 dose of study treatment and either experienced DLT or do not have major protocol deviations during the DLT observation period.
mITT Population	All enrolled participants who have received at least 1 dose of study medication; have a baseline assessment and at least 1 post baseline assessment;
PK Parameter Set	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.
PK Concentration Set	All enrolled participants who are treated and have at least 1 analyte concentration above the lower limit of quantitation.
Response Evaluable Set	All enrolled participants who received at least 1 dose of study treatment and had adequate baseline disease assessment. Participants who discontinued early or died will be included.
Pharmacodynamic/ Biomarker Analysis Set(s)	The Pharmacodynamic/Biomarker analysis population is defined as all enrolled participants with at least 1 of the Pharmacodynamic/Biomarkers evaluated at pre and/or post dose.
Immunogenicity Analysis Set	The immunogenicity analysis set includes all enrolled participants who received at least 1 dose of study treatment and have at least 1 sample tested for ADA.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Unless otherwise specified, summaries will be presented by dose group and overall. Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% CIs using an exact method. Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CIs for each time-to-event endpoint will be provided.

Further details will be provided in the SAP.

9.3.2. Primary Endpoints/Estimands/Analysis

Part 1

Determination of MTD will be performed using Per-protocol analysis set (evaluable for MTD). The dose escalation in Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07260437. Dose toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose for the monotherapy and using BLRM model specifically developed for combinations separately for regimens with and without priming. A mixture of weakly informative prior distribution based on nonclinical/expert opinion information and a MAP prior based on historical data will be used to define the prior distribution for the PF-07260437 monotherapy dose escalation. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data.

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07260437 will be evaluated separately for cohorts with and without priming, taking into account the different DLT observation periods (28 days for the regimen without priming; priming doses plus 2 full doses for the regimen with priming). 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]

Dosing decisions are guided by the EWOC principal (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the risk of overdosing at that dose is less than 25%.

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/RDE determination.

Prior distributions:

Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters for prior distribution in Part 1, see Appendix 9.

A MAP approach will be used to derive the prior distribution for model parameters used in Part 1 with priming based on the data collected in Part 1 without priming. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (Neuenschwander et al, 2010; Schmidli et al, 2014). MAP priors are derived from hierarchical models, which take into account possible differences between the studies. A full description of the application of the MAP approach to derive the prior distributions of the PF-07260437 model parameters is provided in Appendix 9.

Starting dose:

The starting dose for the monotherapy PF-07260437 is SC injection 100 µg Q2W. This dose satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 9.

Stopping criteria:

The sponsor estimates that the maximum number of participants in the Part 1 dose escalation portion of the trial is 40 participants. However, the actual number may be more or less based on observed PK and safety. The dose escalation will stop when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD or RDE.
- The dose d for PF-07260437 satisfies 1 of the following conditions for the mono-escalation part:
  - The probability of target toxicity at dose d exceeds 50%, ie, Pr ($0.16 \leq \pi_d < 0.33$) $\geq 50\%$, or
  - A minimum of 15 participants have been treated in Part 1.

Part 1 and Part 2

Incidence of AEs estimated in the safety analysis population during the AE-evaluation period. defined as the time from the first dose to earliest of 28 days post last dosing date and day of new anti-cancer therapy-1 day.

- **Variable:** Occurrence of AEs. AEs are defined in Section 8.3.
- **Analysis population:** Safety analysis set defined as participants who receive at least 1 dose of study treatment without regard to tolerability or duration of treatment.
- **Population-level summary measure:** Incidence of AEs defined as the number of participants with AEs in the AE-evaluation period divided by the number of participants in the analysis population. AEs will be summarized by type, frequency,

severity (as graded by NCI CTCAE version 5), timing, seriousness, and relationship to treatment.

9.3.3. Secondary Endpoint Analysis

Part 1 and Part 2

Single-Dose and Steady-State PF-07260437 Pharmacokinetic Analysis

Serum concentrations of PF-07260437 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose, cycle, day, and nominal time.

Individual participant serum concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 2 Day 1 will be analyzed using noncompartmental methods to determine single and multiple dose PK parameters.

Single dose PK parameters to be estimated will include the serum C_{max}, T_{max} and AUC_{last}, and as data permit, AUC from time 0 extrapolated to infinity (AUC_{inf}), $t_{½}$, clearance (CL/F for SC dosing and CL for IV dosing) and volume (V_z/F for SC dosing and V_{ss} for IV dosing).

Multiple dose PK parameters to be estimated will include $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, $C_{min,ss}$, clearance (CL_{ss}/F for SC and CL_{ss} for IV) and as data permit, volume (V_z/F for SC or V_{ss} for IV), $t_{½}$, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$). The single dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose level and cycle.

Dose normalized AUC_{inf} (AUC_{τ} at steady state) and C_{max} will be plotted against dose (using a logarithmic scale) by cycle. These plots will include individual participant values and the geometric means for each dose.

Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of participants with positive ADA and neutralizing antibodies each will be summarized. For participants with positive ADA or neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA or neutralizing antibodies response will also be described, if data permit.

Part 2

Efficacy Analysis

Response Evaluable Set will be used for all response-related analyses including ORR, DoR, PFS, and TTP (RECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response. OS will be reported on the Full Analysis Set as well as on the mITT.

Data will be summarized (also graphically where appropriate) and listed by expansion cohort.

9.3.4. Tertiary/Exploratory Endpoint(s)

Part 1

Efficacy Analysis

Response Evaluable Set will be used for ORR and PFS (RECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response.

Data will be summarized (also graphically where appropriate) and listed by dose level.

Part 1 and 2

Analysis of Pharmacodynamics

Results of exploratory endpoint analyses will be described in the CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be complete at the time of CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.5.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. 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/pharmacodynamics modeling approach. If a PK/pharmacodynamics 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 (pre-dose on Cycle 1 Day 1) and on-treatment ECG data.

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 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 by study treatment (ie, monotherapy versus combination therapy) and dose. Individual QT (all evaluated corrections) intervals will be listed by study treatment, 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 study treatment, dose, and time point. Details of additional analysis (if any) will be specified in SAP.

9.3.5.2. AEs

AEs will be graded by the investigator according to the CTCAE version 5 and coded using MedDRA. AE data will be reported in tables and listings. Summaries of AE by appropriate MedDRA terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs 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 according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Listings of DLTs and deaths will be provided.

9.3.5.3. 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. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.3.6. Other Analysis(es)

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

9.3.6.1. Analysis of Biomarker Endpoints

For biopsy samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. Further analysis will be specified in SAP.

Clinically relevant and interpretable biomarker assessments generated for Primary and Secondary objectives will be summarized in the CSR. Other biomarker data might be summarized in a separate technical document.

9.3.6.2. Population Pharmacokinetic Analysis or PK/PD Modeling

PK and PD data from this study may be analyzed using compartmental modeling approaches and may also be pooled with data from other studies to investigate any association between PF-07260437 exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose -escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

Total number of participants for Part 1 and Part 2 combined, is estimated to be approximately 100.

9.5.1. Part 1 Dose Escalation

Approximately 35 participants are expected to be enrolled into 1 of 5-7 sequential dose levels in Part 1 including at least 6 participants treated at the MTD. The actual number of participants enrolled will depend on the tolerability of PF-07260437 and the number of dose levels that are required to determine MTD/RDE.

9.5.2. Part 2 Dose Expansion

Approximately 60 participants are expected to be enrolled into 3 cohorts in Part 2: Part 2A, Part 2B and Part 2C, with approximately n=20 participants in each cohort. Twenty participants for each cohort is clinically sufficient to eluate safety signals.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

No independent oversight committees will be utilized in this study.

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in 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 US law.

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as

individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

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

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

10.2. Appendix 2: Clinical Laboratory Assessments

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

Table 13. Core Lab Tests

Hematology	**Chemistry**	**Serology**	**Pregnancy Test**
Hemoglobin	ALT	HBV: HBsAg, HBcAb[a]	For female participants of childbearing potential, on serum or urine (to be specified in the protocol)
Platelets	AST		
WBC	ALP	HCV antibody[b]	
Absolute Neutrophils	Bicarbonate or CO_2		
Absolute Lymphocytes	Sodium		
Absolute Monocytes	Potassium		
Absolute Eosinophils	Magnesium		
Absolute Basophils	Chloride		
	Total Calcium		
Coagulation	Total Bilirubin[c]	**Urinalysis**	Ad hoc Local Lab Cytokine Analysis[d]
PT or INR	BUN or Urea	Urine dipstick for urine protein: If positive collect 24-h and microscopic (Reflex Testing)	
PTT or aPTT	Creatinine		IL-6, IL-1b, IL-10, IFN-γ, TNFa-, other cytokines
	Uric Acid		
Others	Glucose (non-fasted)		
Amylase	Albumin		
Lipase	Phosphorus or Phosphate	Urine dipstick for urine blood: if positive collect microscopic (Reflex Testing)	
TSH and free T4	LDH		
	CRP		

a. Hepatitis B as clinically indicated: IgM antibody to hepatitis B core antigen (IgM anti-HBc), HBV DNA.
b. Hepatitis C as clinically indicated: HCV-PCR, HCV-RNA, Hepatitis C Viral Load.
c. For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase.
d. Cytokines for local lab evaluation will be collected if CRS is suspected. Local lab evaluation of cytokine is only required if the site require this information for participant management.

Notes: Database should be constructed to allow capture of differential counts as percent and absolute values but only one or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

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

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
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 that 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 preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect.

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

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

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 CTCAE Grade 5 (see the Assessment of Severity section).

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Severity

The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system). 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.

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

Assessment of Causality

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

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

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.3.5. Guidance for Immune-Related Adverse Events

Management of Immune-Related Adverse Events

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 (eg, 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; not interfering with 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.

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hours; 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 5 mg/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 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 and/or Total bilirubin >ULN to 1.5 x ULN	-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 and/or total bilirubin >1.5 to ≤3 x ULN	-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.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	-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.
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 (eg, troponin, 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 (eg, azathioprine, cyclosporine A).

*Local guidelines, or eg, ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

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 free T4 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 -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	-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**
	by corticosteroids taper during at least 1 month -Add prophylactic antibiotics for opportunistic infections	

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	-Withhold study treatment pending clinical investigation	-If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting study treatment -If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	-Withhold study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤1: -Taper steroids over at least 1 month and resume study treatment following steroids taper.
Recurrence of same Grade 3 irAEs	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed -Add prophylactic antibiotics for opportunistic infections -Specialty consult	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	-Permanently discontinue study treatment -Specialty consult	

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 165 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) plus an additional 90 days (a spermatogenesis cycle):

- 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 when engaging in any activity that allows for passage of ejaculate to another person.
- Male participants should 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 WOCBP 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, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Appendix 4, Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 4 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). 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.

A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing and Non-Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.

- A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - Oral;
   - Intravaginal;
   - Transdermal;
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
   - Oral;
   - Injectable.
8. Sexual abstinence:
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
   -

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07260437 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 ms).
• New-onset right bundle branch block (QRS >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAE

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

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

10.8. Appendix 8: 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).

10.8.1. 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 criterion # 17: Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, COVID-19/SARS-CoV2, and known HIV or AIDS-related illness. When the infection resolves, the patient may be considered for re-screening.

10.8.2. Telehealth Visits

Study participants who can attend scheduled study visits on site and complete all study procedures as described in the protocol per the SOA should do so; all other participants should make every effort to participate in study visits by telephone via a telehealth visit. Video contact can be used if available and permitted by local regulations.

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 SOA and Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.3.1 of this appendix regarding pregnancy tests.

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

10.8.3. Alternative Facilities for Safety Assessments

If the study participant is unable to visit the study site, protocol specified safety laboratory tests and/or tumor assessments may alternatively be performed at an alternative local laboratory or facility, where allowable by law or local guidance.

10.8.3.1. 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. The local laboratory may be a standalone institution or within a hospital. All protocol-specified safety laboratory evaluations may be performed at a local laboratory.

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 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Any results that are considered clinically significant must be reported in a timely manner and as directed in the protocol.

10.8.3.2. Imaging

If the participant is unable to visit the study site for planned or unplanned imaging assessments, the participant may visit an alternative facility to have these assessments performed. Qualified study site personnel must order, receive, and review results.

10.8.3.3. 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.

10.8.4. 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.

The following is recommended for the administration of PF-07260437 for participants who have active COVID-19 confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, PF-07260437 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. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in Section 6.8 for any concomitant medication administered for treatment of SARS-CoV2 infection

10.8.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

10.8.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study intervention should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8.7. Efficacy Assessments

The use of alternative measures for efficacy assessments must be evaluated by the sponsor for the impact on data integrity and interpretability.

10.9. Appendix 9: Detailed Dose Escalation/De-Escalation Scheme for BLRM Design

This appendix provides the details of the statistical model, the description of prior distribution. The results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model could be found in the separate Technical supplement to this appendix.

10.9.1. Statistical Model

Let π (d) be the risk of DLT for PF-07260437 given as a single agent at dose d. The dose-DLT model is logistic:

$$\text{logit}\big(\pi(d)\big) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)$$

The parameter d* is the reference dose in the model and is used to scale the doses of PF-07260437. The α, β >0 are the parameters of the model such that α (>0) is the PF-07260437 odds of a DLT at d^*; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

10.9.2. Prior Specifications for Monotherapy Without Priming

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the parameters $\log(\alpha)$ and $\log(\beta)$. A weakly informative prior was used as there were no relevant human historical DLT data available. It was assumed that model parameters will follow a BVN distribution

$$(\log(\alpha), \log(\beta)) \sim N2\ (m, S)$$

with prior means m = (m1, m2), and prior covariance matrix S composed of standard deviations s1, s2 and correlation ρ. It was assumed that

$$(m1, m2, s1, s2, \rho) = (\text{logit}(p^*), 0, 2, 1, 0)$$

Here, p* is the anticipated DLT rate at the scaling dose d*.

This prior is considered to be weakly informative (Neuenschwander et al, 2015).

10.10. Appendix 10. Bone Marrow Reserve in Adults

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM	Head:			136.6		
AND	Cranium	165.8	0.75	124.3	13.1	**13.1**
MANDIBLE	Mandible	16.4	0.75	12.3		
	Upper Limb Girdle:			86.7		
HUMERI, SCAPULAE,	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
CLAVICLES	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
STERNUM	4	18.6		7.4		
AND	5	23.8		9.5	7.9	**10.2**
RIBS	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
	Sacrum	194.0	0.75	145.6	13.9	
PELVIC BONES	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	28.4
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		1497.7		1045.7	100.0	100.0

10.11. Appendix 11: CRS and ICANS Grading, Mitigation, and Management

10.11.1. Cytokine Release Syndrome

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-base therapies for cancer (antibodies and adoptive T cell therapies). CRS is likely to be a common toxicity that can be managed through supportive care and anti-cytokine interventions.

In cases of suspected CRS, a serum sample should be provided for cytokine release assay analysis by the local lab (see Appendix 2) so as long as the sampling does not interfere with the medical treatment of the participant.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension and are temporally related to PF-07260437 in the absence of alternative etiologies.

The ASTCT CRS criteria proposed by Lee et al (Lee et al, 2019) as presented in Table 14 will be used for the assessment of the CRS severity grade which will be captured on the AE CRF and on the CRS CRF.

Table 14. ASTCT CRS Grading System

CRS parameter:	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

* Fever is defined as temperature ≥38°C and not attributable to any other cause. In participants who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
‡ Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.
Organ toxicities associated with CRS should still be graded according to CTCAE v5.0 and do not influence CRS grading.
Adapted from Lee DW, et al (Lee et al, 2019).

The definitions for high dose- vasopressors are shown in Table 15.

Table 15. Definition of High Dose Vasopressor

Pressor	High Dose (doses less than these would be considered low)
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min*

* VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷10

CRS Management Guidelines (Neelapu et al, 2018; Neelapu, 2019):
These may be modified as needed by the responsible Investigator according to the best practices at their institute.

ASTCT Grade 1 CRS:

Monitor vital signs for worsening of condition.

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- NSAIDs such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.
- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.
- Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

ASTCT Grade 2 CRS:

Monitor vital signs every 4 hours for worsening of condition.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV fluid bolus of 500-1000 ml of normal saline. Can give second IV fluid bolus if systolic blood pressure remains <90 mmHg.
- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for treatment of hypotension refractory to fluid boluses; tocilizumab can be repeated after 6 h if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring.
- In participants at high-risk (bulky disease, older age, or comorbidities) or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hours.

Hypoxia

- Supplemental oxygen.
- Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.

ASTCT Grade 3 CRS:

Monitor participant (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab and siltuximab as recommended for Grade 2 CRS if not administered previously.
- Vasopressors as needed.

- Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours.

Hypoxia

- Supplemental oxygen including high-flow oxygen delivery.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

ASTCT Grade 4 CRS:

Monitor participant (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as recommended for grade 3 CRS.
- Methylprednisolone 1 g/day IV.

Hypoxia

- Supplemental oxygen via positive pressure/mechanical ventilation.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

10.11.2. Immune effector cell-associated neurotoxicity syndrome (ICANS)

Although less commonly seen than CRS, ICANS has been observed with some T-cell directed therapies and may manifest as aphasia, delirium, encephalopathy, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral edema (Lee et al, 2019). If ICANS is observed in relation to PF-07260437, the ASTCT criteria will be used for grading (Lee et al, 2019) in and published guidelines are recommended for management (Neelapu et al, 2018; Lee et al, 2019; Neelapu, 2019).These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute. See Table 16 for ICE score determination and Table 17 for ASTCT ICANS grading.

Table 16. Immune Effector Cell-Associated Encephalopathy (ICE) Score

Category	Task	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects	3
Following commands	Ability to follow simple commands	1
Writing	Ability to write a standard sentence	1
Attention	Ability to count backwards from 100 by 10	1

Table 17. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI (abducens nerve) palsy; or papilledema; or Cushing's triad

a. A participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable
b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0; these symptoms do not influence ICANS grading.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It should be graded according to CTCAE v5.0.
Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a participant with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.
Source: (Lee et al, 2019).

ICANS Management Guidelines Per ASTCT (Neelapu et al, 2018; Neelapu, 2019)

ICANS Grade 1:

- Vigilant supportive care; aspiration precautions; IV hydration.
- Withhold oral intake of food, medicines, and fluids; assess swallowing.
- Convert all oral medications and/or nutrition to IV if swallowing is impaired.
- Avoid medications that cause CNS depression.
- Neurology consultation.
- If suspected, evaluate for elevated ICP with fundoscopic exam for papilledema and lumbar puncture for CSF opening pressure.
- MRI of the brain with and without contrast; CT scan of the brain can be performed if MRI is not feasible.
- Daily 30 min EEG until symptoms resolve.
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg (maximum 800 mg) IV or siltuximab 11 mg/kg IV in case of concurrent CRS.

ICANS Grade 2:

- Supportive care and neurological work-up as described for Grade 1 ICANS.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 1 ICANS and if not administered previously.
- Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS.
- Consider transferring participant to ICU if ICANS associated with Grade ≥2 CRS.

ICANS Grade 3:

- Supportive care and neurological work-up as indicated for Grade 1 ICANS.
- ICU transfer is recommended.
- If EEG shows non-convulsive status epilepticus:
  - Assess airway, breathing, and circulation; check blood glucose.
  - Lorazepam 0.5 mg IV, with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures.
  - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
  - If seizures persist, transfer to ICU, and treat with phenobarbital loading dose of 60 mg IV.

- Recommended maintenance therapy after resolution of non-convulsive status epilepticus are as follows:
  - lorazepam 0.5 mg IV every 8 hours for 3 doses;
  - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
  - phenobarbital 30 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
- Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.

- For convulsive status epilepticus:
  - Assess airway, breathing, and circulation; check blood glucose.
  - Transfer to ICU.
  - Lorazepam 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
  - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
  - If seizures persist, add phenobarbital at a loading dose of 15 mg/kg IV.
  - Maintenance doses after resolution of convulsive status epilepticus:
    - lorazepam 0.5 mg IV every 8 hours for 3 doses;
    - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
    - phenobarbital 1-3 mg/kg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
  - Continuous EEG monitoring should be performed if seizures are refractory to treatment.
- High-dose methylprednisolone IV 1 g/day for focal/local edema.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 1 ICANS and if not administered previously.
- Corticosteroids as outlined for Grade 2 ICANS if symptoms worsen despite anti-IL-6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to Grade 1 ICANS and then taper.

ICANS Grade 4:

- Supportive care and neurological work-up as outlined for Grade 1 ICANS.
- ICU monitoring; consider mechanical ventilation for airway protection.
- Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 ICANS.
- High-dose corticosteroids continued until improvement to Grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
- For convulsive status epilepticus, treat as described for Grade 3 ICANS.
- MRI of the spine should be obtained for focal motor weakness.
- To manage elevated ICP:
  - Elevate head of the participant's bed to an angle of 30 degrees.
  - Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hours.
  - Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below):
    - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40.
    - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50-75 ml/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/l.
    - For participants with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed.
- If patient has Ommaya reservoir, drain CSF to target opening pressure of <20 mmHg
- Consider neurosurgery consultation for ventriculoperitoneal shunt in participants with cerebral edema, and IV anesthetics for burst-suppression pattern on EEG.
- Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

10.12. Appendix 12: RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al (Eisenhauer et al, 2009):

Categorizing Lesions at Baseline

Measurable Lesions

Lesions that can be accurately measured in at least 1 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 14.9 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 participant live 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 study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Note: For the participant population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

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 on study.

If 2 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 a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

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, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in 1 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 must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

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. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

Stable: 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, 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.

Indeterminate: Progression has not been documented, and

- one or more target measurable 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. 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 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.

Indeterminate: Progression has not been determined and 1 or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

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 objective progression even after discontinuation of treatment.

Table 18. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	NonCR/-Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	NonCR/-NonPD-, Indeterminate, or Missing	No	PR
SD	NonCR/-NonPD-, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 19. Objective Response Status at Each Evaluation for Participants with Non-Target Disease Only

Non-target Disease	New Lesions	Objective Status
CR	No	CR
NonCR/-Non-PD	No	NonCR/-Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

10.13. Appendix 13: Immune Related Response Criteria Derived from RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

The irRECIST tumor assessment system has been developed to incorporate delayed or flare type- responses into the RECIST v1.1 (Nishino et al, 2014).

For irRECIST, only target and measurable lesions are taken into account. In contrast to RECIST v1.1, irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST is defined as follows:

- Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.
- Overall immune-related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).
- Overall immune-related progressive disease (irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion

and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

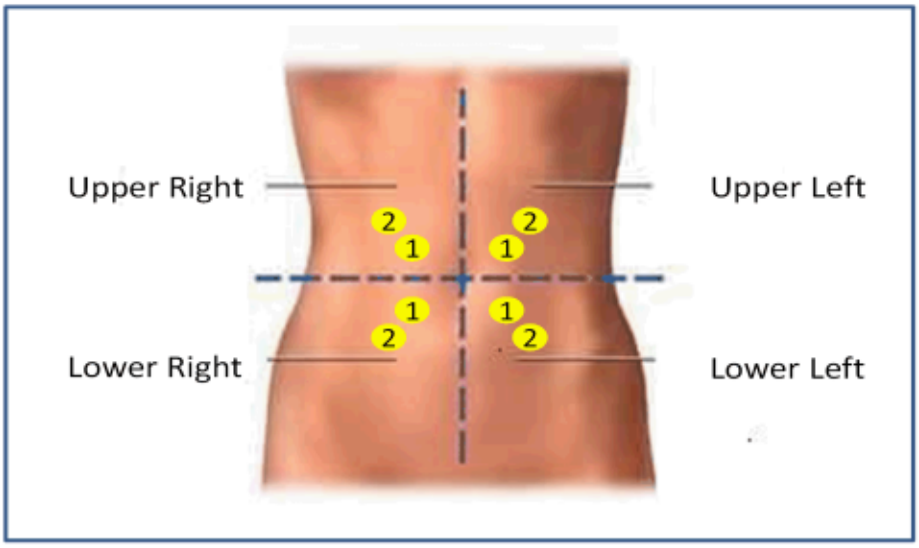
Overall responses derived from changes in index, nonindex, and new lesions are outlined in Table 20.

Table 20. Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable Response	Nonmeasurable- Response		Overall Response Using irRECIST[b]
Index and New Measurable Lesions (Tumor Burden)[a]	NonIndex- Lesions	Measurable Lesions	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

10.14. Appendix 14: Subcutaneous Injection Site Locations



Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

1. Lower Left Quadrant Location 1;
2. Lower Right Quadrant Location 1;
3. Lower Left Quadrant Location 2;
4. Lower Right Quadrant Location 2;
5. Upper Right Quadrant Location 1;
6. Upper Left Quadrant Location 1;
7. Upper Right Quadrant Location 2;
8. Upper Left Quadrant Location 2.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the participant's injection site(s) sequentially on this diagram with a red pen and mark the injection sites on the patient's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any ISRs in the participant's source records and study CRF. Complete 1 CRF per injection.

10.15. Appendix 15. Cautionary Use of Concomitant Medications with Narrow Therapeutic Index Due to Drug-Drug Interaction (DDI) Potential.

Medications listed below have narrow therapeutic index and should be used with caution as concomitant treatment with PF-07260437. It has been known that CRS is mostly likely to occur within the first few days after the first dose, and the increased cytokine level could potentially down-regulate CYP450 enzymes and alter the exposure of drugs that are substrates of these enzymes. The Pfizer study team should be notified of any listed medications taken during the study for consultation.

This list of drugs for potential DDI concerns with the PF-07260437 may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for PF-07260437, new information in literatures on the DDI potential of other drugs).

This is not an all-inclusive list. Shared substrates for multiple CYP450 enzymes are listed one time to avoid duplication. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs
CYP3A4 Substrate	alfentanil amiodarone argatroban carbamazepine cyclosporine dihydroergotamine ergotamine everolimus fentanyl pimozide quinidine rifampin sirolimus tacrolimus valproate
CYP2C9 Substrate	acenocoumarol isotretinoin phenytoin Phenobarbital phenprocoumon warfarin
CYP2C19 Substrate	mephenytoin
CYP1A2 Substrate	theophylline tizanidine
CYP2B6 Substrate	carbamazepine

Drug Category	Drugs
	cyclophosphamide

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.16. Appendix 16: 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 housework, 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.

10.17. Appendix 17: Abbreviations

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

Abbreviation	Term
2L+	after first line standard of care
ACTH	adrenocorticotropic hormone
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AT	aminotransferases
AUC	area under the 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
$AUC_{sd,\tau}$	area under the concentration-time curve after single dose over dosing interval τ
$AUC_{ss,\tau}$	area under the concentration-time curve at steady state over dosing interval τ
AV	atrioventricular
B	B cells
BBS	Biospecimen Banking System
BiPAP	bilevel positive airway pressure
BLRM	Bayesian logistic regression model
BNP	brain natriuretic peptide
BP	blood pressure
Bpm	beats per minute
BrCa	breast cancer
BUN	blood urea nitrogen
BVN	bivariate normal
C	cycle
CAR	chimeric antibody receptor
CD3	Cluster-Defined 3
CDC	The Centers for Disease Control and Prevention

Abbreviation	Term
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CISH	chromogenic in situ hybridization
CK	creatine kinase
CK-MB	creatine kinase-muscle type, myocardial band
CL	clearance
CL/F	apparent clearance
CL_{SS}/F	apparent clearance at steady state
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum concentration at steady state
$C_{min,ss}$	minimum concentration at steady state
CNS	central nervous system
CO_2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CSR	clinical study report
CT	clinical trial/ computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLs	Cytotoxic T lymphocytes
CYP	cytochrome P-450 enzymes;
D	day
DDI	drug-drug interaction
DILI	drug-induced liver injury
DISH	dual in situ hybridization
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
DRE	disease related events
DU	dispensable unit

Abbreviation	Term
EC	ethics committee
EC_{50}	half maximal effective concentration
ECC	emergency contact card
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EEG	electroencephalogram
EMA	European Medicines Agency
EOT	end of treatment
ER	estrogen receptor
ESC	European Society of Cardiology
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FFPE	formalin fixed -paraffin-embedded
FIH	first in human
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GLP	Good Laboratory Practice
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2-	human epidermal growth factor receptor 2 negative
HER+	human epidermal growth factor receptor positive
HIV	human immunodeficiency virus
HLA-DR	human leukocyte antigen-antigen D related
HNSTD	highest non-severely toxic dose
HR	heart rate
HR+	hormone receptor positive

Abbreviation	Term
HRT	hormone replacement therapy
IB	investigator's brochure
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICD	informed consent document
ICE	immune effector cell-associated encephalopathy
ICH	International Council for Harmonisation
ICP	intracranial pressure
ICU	intensive care unit
ID	identification
IFN-γ	interferon-gamma
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IgG2	immunoglobulin G2
IgM	immunoglobulin M
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
ir	immune-related
irAE	immune-related adverse events
IRB	institutional review board
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
IRR	infusion related reaction
irRECIST	immune related response criteria derived from RECIST 1.1
irSD	immune-related stable disease
IRT	interactive response technology
ISH	in situ hybridization
ISR	injection site reaction
IV	intravenous
IWR	interactive Web-based response
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDT	Laboratory Developed Test
LFT	liver function test
LH	luteinizing hormone
mAb	monoclonal antibody

Abbreviation	Term
MABEL	minimum anticipated biological effect level
MAP	meta-analytic-predictive
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescence intensity
MHC	Major Histocompatibility Complex
mITT	modified intent to treat
MoA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTNBC	metastatic triple negative BrCa
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NK	natural killer cells
NOAEL	no-observed-adverse-effect level
NSAIDs	non-steroidal anti-inflammatory drugs
OR	objective response
ORR	objective response rate
OS	overall survival
OvCa	ovarian cancer
$PaCO_2$	partial pressure of carbon dioxide
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics(s)/progressive disease
PD-1	programmed death-1
PD-L1	programmed death-Ligand 1
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response/progesterone receptor/ pulse rate
PRL	prolactin
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q1W	every 1 week
Q2W	every 2 weeks
Q3W	every 3 weeks

Abbreviation	Term
Q4W	every 4 weeks
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
R_{ac}	accumulation ratio
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SC	subcutaneous
SD	single dose/stable disease/standard deviation
SISH	silver enhanced in situ hybridization
SOA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
ss	steady state
SUSAR	suspected unexpected serious adverse reaction
T	T cell
$t_{½}$	terminal elimination half-life
T4	thyroxine
TBili	total bilirubin
TCR	T cell receptor
TIL	tumor infiltrating lymphocytes
T_{max}	time to maximum concentration
$T_{max,ss}$	time to maximum concentration at steady state
TME	tumor microenvironment
TNBC	triple negative BrCa
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTP	time to progression
ULN	upper limit of normal
US	United States
V_{ss}	volume at steady-state
VAAST	Vasopressin and Septic Shock Trial
CCI	[redacted]

Abbreviation	Term
V_z/F	apparent volume of distribution during terminal phase
WBC	white blood cell
WNL	within normal limits
WOCBP	woman/women of childbearing potential

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