A RANDOMIZED, DOUBLE-BLIND BRIDGING SAFETY AND EFFICACY STUDY OF PF-06439535 (CN) PLUS PACLITAXEL-CARBOPLATIN VERSUS BEVACIZUMAB PLUS PACLITAXEL-CARBOPLATIN FOR THE FIRST-LINE TREATMENT OF CHINESE PARTICIPANTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Investigational Product Number:	PF-06439535 (CN)
Investigational Product Name:	Bevacizumab Injection
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	B7391007
Phase:	3

Short Title: A BRIDGING STUDY OF PF-06439535 (CN) PLUS PACLITAXEL-CARBOPLATIN VERSUS BEVACIZUMAB PLUS PACLITAXEL-CARBOPLATIN IN CHINESE PARTICIPANTS WITH ADVANCED NON-SQUAMOUS NSCLC

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	27 Jun 2019	Not applicable (N/A)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A Randomized, Double-blind Bridging Safety and Efficacy Study of PF-06439535 (CN) plus Paclitaxel-Carboplatin versus Bevacizumab plus Paclitaxel-Carboplatin for the First-line Treatment of Chinese Participants with Advanced Non-Squamous Non-Small Cell Lung Cancer

Short Title: A Bridging Study of PF-06439535 (CN) plus Paclitaxel-Carboplatin versus Bevacizumab plus Paclitaxel-Carboplatin in Chinese Participants with Advanced Non-Squamous NSCLC

Rationale

Bevacizumab (marketed under the brand name AVASTIN) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to and inhibits the biological activity of vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. In its United States (US) and European Union (EU) product labeling, bevacizumab is indicated for metastatic colorectal cancer, glioblastoma, metastatic breast cancer, non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer, and epithelial ovarian, fallopian tube, and primary peritoneal cancers. National Medical Products Administration (NMPA) has approved bevacizumab for the treatment of metastatic colorectal cancer and NSCLC. PF-06439535 (China [CN]) is a humanized IgG1 monoclonal antibody designed as a potential biosimilar to bevacizumab.

Pfizer plans to demonstrate that PF-06439535 (CN) is biosimilar to bevacizumab sourced from EU (bevacizumab-EU). PF-06439535 manufactured locally in China will be referred to as PF-06439535 (CN) to differentiate from the global PF-06439535 which was not manufactured in China. Likewise, the general term bevacizumab is sometimes used for convenience when discussing the 2 blinded investigational products (ie, PF-06439535 [CN] and bevacizumab-EU), but is not a claim of biosimilarity. Biosimilarity will be assessed and supported by analytical, non-clinical, clinical pharmacokinetic (PK), and safety and efficacy studies, as needed.

Although clinical data with PF-06439535 (CN) are not yet available, an extensive clinical development program has been conducted with globally manufactured PF-06439535. Pfizer has performed a single-dose pharmacokinetic similarity trial in healthy volunteers (Study B7391001) and a comparative efficacy and safety trial (Study B7391003) in advanced non-squamous NSCLC, both of which provided robust data to demonstrate the biosimilarity of PF-06439535 and bevacizumab-EU. CCI

CCI [redacted]

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To explore similarity in efficacy of PF-06439535 (CN) and bevacizumab-EU, each in combination with paclitaxel and carboplatin, based on a descriptive estimation of objective response rate (ORR).	• The primary estimand is the treatment effect of PF-06439535 (CN) relative to bevacizumab-EU by Week 19 and subsequently confirmed by Week 25 without regard to discontinuation of treatment or use of concomitant therapy. If a participant takes anti-cancer medication, all responses after that timepoint are excluded from the analysis.	• ORR, evaluating best overall responses achieved by Week 19 and subsequently confirmed by Week 25, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety of PF-06439535 (CN) plus paclitaxel and carboplatin, versus bevacizumab-EU plus paclitaxel and carboplatin; • To evaluate the pharmacokinetics (PK) of PF-06439535 (CN) and bevacizumab-EU; • To evaluate the immunogenicity of PF-06439535 (CN) and bevacizumab-EU.	• The estimand for safety evaluation is to compare the safety characteristics for PF-06439535 (CN) relative to bevacizumab-EU without regard to discontinuation of treatment or use of concomitant therapy; • The estimand for PK evaluation is to compare the PK characteristics of PF-06439535 (CN) relative to bevacizumab-EU under the scenario of no major protocol deviations that may influence the PK assessment; • The estimand for immunogenicity evaluation is to compare	• Safety characterized by type, incidence, severity, timing, seriousness, and relationship to investigational product of adverse events, including cardiotoxicity and infusion related reactions, and laboratory abnormalities; • Trough and apparent peak PF-06439535 (CN) and bevacizumab-EU concentrations; • Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb).

Objectives	Estimands	Endpoints
	the immunogenicity. characteristics of PF-06439535 (CN) relative to bevacizumab-EU without regard to discontinuation of treatment or use of concomitant therapy.	

Overall Design

This is a double-blind, randomized, parallel-group, bridging clinical trial evaluating the efficacy and safety of PF-06439535 (CN) plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for participants with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

Approximately 108 participants will be enrolled in each treatment arm for a total of approximately 216 participants at over 30 centers. Participants will be randomized (1:1) to receive either PF-06439535 (CN) plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least 4 and no more than 6 cycles, followed by the assigned blinded bevacizumab monotherapy until investigator-assessed disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, unacceptable toxicity, death, withdrawal of consent occurs, lost to follow-up, or 25 weeks, whichever comes first. At Week 25, all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator, will receive PF-06439535 (CN) monotherapy for up to 2 years from randomization in this study, or until no further benefit from treatment (eg, investigator assessed disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up), whichever occurs first. Randomization will be stratified by sex (male/female) and smoking history (yes/no). Efficacy, safety, PK and immunogenicity assessments and procedures will be undertaken as described in the Schedule of Activities, Study Flowchart 1 and 2.

Actual length of participation for individual participants will depend upon the actual duration of treatment. Participants will be expected to participate in the study for approximately 26 months. This includes up to 1 month of screening, 24 months for treatment and 28 days of safety follow-up. A participant has completed the study if he/she has completed all phases of the study including the last visit. The end of the study is defined as the date of the last visit of the last participant in the study.

Number of Participants

A total sample size of approximately 216 participants (108 per treatment arm) will be randomized to achieve the target sample size of 200.

Intervention Groups and Duration

There are two treatment arms:

Arm A PF-06439535 (CN) + paclitaxel + carboplatin.

Arm B Bevacizumab-EU + paclitaxel + carboplatin.

Assigned PF-06439535 (CN) or bevacizumab-EU monotherapy following completion of at least 4 and no more than 6 cycles of combination with chemotherapy will proceed until investigator-assessed disease progression defined by RECIST 1.1, unacceptable toxicity, death, withdrawal of consent occurs, or lost to follow-up or 25 weeks, whichever comes first.

At Week 25, all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator, will receive PF-06439535 (CN) monotherapy for up to 2 years from randomization in this study, or until no further benefit from treatment (eg, investigator assessed disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up), whichever occurs first. This will require participants initially randomized to Arm B to switch from bevacizumab-EU to PF-06439535 (CN) monotherapy starting at Week 25 (Cycle 9).

Data Monitoring Committee:

This study will use an external data monitoring committee (E-DMC).

Statistical Methods:

This study is descriptive in nature, and hence no statistical hypothesis testing will be done. For efficacy, descriptive statistics for complete response (CR), partial response (PR) and objective response rate (ORR) by treatment group will be presented. The frequency, percentage and 90% confidence interval of these response rates will be constructed. The estimated risk difference and risk ratio in ORR between PF-06439535 (CN) and bevacizumab-EU will be computed, and the corresponding 90% confidence intervals will be calculated using Miettinen and Nurminen (1985) method. Safety, pharmacokinetics (PK), and immunogenicity will be summarized by treatment group.

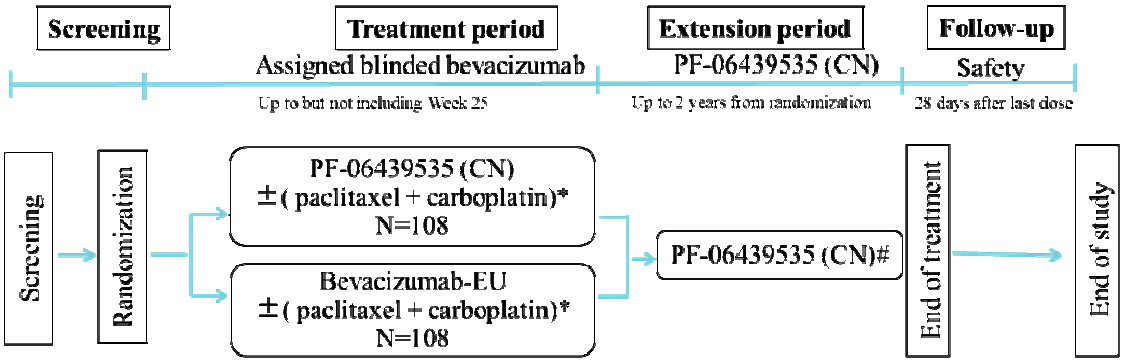
After all participants have completed the Week 25 visit (ie, the last participant randomized has completed the Week 25 visit) or have otherwise died, withdrawn consent, or are lost to follow-up, primary study completion will be achieved. A database snapshot (containing data up to and including the Week 25 visit for every participant) will be performed after the primary completion date (PCD) and a study report will be developed to support the new drug application. Data collected after the Week 25 visit will be summarized in a supplemental clinical study report which will describe safety results during the monotherapy extension period and will be considered as supplemental to the clinical study report for the PCD.

In general, efficacy, safety, PK and immunogenicity as of the Week 25 visit will be analyzed by treatment group in the study report for the PCD. In the supplemental clinical study report, safety will be summarized across all patients, and PK and immunogenicity (which are to be collected at end of treatment/withdrawal visit) will be listed.

1.2. Schema

Figure 1. B7391007 Study Schema

B7391007 Study Schema



* Following completion of at least 4 and no more than 6 cycles of chemotherapy, assigned PF-06439535 (CN) or bevacizumab-EU monotherapy for up to but not including Week 25.

PF-06439535 (CN) will be provided for all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator up to 2 years from randomization.

1.3. Schedule of Activities (SoA)

STUDY FLOWCHART 1 (Overall Schedule of Events – Investigational Product)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10, up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		0	±4	±4	±4	±4	±4	±4	±4	±4	+7
Pre-treatment Documentation											
Informed Consent[1]	X										
Demography, Medical/ Cancer History, Driver Genetic Alteration status[2]	X										
Complete Physical Exam[3]	X										
Brief Physical Exam[4]		X	X	X	X	X	X	X	X		X
Vital signs[5]	X	X	X	X	X	X	X	X	X		X

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10，up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		0	±4	±4	±4	±4	±4	±4	±4	±4	+7
Baseline Signs and Symptoms[6]		X									
ECOG Performance Status (Appendix 8)	X	X	X	X	X	X	X	X	X		X
Inclusion/Exclusion Criteria[7]	X										
Laboratory Studies and Tests											
Hematology[8]	X	X	X	X	X	X	X	X	X		X
Blood Chemistry[9]	X	X	X	X	X	X	X	X	X		X
Coagulation[10]	X										X
Pregnancy Test[11]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[12]	X	X	X	X	X	X	X	X	X		X
Serological Tests[13]	X										
Immunogenicity (ADA/NAb)	Refer to Study Flowchart 2										
Pharmacokinetics	Refer to Study Flowchart 2										
Tumor Assessments											
Head scan[14]	X	As clinically indicated and at time of confirmatory scan for PR/CR									
CT or MRI of Chest, Abdomen, and other disease sites[14]	X	Every 6 weeks (±7 days) until Week 25 (based on date of randomization).									X

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10, up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	+7
Randomization											
Randomization[15]		X									
Drug Administration											
Paclitaxel and Carboplatin[16]		X	X	X	X	Optional	Optional				
PF-06439535 (CN) or Bevacizumab[17]		X	X	X	X	X	X	X			
PF-06439535 (CN)[18]									X	X	
Other Clinical Assessments											
12-lead ECG[19]	X	As clinically indicated									X
MUGA or ECHO[20]	X										X
Contraception check[21]	X	X	X	X	X	X	X	X	X	X	X
Serious and nonserious adverse events[22]	Monitored continuously										
Prior Medications/ Treatments[23]	X										
Concomitant Treatments[24]	Monitored continuously										

Footnotes
Abbreviations: C=cycle; ECOG= Eastern Cooperative Oncology Group; ADA=anti-drug antibodies; NAb=neutralizing antibodies; CT= computed tomography; MRI= magnetic resonance imaging; SOC=standard of care.

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10, up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		0	±4	±4	±4	±4	±4	±4	±4	±4	+7

1. Informed Consent: Must be obtained prior to undergoing any study specific procedure.
2. Demographics and Medical/Cancer History, Driver Genetic Alterations: To include information on prior anti-tumor regimens (including chemotherapy and radiation therapy and duration of treatment), driver genetic alteration test results, if known, and progression or relapse date. Testing for driver genetic alterations is not required, however participant records are to be reviewed for known EGFR activating mutations (for example, exon 19 deletion or exon 21 L858R substitution mutations) or ALK rearrangements. If EGFR or ALK testing is performed, samples must be tested by local certificated laboratories, and the results must be reviewed and confirmed as negative for EGFR and ALK prior to randomization.
3. Physical Examination: includes, at a minimum, head, ears, eyes, nose, mouth, skin, neck, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, neurological systems, and weight. Height will be recorded at Screening only. Genitourinary examination is only required if directed by signs or symptoms.
4. Brief Physical Examination: performed as directed by signs and symptoms on Day 1 (pre-dose) of each cycle after Screening. Weight should be taken at the beginning of each cycle and will be used for dose calculation in accordance with Section 6.1.1.
5. Vital Signs: Oral temperature, blood pressure, pulse rate, and respiratory rate will be assessed. Temperature should be taken using the same method throughout the study. Blood pressure, pulse rate, and respiratory rate should be taken with the participant in the supine or sitting position after the participant has been resting quietly for at least 5 minutes and prior to dosing on dosing days. On days of an infusion, vital signs should be taken within 30 minutes before the first infusion and within 30 minutes of the end of the last infusion.
6. Baseline Signs and Symptoms: Observed after Screening and before Cycle 1, Day 1 pre-dose are recorded as part of Medical History.
7. Inclusion/Exclusion Criteria: To be reviewed to confirm eligibility prior to randomization.
8. Hematology: Tests include hemoglobin, white blood cells, platelets, and absolute neutrophil count. Results of tests must be reviewed prior to each cycle of therapy.
9. Blood Chemistry: Tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, serum or plasma creatinine, sodium, potassium, total calcium, BUN or urea, magnesium, and albumin, and results must be reviewed prior to each cycle of therapy.
10. Coagulation: Tests include International Normalized Ratio (INR)/prothrombin time (or prothrombin time if INR is not available) and activated partial thromboplastin time. Tests may be performed more frequently if clinically indicated. Results of tests must be reviewed prior to dosing on Cycle 1 Day 1.
11. Pregnancy Test: For Woman of Childbearing Potential (WOCBP), a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed by the local certified laboratory. 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 the participant's receiving the investigational product. 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 treatment visit. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive. See protocol Section 8.2.6 for details.

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10, up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		0	±4	±4	±4	±4	±4	±4	±4	±4	+7

12. Urinalysis: pH, protein, glucose, ketones, bilirubin, blood, leukocyte esterase. If the results of the dipstick urine protein indicate ≥2+ proteinuria during study, follow-up should be performed with a quantitative urine protein analysis according to local standard practices with data captured on the adverse event (AE) case report form (CRF) if AE criteria are met. The results of the dipstick must be reviewed prior to each cycle of therapy.
13. Serological tests: See Exclusion criteria #18 and 19 for specifications. Tests include human immunodeficiency virus antibody (anti-HIV), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc), and hepatitis C virus antibody (anti-HCV). Serum hepatitis B virus (HBV) DNA must be tested for participants as 1) HBsAg-positive, or 2) HBsAg-negative, anti-HBc positive. Hepatitis C virus (HCV) RNA should be tested for anti-HCV positive participants. Samples must be tested by local certified laboratories, and the results must be reviewed and eligibility confirmed prior to randomization.
14. Tumor Assessments: Assessments must include CT with contrast or MRI of head, chest, abdomen (including adrenals) and other disease sites (such as pelvis), if clinically indicated. Tumor assessments are NOT to be scheduled based on cycle length or number of cycles received. Assessment delay to conform to treatment delays is not permitted. The same method of tumor assessments should be used throughout the trial. A confirmatory scan is required approximately 6 weeks (+7 days) for a CR/PR. Additional tumor assessments can occur as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression. Participants who have already demonstrated disease progression do not need to have scans repeated at the End of Treatment (EOT)/Withdrawal visit. Furthermore, additional scans are not required at the EOT/Withdrawal visit for participants with stable disease, PR or CR unless the EOT/Withdrawal visit was conducted greater than 6 weeks from last scan and the participant did not go onto a subsequent anti-cancer therapy.
15. Randomization: Unless clinically indicated, screening physical examination and laboratory assessments including blood chemistry, hematology, and urinalysis, are not required to be repeated for randomization if they are performed ≤7 days prior to Cycle 1, Day 1, and results meet eligibility criteria. Randomization of eligible participants is required no more than 1 day prior to administration of first dose.
16. Paclitaxel and carboplatin administration: per dosing algorithm in protocol for a total of at least 4 and no more than 6 cycles. Premedication is to be administered according to the local label or institutional guidelines. Dose delay (up to 2 weeks) and dose reduction will be permitted per local guidelines. See protocol Section 6 for details.
17. Blinded PF-06439535 (CN) or bevacizumab-EU: 15 mg/kg by intravenous (IV) infusion on Day 1 of each of the 3-week (21-day) cycles up to, but not including Week 25. See protocol Section 6 for details.
18. At Week 25, PF-06439535 (CN) will be provided in a blinded manner for all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator up to 2 years from randomization. All of the protocol specified assessment, including tumor assessment and laboratory tests at Week 25 should be completed before PF-06439535 (CN) is administered. Continued treatment in the study will be based on documented evidence of clinical benefit provided to the Sponsor at regular intervals as determined by local SOC.
19. ECG: 12-lead ECG will be obtained at Screening, as clinically indicated, and at the End-of-Treatment Visit, using an ECG machine that automatically calculates the heart rate and measures PR, QT intervals, and QTc and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes.

Protocol Activity/Cycle	Screening	Treatment Period (Combination Therapy)						Treatment Period (Monotherapy)	Extension Period (Monotherapy)[25]		End of Treatment/ Withdrawals[26]
		PF-06439535 (CN) or bevacizumab with chemotherapy						PF-06439535 (CN) or bevacizumab only	PF-06439535 (CN) only		
		Cycle									
(1 Cycle = 21 days)	≤28 Days Prior to Randomization	C 1 Week 1	C 2 Week 4	C 3 Week 7	C 4 Week 10	C 5 Week 13	C 6 Week 16	C7, C8 Weeks 19 and 22	C9 Week 25	From C10，up to 2 years from randomization	28 days from last investigational product administration
Study Visit Window (days)		**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	+7

20. MUGA or ECHO: to assess left ventricular ejection fraction (LVEF); the original methodology used for each participant must be used throughout the trial.
21. Contraception Check: 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. See Section 5.3.1 for details.
22. Adverse Events: Serious adverse events should be monitored and reported from the time that the participant provides informed consent through and up to 28 days after the last dose of investigational product. Participants must be followed for non-serious adverse events from the time that the participant provides informed consent through and up to 28 days after the last dose of investigational product or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose, whichever comes first. (See Section 8.3 and Appendix 3).
23. Prior Medication/ Treatments: Medications and non-drug treatments delivered prior to the first day of investigational product will be recorded from 28 days prior to the start of investigational product.
24. Concomitant Treatments: recorded from the first day of investigational product and monitored continuously by the investigator until at least 28 days following the last dose of investigational product or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose, to coincide with the safety evaluation period.
25. Extension period: The safety assessments, including hematology, blood chemistry, urinalysis, brief physical exam, vital signs and ECOG, as well as the tumor assessment will be performed per standard of care during the extension period. Pregnancy test and contraception check will be performed every treatment cycle as required. AEs and SAEs will be monitored continuously. Please refer to the CRF Completion Guidelines for further information on data collection requirements during this period.
26. End-of-Treatment/Withdrawals: When participants discontinue investigational product, participants should be evaluated for safety for 28 days after last dose or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose.

STUDY FLOWCHART 2 (Schedule of Events for Pharmacokinetic and Anti-Drug Antibodies)

Protocol Activity/Cycle	Treatment Period (Combination Therapy)				End of Treatment/Withdrawals
	Blinded bevacizumab with Chemotherapy				
	Cycle				
(1 Cycle = 21 days)	C 1 Week 1		C 5 Week 13		
Study Visit Window (days)	0	0	±4		+7
Collection Time (relative to bevacizumab infusion)	Pre-dose	2.5 hrs after the initiation of infusion	Pre-dose	1.5 hrs after the initiation of infusion	Pre-dose
Collection Time window	-2.5 hrs to -5 min	±0.5 hrs	-2.5 hrs to -5 min	±0.5 hrs	
Pharmacokinetics[1]	X	X	X	X	X
Immunogenicity (ADA/NAb)[2]	X		X		X

Footnotes

Abbreviations: ADA=anti-drug antibodies; NAb=neutralizing antibodies.

1. **Pharmacokinetics**: Blood Sampling for Drug Concentration -2.5 hrs to -5 minutes prior to blinded bevacizumab for Cycle 1, Cycle 5 and End of Treatment (if participant received Cycle 5). Post-dose samples will also be collected at 2.5 hrs (±0.5 hrs) after the initiation of planned 90 minute blinded bevacizumab infusion for Cycle 1 and at 1.5 hrs (±0.5 hrs) after the initiation of planned 30 minute blinded bevacizumab infusion for Cycle 5 (if participant received Cycle 5). If the duration of infusion differs from the planned duration, the sampling time will adjust accordingly to occur at 1 hour (±0.5 hrs) post the end of infusion. If ADA/NAb sampling is conducted at the time of immunogenicity-related adverse events, a serum sample for drug concentration will also be collected at that same time point. Every effort will be made to collect these PK samples at the exact nominal times relative to the infusions of bevacizumab, while a variation window is allowed for each sampling time point. The actual time of each sample collection will be recorded on the source document and case report form (eg, CRF).
2. **Immunogenicity:** Blood Sampling for ADA/NAb prior to blinded bevacizumab. If adverse events are considered possibly related to ADA formation, an additional sample may be collected at the time of the immunogenicity-related adverse events.

2. INTRODUCTION

PF-06439535 (CN) is a humanized IgG1 monoclonal antibody being developed as a potential biosimilar to bevacizumab. Bevacizumab (marketed under the brand name AVASTIN) is the commercially available bevacizumab product in the United States (bevacizumab-US), European Union (bevacizumab-EU), China (bevacizumab-CN), Japan, and other regions. In its United States (US)[1] and European Union (EU)[2] product label, bevacizumab is indicated for metastatic colorectal cancer, glioblastoma, metastatic breast cancer, non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer, and epithelial ovarian, fallopian tube, and primary peritoneal cancers. In China, National Medical Products Administration (NMPA) has approved bevacizumab for the treatment of metastatic colorectal cancer and NSCLC.[3]

Development of a biosimilar requires head-to-head comparison to a licensed reference product. The European Union (EU) has a legal basis for approval of biosimilars, published with Directive 2001/83/EC, as amended with Directive 2004/27/EC. The legislation came into effect in 2005 and requires that the EU-approved originator product is the reference product in the EU. In the US, the Biologics Price Competition and Innovation Act creates an abbreviated approval pathway for biological products that are demonstrated to be biosimilar to a licensed reference which must be with a Food and Drug Administration (FDA)-licensed biological product. National Medical Products Administration (NMPA) issued the guidance on development and evaluation of biosimilars in 2015, which requires that the reference product used for head-to-head comparison must be approved in China. Additional draft guidance specific to bevacizumab biosimilar clinical development was issued by NPMA on 18 July 2017 entitled, "Considerations regarding Bevacizumab Clinical Research Design and Review".

Pfizer plans to demonstrate that PF-06439535 (CN) is biosimilar to bevacizumab sourced from Europe (bevacizumab-EU). PF-06439535 manufactured locally in China will be referred to as PF-06439535 (CN) to differentiate it from the global PF-06439535 manufactured outside China. Likewise, the general term bevacizumab is sometimes used for convenience when discussing the 2 blinded investigational products (ie, PF-06439535 [CN] and bevacizumab-EU), but is not a claim of biosimilarity. Biosimilarity will be assessed and supported by analytical, non-clinical, and clinical pharmacokinetic (PK), and safety and efficacy studies as needed.

2.1. Study Rationale

Although clinical data with PF-06439535 (CN) are not yet available, an extensive clinical development program has been conducted with globally manufactured PF-06439535. Pfizer has performed a single-dose pharmacokinetic similarity trial in healthy volunteers (Study B7391001) and a comparative efficacy and safety trial (Study B7391003) in advanced non-squamous NSCLC, both of which provided robust data to demonstrate the biosimilarity of PF-06439535 and bevacizumab-EU. CCI [redacted]

2.2. Background

Biological therapeutics are large complex protein molecules that require a wide variety of analytical methods to ensure consistent quality. As a result of their complexity and manufacturing methods, biologic products have inherent variability and the development of an exact replicate is not possible. Biosimilars are structurally highly similar versions of marketed biological medicines that are supported by appropriate analytical testing and clinical trials to demonstrate that they are sufficiently "similar" (both in structure and clinical function) to the marketed biological product.

2.2.1. Clinical Overview

2.2.1.1. Bevacizumab

Bevacizumab is an extensively studied and effective therapy that is approved in the US and EU for the treatment of patients with metastatic colorectal cancer, glioblastoma, metastatic breast cancer, NSCLC, advanced and/or metastatic renal cell cancer, and epithelial ovarian, fallopian tube, and primary peritoneal cancers.[1,2] In China, bevacizumab is approved for the treatment of metastatic colorectal cancer and NSCLC.[3] Information contained in the following sections focuses on the efficacy, safety and immunogenicity of bevacizumab based on publically available information for AVASTIN. Background clinical information represents the expectations for PF-06439535 (CN) and should not be considered a claim of biosimilarity.

Bevacizumab is a humanized IgG1 recombinant monoclonal antibody that is composed of 2 heavy (H) chains and 2 light (L) chains, which are linked by disulfide bonds. It has an approximate molecular weight of 149 kD and is produced in mammalian Chinese hamster ovary cells.

Bevacizumab binds VEGF and prevents the interaction of VEGF with its receptors; Flt 1 and kinase insert domain receptor (KDR), on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis.[1,2] The blockade interaction of VEGF by bevacizumab inhibits angiogenesis and tumor growth. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

2.2.1.1.1. Efficacy of Bevacizumab

Across tumor types, randomized controlled trials have demonstrated that bevacizumab plus chemotherapy is associated with benefits such as improved overall survival (OS) and progression-free survival (PFS) relative to chemotherapy alone[4,5,6] and bevacizumab continues to have a prominent position in cancer treatment algorithms.[7,8]

2.2.1.1.2. Safety of Bevacizumab

Bevacizumab has a well-established safety profile in all approved indications based on clinical trial experience in more than 5700 participants.[2]

The most serious adverse reactions with bevacizumab include gastrointestinal (GI) perforation, hemorrhage including pulmonary hemorrhage/haemoptysis (more common in NSCLC patients) and arterial thromboembolism (ATE), as described in the US and EU product labels.[1,2] The most common adverse reactions associated with bevacizumab treatment include hypertension, fatigue or asthenia, diarrhea and abdominal pain.[1]

2.2.1.1.3. Immunogenicity of Bevacizumab

As with all therapeutic proteins, there is a potential for immunogenicity. Anti-drug antibodies (ADA) have been evaluated in studies with bevacizumab in cancer patient populations. Using an electrochemiluminescent based assay, 14 of 2,233 evaluable participants (0.63%) treated in clinical trials tested positive for anti-bevacizumab antibodies. Among these 14 participants, 3 tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay. The clinical significance of anti-product antibody formation is unknown.[1]

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2.2.1.3.1. Similarity in Pharmacokinetics

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The PK of PF–06439535 and bevacizumab–EU were also assessed as a secondary endpoint of the comparative efficacy and safety trial in non-squamous NSCLC (B7391003) participants. Trough and peak serum concentrations of PF–06439535 and AVASTIN measured at select cycles were similar between the two treatment groups

In summary, the PK profiles are similar between PF-06439535 and AVASTIN reference product (bevacizumab–US and bevacizumab–EU), providing the first level of clinical evidence of similarity between PF-06439535 and AVASTIN.[10]

2.2.1.3.2. Similarity in Efficacy – Study B7391003

A single, comparative clinical efficacy and safety trial (B7391003) was conducted to compare the efficacy profiles of PF-06439535 and bevacizumab-EU in the sensitive population of participants with non-squamous NSCLC. The results of this study are summarized below.

The ORR results for the primary endpoint met the pre-specified equivalence criterion; refer to Table 2. In the Intent to Treat (ITT) population, the ORR was similar between both treatment groups (45.3% in the PF-06439535 group and 44.6% in the bevacizumab–EU group).

The ORR analysis showed an un-stratified risk ratio of 1.0146 (PF-06439535 versus bevacizumab-EU), with a 95% CI of (0.8628, 1.1933) and a 90% CI of (0.8856, 1.1625), and an un-stratified risk difference of 0.6531% (PF-06439535 versus bevacizumab-EU), with a 95% confidence interval (CI) of (-6.6080%, 7.9082%), all of which fell entirely within the equivalence margins as described in Table 2. The 95% CI and 90% CI of stratified risk ratios (stratified by region, gender, and smoking history) and the 95% CI of the stratified risk difference (stratified by region, gender, and smoking history) in ORR (PF-06439535 versus bevacizumab-EU), also fell entirely within the equivalence margins.

Table 2. Summary of BOR and ORR (Week 19) (Unstratified) – ITT Population

Number (%) of Participants	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Best overall response (BOR)			
Complete response (CR)	9 (2.5)	4 (1.1)	13 (1.8)
Partial response (PR)	153 (42.7)	157 (43.5)	310 (43.1)
Stable disease	154 (43.0)	166 (46.0)	320 (44.5)

Table 2. Summary of BOR and ORR (Week 19) (Unstratified) – ITT Population

Number (%) of Participants	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Objective progression	15 (4.2)	14 (3.9)	29 (4.0)
Indeterminate[a]	27 (7.5)	20 (5.5)	47 (6.55)
Objective response rate (CR+PR)	162 (45.3)	161 (44.6)	323 (44.9)
95% Exact CI[b]	[40.01, 50.57]	[39.40, 49.89]	[41.25, 48.64]
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk difference in ORR (%)[c]	0.6531		
95% CI of difference (%)[c]	[-6.6080, 7.9082]		
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk ratio[d]	1.0146		
95% CI of risk ratio[d]	[0.8628, 1.1933]		
90% CI of risk ratio[d]	[0.8856, 1.1625]		

ORR data from the primary completion date, PCD (08 May 2017).
ORR was defined as the percentage of participants within each treatment group who achieved CR or PR by Week 19 of the study, which was subsequently confirmed by Week 25, in accordance with RECIST, Version 1.1.
Abbreviations: BOR=best overall response; CI=confidence interval; CR=complete response; EU=European Union; ITT=intent-to-treat; N=total number of participants; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

a. Indeterminate: Early deaths, unevaluable tumor assessment, and early study discontinuations.
b. Exact method based on F-distribution was used.
c. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk difference for confirmed response. EU equivalence margins (95% CI in -13% to 13%).
d. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response. US equivalence margins (90% CI in 0.73 to 1.37) and Japan equivalence margins (95% CI in 0.729 to 1.371).

There were no clinically meaningful differences between PF–06439535 and bevacizumab-EU shown in the analyses for all the secondary efficacy endpoints.

The results support an overall conclusion of no clinically meaningful difference in efficacy between PF–06439535 and AVASTIN (bevacizumab–EU).

2.2.1.3.3. Similarity in Safety – Study B7391003

A single, comparative clinical efficacy and safety trial (B7391003) was conducted to compare the safety profiles of PF-06439535 and bevacizumab-EU in the sensitive population of participants with non-squamous NSCLC. The results of this study are summarized below.

A summary of all causality TEAEs, SAEs, discontinuations of any treatment, temporary discontinuations, dose reductions and infusion rate reductions are provided in Table 3. Overall, these events were comparable between the PF-06439535 group and the bevacizumab-EU group.

Table 3. Treatment-Emergent Adverse Events (All Causalities) - Safety Population

Number (%) of Participants	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Number of adverse events	2442	2470	4912
Participants with adverse events	344 (96.6)	347 (96.9)	691 (96.8)
Participants with serious adverse events	81 (22.8)	80 (22.3)	161 (22.5)
Participants with Grade 3 or 4 adverse events	159 (44.7)	159 (44.4)	318 (44.5)
Participants with Grade 5 adverse events	21 (5.9)	24 (6.7)	45 (6.3)
Participants discontinued any treatment due to adverse events	85 (23.9)	86 (24.0)	171 (23.9)
Participants discontinued bevacizumab only due to adverse events	37 (10.4)	29 (8.1)	66 (9.2)
Participants discontinued bevacizumab and chemotherapy due to adverse events	30 (8.4)	28 (7.8)	58 (8.1)
Participants discontinued paclitaxel due to adverse events	53 (14.9)	60 (16.8)	113 (15.8)
Participants discontinued carboplatin due to adverse events	49 (13.8)	54 (15.1)	103 (14.4)

Table 3. Treatment-Emergent Adverse Events (All Causalities) - Safety Population

Number (%) of Participants	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Participants temporarily discontinued bevacizumab only due to adverse events	42 (11.8)	39 (10.9)	81 (11.3)
Participants temporarily discontinued bevacizumab and chemotherapy due to adverse events	52 (14.6)	52 (14.5)	104 (14.6)
Participants temporarily discontinued paclitaxel due to adverse events	56 (15.7)	59 (16.5)	115 (16.1)
Participants temporarily discontinued carboplatin due to adverse events	53 (14.9)	51 (14.2)	104 (14.6)
Participants with dose reduction of bevacizumab only due to adverse events	0	0	0
Participants with dose reduction of bevacizumab and chemotherapy due to adverse events	0	0	0
Participants with dose reduction of paclitaxel due to adverse events	27 (7.6)	38 (10.6)	65 (9.1)
Participants with dose reduction of carboplatin due to adverse events	22 (6.2)	38 (10.6)	60 (8.4)
Participants with infusion rate reduced for bevacizumab only due to adverse events	0	0	0
Participants with infusion rate reduced for bevacizumab and chemotherapy due to adverse events	0	0	0
Participants with infusion rate reduced for paclitaxel due to adverse events	2 (0.6)	0	2 (0.3)
Participants with infusion rate reduced for carboplatin due to adverse events	1 (0.3)	0	1 (0.1)

Table 3. Treatment-Emergent Adverse Events (All Causalities) - Safety Population

Number (%) of Participants	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)

Included data up to 28 days after the last dose of study drug or to start of subsequent anti-cancer therapy (whichever occurred first).
Except for the "number of adverse events", participants were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA version 20.1 coding dictionary applied.
Abbreviations: EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants evaluable for adverse events.

The majority of the participants in this study had at least 1 treatment emergent adverse event (TEAE (all causality), with 344 (96.6%) participants in the PF-06439535 group, and 347 (96.9%) participants in the bevacizumab-EU group reporting a total of 2442 and 2470 TEAEs (Table 3).

A total of 161 (22.5%) participants had at least 1 serious adverse event (SAE) (all causality) with 81 (22.8%) participants in the PF-06439535 group, and 80 (22.3%) participants in the bevacizumab-EU group. The most frequently reported SAEs (>1% of participants in either treatment group) were pneumonia, with 8 (2.2%) participants in the PF-06439535 group, and 6 (1.7%) participants in the bevacizumab-EU group; febrile neutropenia (5 [1.4%] participants in the PF-06439535 group and 7 [2.0%] participants in the bevacizumab-EU group); and pulmonary embolism (7 [2.0%] participants in the PF-06439535 group, and 2 [0.6%] participants in the bevacizumab-EU group).

TEAEs of special interest were selected based on the established safety profile of bevacizumab and reported as Tier-1 AEs. The identified TEAEs of special interest included ATE events, bleeding/hemorrhage (including pulmonary hemorrhage), cardiac disorders, congestive heart failure, hypertension (Grade 3 or higher), proteinuria/nephrotic syndrome, venous thromboembolic events (VTE), gastrointestinal (GI) perforations, and wound healing complications. Overall, all causality TEAEs of special interest were comparable and no clinically meaningful differences were noted between the 2 treatment groups.

Nineteen (19 [5.3%]) participants in the PF-06439535 group, and 22 (6.1%) participants in the bevacizumab-EU group reported infusion related reactions (IRRs) as per the investigator's assessment. A total of 21 (2.9%) participants (12 [3.4%] participants in the PF-06439535 group, and 9 [2.5%] participants in the bevacizumab-EU group reported bevacizumab-related IRRs in this study. IRRs reported by the investigators were comparable between the two treatment groups. In addition, the incidence of potential hypersensitivity TEAEs was comparable among the 2 treatment groups in the retrospective analysis of TEAEs retrieved by using standardized Medical Dictionary for Regulatory Activities [MedDRA] queries (SMQs) of hypersensitivity and anaphylactic reactions.

Overall, the safety profiles of PF-06439535 and AVASTIN were comparable between the 2 treatment groups with no clinically meaningful differences observed, and consistent with the established safety profile of AVASTIN.

2.2.1.3.4. Similarity in Immunogenicity

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The collective results from both clinical trials support a low and similar immunogenicity profile of PF-06439535 compared to AVASTIN (bevacizumab-EU).

2.2.1.4. Paclitaxel as Background Therapy for Study B7391007

Paclitaxel is a natural product with antitumor activity and is obtained via a semi-synthetic process from *Taxus baccata*. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.[11]

While the paclitaxel prescribing information does not include combination with bevacizumab, the bevacizumab prescribing information specifies bevacizumab is indicated for treatment of NSCLC in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

Common adverse events associated with the use of paclitaxel include neutropenia, leucopenia, thrombocytopenia, anemia, infections, hypersensitivity reactions, peripheral neuropathy, arthralgia, myalgia, gastrointestinal symptoms include nausea, vomiting, diarrhea, and mucositis, and alopecia.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of participants receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Paclitaxel should not come in contact with plasticized polyvinylchloride (PVC) equipment or devices. Diluted paclitaxel must be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (eg, cyclosporine) should not be treated with paclitaxel. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension.

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times upper limit of normal (ULN). Extreme caution should be exercised when administering paclitaxel to such patients, with dose reduction as recommended in the prescribing information.

Injection site reactions to paclitaxel, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported with paclitaxel. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, ie, “recall,” has been reported.

In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

2.2.1.5. Carboplatin as Background Therapy for Study B7391007

Carboplatin is a platinum coordination compound used as a cancer chemotherapeutic agent. It produces predominantly interstrand deoxyribonucleic acid (DNA) cross-links rather than DNA-protein cross links for a cell-cycle nonspecific effect. With the exception of carboplatin, there are no significant quantities of protein-free ultrafilterable platinum-containing species present in plasma. Platinum from carboplatin becomes bound irreversibly to plasma proteins and is slowly eliminated with a half-life of 5 days at minimum.[12]

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents and for treatment of ovarian carcinoma recurrent after prior chemotherapy. While the carboplatin prescribing information does not include combination with bevacizumab, the bevacizumab prescribing information specifies bevacizumab is indicated for treatment of NSCLC in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

Common adverse events associated with the use of carboplatin include bone marrow suppression, anemia, thrombocytopenia, neutropenia, leucopenia, infections, bleedings, gastrointestinal toxicity including vomiting and nausea, peripheral neuropathies, nephrotoxicity, hepatic toxicity, electrolyte abnormalities, allergic reactions, injection site reactions, pain, and asthenia.

Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds; patients with pre-existing severe renal impairment, unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks; patients with severe myelosuppression; and patients with bleeding tumors.

As is the case with other platinum compounds, allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions, including anaphylaxis, in patients previously exposed to platinum therapy.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity and caution must be exercised when a patient receives both drugs.

Carboplatin can cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis.

Needles or intravenous sets containing aluminum parts that may come in contact with carboplatin should not be used for preparation or administration. Aluminum reacts with carboplatin causing precipitate formation and/loss of potency.

Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds. Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.[12]

2.3. Benefit/Risk Assessment

PF-06439535 (CN) is being developed as a potential biosimilar to bevacizumab, marketed under the brand name AVASTIN. Bevacizumab (AVASTIN) is commercially available in the United States (bevacizumab-US), European Union (bevacizumab-EU), China (bevacizumab-CN), Japan, and other regions. In China, bevacizumab is licensed for the treatment of metastatic colorectal cancer (mCRC) and first-line non-squamous NSCLC.

Lung cancer is the most common cancer among men and the leading cause of cancer related morbidity and mortality worldwide. NSCLC accounts for 85% of total lung cancer cases.[13] Bevacizumab has shown anti-tumor activity in previously untreated NSCLC patients, which also represent a population with well categorized safety and efficacy profile for treatment with bevacizumab and paclitaxel and carboplatin. As such, this population is considered to be a sensitive population to demonstrate that there are no clinically meaningful differences between PF-06439535 (CN) and bevacizumab-EU.

For the potential risk, the overall safety profile of AVASTIN is based on data from over 5700 patients with various malignancies, predominantly treated with AVASTIN in combination with chemotherapy in clinical trials. The most frequently observed adverse reactions across clinical trials in participants receiving AVASTIN were hypertension, fatigue or asthenia, diarrhea and abdominal pain. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with AVASTIN therapy are likely to be dose-dependent.[1,2]

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06439535 (CN) and bevacizumab may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To explore similarity in efficacy of PF-06439535 (CN) and bevacizumab-EU, each in combination with paclitaxel and carboplatin, based on a descriptive estimation of objective response rate (ORR).	• The primary estimand is the treatment effect of PF-06439535 (CN) relative to bevacizumab-EU by Week 19 and subsequently confirmed by Week 25 without regard to discontinuation of treatment or use of concomitant therapy. If a participant takes anti-cancer medication, all responses after that timepoint are excluded from the analysis.	• ORR, evaluating best overall responses achieved by Week 19 and subsequently confirmed by Week 25, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety of PF-06439535 (CN) plus paclitaxel and carboplatin, versus bevacizumab-EU plus paclitaxel and carboplatin; • To evaluate the pharmacokinetics (PK) of PF-06439535 (CN) and bevacizumab-EU; • To evaluate the immunogenicity of PF-06439535 (CN) and bevacizumab-EU.	• The estimand for safety evaluation is to compare the safety characteristics for PF-06439535 (CN) relative to bevacizumab-EU without regard to discontinuation of treatment or use of concomitant therapy; • The estimand for PK evaluation is to compare the PK characteristics of PF-06439535 (CN) relative to bevacizumab-EU under the scenario of no major protocol deviations that may influence the PK assessment; • The estimand for immunogenicity evaluation is to compare the immunogenicity characteristics of PF-06439535 (CN) relative to bevacizumab-EU without regard to discontinuation of treatment or use of concomitant therapy.	• Safety characterized by type, incidence, severity, timing, seriousness, and relationship to investigational product of adverse events, including cardiotoxicity and infusion related reactions, and laboratory abnormalities; • Trough and apparent peak PF-06439535 (CN) and bevacizumab-EU concentrations; • Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb).

4. STUDY DESIGN

4.1. Overall Design

This is a double-blind, randomized, parallel-group clinical bridging trial evaluating the efficacy and safety of PF-06439535 (CN) plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for participants with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

Approximately 108 participants will be enrolled in each treatment arm for a total of approximately 216 participants at over 30 centers in China, aim to achieve a target sample size of 200. Participants will be randomized (1:1) to receive either PF-06439535 (CN) plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least 4 and no more than 6 cycles, followed by the assigned blinded bevacizumab monotherapy until investigator assessed disease progression defined by RECIST 1.1, unacceptable toxicity, death, withdrawal of consent occurs, lost to follow-up, or 25 weeks, whichever comes first. At Week 25, all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator, will receive PF-06439535 (CN) monotherapy for up to 2 years from randomization in this study, or until no further benefit from treatment (eg, investigator assessed disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up), whichever occurs first. Randomization will be stratified by sex (male/female) and smoking history (yes/no). Efficacy, safety, PK and immunogenicity assessments and procedures will be undertaken as described in the Schedule of Activities, Study Flowchart 1 and 2.

Actual length of participation for individual participants will depend upon the actual duration of treatment. Participants will be expected to participate in the study for approximately 26 months. This includes up to 1 month of screening, 24 months for treatment, and 28 days of safety follow-up. A participant has completed the study if he/she has completed all phases of the study including the last visit. The end of the study is defined as the date of the last visit of the last participant in the study.

4.2. Scientific Rationale for Study Design

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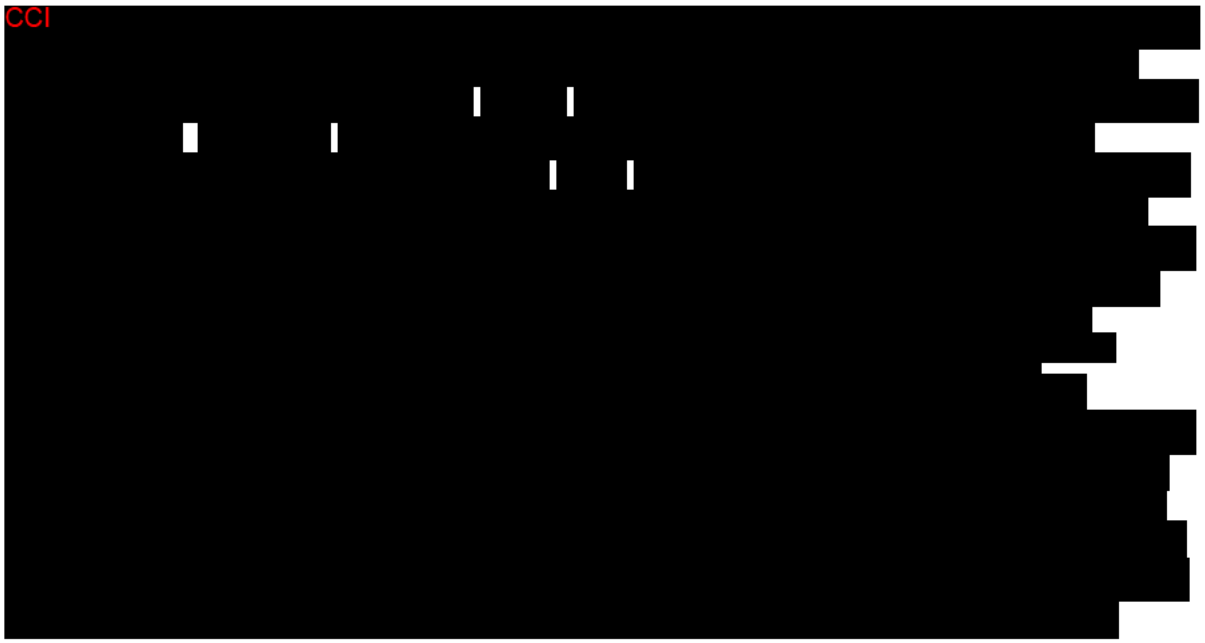
AVASTIN approved in Chinese market is from Europe, therefore European sourced product (bevacizumab-EU) is selected as the comparator.

Patients with previously untreated advanced non-squamous NSCLC represent a population with well categorized safety and efficacy profile for treatment with bevacizumab and paclitaxel and carboplatin. As such, this population is considered to be a sensitive population to summarize the efficacy, safety, PK and immunogenicity profile of PF-06439535 (CN) and bevacizumab-EU.

In order to keep this study in historical context, 3 randomized studies of bevacizumab plus paclitaxel and carboplatin were reviewed and key features were incorporated.[5,14,15] For example, the patient population is similar to that of the Phase 3 study conducted by the Eastern Cooperative Oncology Group (ECOG).[5] Participants in that trial had recurrent or advanced non–small-cell lung cancer (Stage IIIB or IV). Eligible participants were required to have histologically or cytologically confirmed, newly diagnosed stage IIIB (malignant pleural effusion) or Stage IV cancer or recurrent NSCLC for which they had not received chemotherapy. Other inclusion criteria were measurable or non-measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), an ECOG performance status of 0 or 1, and adequate hematologic, hepatic, and renal function (including urinary excretion of ≤500 mg of protein per day). Exclusion criteria included but were not limited to histologic evidence of predominantly squamous-cell cancer; central nervous system (CNS) metastases (to reduce concern about possible CNS hemorrhage); pregnancy or lactation; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin (>325 mg per day), nonsteroidal anti-inflammatory agents, or other agents known to inhibit platelet function; radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment; clinically significant cardiovascular disease; and medically uncontrolled hypertension.



4.3. Justification for Dose

The dose and regimen for PF-06439535 (CN) and bevacizumab-EU in this comparative trial was chosen to be consistent with product labeling of bevacizumab-EU. The chemotherapy given with the investigational products and the regimens used are considered standard of care locally.

For detailed information, please see Section 6.1.1 Administration and Section 6.6 Dose Modification.

4.4. End of Study Definition

A participant has completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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. Male and female participants age ≥18 years of age.

    - 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. Newly diagnosed Stage IIIB, IIIC or IV non-small cell lung cancer (NSCLC) (according to American Joint Committee on Cancer (AJCC) Staging Manual, 8th Edition, last updated 05 June 2018, see Appendix 7) or recurrent NSCLC.

4. Histologically or cytologically confirmed diagnosis of non-squamous NSCLC.

5. At least one measurable lesion as defined by RECIST v1.1.

6. For participants with recurrent disease, at least 6 months must have elapsed since completing adjuvant or neoadjuvant treatment.

7. Screening scan (computed tomography [CT] or magnetic resonance imaging [MRI]) of the head, chest, abdomen (with adrenal glands), and other disease sites as clinically indicated, to assess disease burden.

8. ECOG Performance Status of 0 or 1.

9. Recovery (to Grade 1 or baseline) from all clinically significant adverse effects of prior therapies (excluding alopecia).

10. Be eligible to receive investigational product of bevacizumab, paclitaxel, and carboplatin based on local standard of care, for the treatment of advanced or metastatic non-squamous NSCLC.

Informed Consent:

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

5.2. Exclusion Criteria

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

Disease Characteristics:

1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumors and mixed adenosquamous carcinomas.

2. Evidence of a tumor that compresses or invades major blood vessels or tumor cavitation that, in the opinion of the investigator, is likely to bleed.

3. Known EGFR activating mutations (for example, exon 19 deletion or exon 21 L858R substitution mutations) or ALK rearrangements. If EGFR or ALK testing is performed, the results must be reviewed and confirmed as negative for EGFR and ALK prior to randomization.

4. Prior systemic therapy for advanced NSCLC; prior neoadjuvant or adjuvant therapy is allowed if surgical resection for primary disease was performed.

5. History of local radiation for painful bone metastases in the last 2 weeks. (Participants with bone metastases are eligible, however those with symptomatic or painful bone metastases should not have received palliative local radiation for at least 2 weeks prior to randomization and should not expect to require palliative local radiation during the study.)

6. Active uncontrolled or symptomatic central nervous system (CNS) metastases, as evidenced by clinical symptoms, cerebral edema, and/or progressive growth (if a suspected CNS lesion is not confirmed by pathology). Treated and stable (asymptomatic; off steroids at least 4 weeks) brain metastases are allowed.

7. Prior treatment with immunotherapy or bevacizumab for lung cancer.

Medical Conditions:

8. History of other cancer within 5 years prior to screening for this study, with the exception of adequately treated ductal carcinoma in situ of the breast, cervical carcinoma in situ, or basal or squamous cell skin cancer.

9. History of hemoptysis (>2.5 mL per event) in the last 3 months or severe bleeding. Evidence of current thrombotic or bleeding disorders. Therapeutic anticoagulation and/or coagulation abnormalities (eg, international normalized ratio (INR) >1.5 and aPTT greater than ULN unless on prophylactic anticoagulation).

10. Medically uncontrolled hypertension or systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg.

11. Peripheral motor or sensory neuropathy with value of ≥grade 2.

12. Major surgery or any investigational agents, within 4 weeks prior to the start of the first dose of investigational product. Planned major surgery during the treatment period.

13. Any unhealed wound or bone fracture.

14. Active infection. Participants must not be taking anti-infective agents.

15. Active uncontrolled cardiac disease, such as cardiomyopathy, congestive heart failure (CHF) New York Heart Association (NYHA) functional classification of ≥3, unstable angina, or myocardial infarction within 12 months before first dose of investigational product. Clinically significant cardiovascular disease, peripheral vascular disease, transient ischemic attack, cerebrovascular accident.

16. History of severe hypersensitivity reaction to any of the products to be administered during the study, including mammalian cell derived drug products, taxanes, bevacizumab, murine proteins, or excipients in their formulations.

17. Clinical contraindication to treatment with steroids preventing use as part of paclitaxel premedication.

18. Immunocompromised participants, including known seropositivity for human immunodeficiency virus (HIV).

19. Known or demonstrated hepatitis infection as listed below.

    a. Hepatitis B infection as detected by positive testing for hepatitis B surface antigen (HBsAg), and detectable viral load; or negative for HBsAg, positive for hepatitis B core antibody (anti-HBc), and detectable viral load.

    b. Hepatitis C infection as detected by positive hepatitis C antibody (anti-HCV) and detectable viral load.

20. Comorbidities that (in the opinion of the investigator) would increase the risk of toxicity.

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

Prior/Concomitant Therapy:

22. Concurrent administration of other anticancer therapies. Bisphosphonate or Rank-Ligand inhibitor therapy already given before randomization for pre-existing bone metastases or osteoporosis is allowed.

Prior/Concurrent Clinical Study Experience:

23. Participation in other studies involving investigational drug(s) within 4 weeks prior to the start of the first dose of investigational product and/or during study participation. Participants participating in observational studies not involving investigational drug(s) and/or long-term follow up of studies involving investigational drug(s) in which treatment was completed ≥4 weeks prior to the start of the first dose of investigational product are not excluded.

Diagnostic Assessments:

24. Inadequate organ function, evidenced from the screening laboratory values (where deviation of up to 10% is acceptable for any single value if in the investigator's opinion the participant does not have an increased safety risk):

    Bone Marrow Function

    a. Absolute neutrophil count (ANC) <1.5 x 10^9 cells/L (1500/mm^3);

    b. Platelet count <100 x 10^9 cells/L (100,000/mm^3);

    c. Hemoglobin <9.0 g/dL (90 g/L).

    Renal Function

    a. Serum or plasma creatinine >1.5 x upper limit of normal (ULN);

    b. Urine dipstick proteinuria ≥2+. If urine dipstick is >1+ then a 24 hour urine for protein must have demonstrated urinary excretion of ≤500 mg of protein per day or urine protein to creatinine ratio (UPC) ratio <1 can be included.

    Liver Function

    a. Total bilirubin >1.5 x ULN (≥3 ULN if Gilbert's disease);

    b. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN (>5 x ULN if liver metastases are present).

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

In this study, participants of childbearing potential will receive bevacizumab-EU as well as paclitaxel and carboplatin, which have been associated with teratogenic risk. Participants should be advised to avoid becoming pregnant and not to father a child while receiving treatment in this study. While the teratogenicity of PF-06439535 (CN) has not been studied, it is expected to be the same as that of bevacizumab-EU.

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). 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 randomly assigned to investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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

6. INVESTIGATIONAL PRODUCT

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

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

6.1. Investigational Product(s) Administered

Intervention Name	PF-06439535 (CN)	Bevacizumab-EU
ARM Name	Arm A	Arm B
Type	Intervention Type: Drug	
Dose Formulation	solution for injection	
Unit Dose Strength(s)	Each vial contains 100 mg of bevacizumab in 4 ml of solution at a concentration of 25 mg/mL	
Dosage Level(s)	15 mg/kg	
Route of Administration	Injection	
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	Investigational product will be provided in a glass vial with a rubber stopper. Each glass will be labeled as required per country requirement.	

Paclitaxel and **carboplatin** are background therapies and will be provided by the sponsor. Refer to the paclitaxel and carboplatin Package Insert for information on formulation, preparation, and administration.

6.1.1. Administration

The dosing algorithm for paclitaxel, carboplatin, and PF-06439535 (CN) or bevacizumab-EU are shown below.

Paclitaxel, carboplatin, and PF-06439535 (CN) or bevacizumab-EU are administered on 21-day cycles. On treatment days when both bevacizumab and paclitaxel-carboplatin are administered, the order of administration should be: 1) paclitaxel, 2) carboplatin, 3) PF-06439535 (CN) or bevacizumab-EU.

Dose recalculation at the beginning of each cycle is recommended but not required if the weight is within 10% of baseline (Cycle 1 Day 1 dosing). The dose should be recalculated if the participant's weight changes more than 10% from baseline or if the dose has been reduced, and should be used as the new baseline going forward for future dose calculations.

Regional standards for derivation of dose calculations such as rounding conventions or body surface area (BSA)/dose capping for safety concerns are acceptable. Excluding these expected variations, administered doses of carboplatin, paclitaxel, or PF-06439535 (CN) or bevacizumab-EU within a range of ±10% from the intended dose would not be considered a deviation.

Missed dose(s) of investigational product will not be made up.

Table 4. Dosing Algorithm

Dose Level	Paclitaxel	Carboplatin	PF-06439535 (CN) or bevacizumab-EU
Starting dose	175 mg/m2	AUC 5 (max=750mg)	15 mg/kg
Dose level -1 (first episode of AE*)	150 mg/m2	AUC 4 (max=600mg)	7.5mg/kg after discussion with sponsor
Dose level -2 (second episode of AE*)	135 mg/m2	Discontinue	Discontinue
Dose level -3 (third episode of AE*)	Discontinue Therapy		--

*for carboplatin/paclitaxel: Grade 3 or 4 febrile neutropenia, nausea, vomiting, stomatitis.

6.1.1.1. Bevacizumab

6.1.1.1.1. Dosage Form(s) and Packaging

Bevacizumab (PF-06439535 [CN] or bevacizumab-EU) will be provided by the sponsor in which the external packaging for each vial will appear identical and will be identified with a unique container number. After randomization, bevacizumab (PF-06439535 [CN] or bevacizumab-EU) will be provided as blinded supplies. Each container will be packaged with a tamper-resistant seal. Only the unblinded pharmacist or appropriately qualified unblinded staff member preparing the study medication is allowed to break the tamper-resistant seal. The sponsor must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used.

PF-06439535 (CN) and bevacizumab-EU are clear, colorless to pale brown liquid in a glass vial with a rubber stopper. Each appropriately sized glass vial contains 100 mg of bevacizumab in 4 ml of solution.

For additional information please refer to the Investigational Product (IP) Manual.

6.1.1.1.2. Bevacizumab Regimen

PF-06439535 (CN) or bevacizumab-EU will be administered once at the start of every 21-day cycle. The initial dose is 15 mg/kg delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, subsequent infusions may be administered over 30 minutes up until Week 25 (Cycle 9). The Week 25 (Cycle 9) infusion time should be increased to 90 minutes in the interest of patient safety considering the potential switch in treatments, and if tolerable the subsequent infusion at Week 28 (Cycle 10) may be administered over 60 minutes. If this 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. If during the shortened infusions, infusion related reactions occur, the duration of the infusion can be lengthened at the discretion of the investigator. For the infusion of bevacizumab in participants over 110 kg, the dilution volume and infusion time should be increased per Investigational Product Manual and institutional standards. The concentration of diluted bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml.

Infusions should not be administered as an intravenous push or bolus injection. Infusions should not be administered or mixed with dextrose solutions.

Assigned blinded bevacizumab may continue to be administered after the chemotherapy has been discontinued until RECIST 1.1 defined disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurs, or 25 weeks, whichever comes first.

At Week 25, participants continuing to demonstrate clinical benefit in the opinion of the investigator will receive PF-06439535 (CN) monotherapy in a blinded manner for up to 2 years following randomization in this study or until no further benefit from treatment (eg, investigator assessed disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up), whichever occurs first.

6.1.1.2. Paclitaxel and Carboplatin

6.1.1.2.1. Paclitaxel and Carboplatin Provision

Paclitaxel and carboplatin to be administered during this study will be centrally provided by the sponsor. Paclitaxel and carboplatin are to be stored, prepared and administered according to the product labeling.

6.1.1.2.2. Premedication for Administration

Premedication to ameliorate the toxicities associated with the chemotherapy are to be administered according to the local label or institutional guidelines.

6.1.1.2.2.1. Paclitaxel

All participants should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reaction. Such premedication may consist of dexamethasone 20 mg orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg intravenous (IV) 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. Premedication regimens that are standard for the institution or region may be used instead. Premedication will be supplied by the site.

6.1.1.2.2.2. Carboplatin

Carboplatin is administered as the second drug of the chemotherapy doublet combination.

Carboplatin can induce emesis, which can be more severe in participants with prior emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics which should be given per local standard of care. Because anti-emetics may be given prior to the paclitaxel, extra doses as premedication may not be necessary, although additional doses may be required if the participant develops emesis. Premedication according to institutional guidelines should be used if paclitaxel has been discontinued.

6.1.1.2.3. Regimen and Starting Dose(s)

6.1.1.2.3.1. Paclitaxel

Following pre-medication, paclitaxel is administered as the first drug when chemotherapy is administered. Paclitaxel at a dose of 175 mg/m^2 will be administered by IV infusion over 3 hours on Day 1 in 21-day cycles. In the absence of progressive disease, participants will receive paclitaxel treatment for at least 4 but no more than 6 cycles. Dose reduction for toxicity is allowed.

6.1.1.2.3.2. Carboplatin

Carboplatin is administered over a minimum of 15 minutes, and can be administered immediately after the paclitaxel infusion has completed. Participants will be administered carboplatin for at least 4 and no more than 6 cycles. Dose reduction for toxicity is allowed.

The initial dose of carboplatin is based on the use of mathematical formulae, which are based on a participant's pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for participant variations in pretreatment renal function that might otherwise result in either under dosing (in participants with above average renal function) or over dosing (in participants with impaired renal function).

A simple formula for calculating dosage, based upon a participant's glomerular filtration rate (GFR in mL/min) and carboplatin target area under the concentration versus time curve (AUC in mg/mL.min), has been proposed by Calvert.[3]

$$\text{Total Dose (mg)} = (\text{target AUC is } 5.00) \times (\text{GFR (ml/min)} + 25)$$

Glomerular filtration rate (GFR) is estimated for males as:

$$\text{GFR} = \frac{[(140 - \text{age}) \times (\text{weight in kg})]}{(72 * \text{creatinine in mg/dL})}$$

For females, a correction factor of 0.85 is used.

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m^2.

Alternate formulas per local standard of care may be utilized to derive the dose of carboplatin.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational products received and any discrepancies are reported and resolved before use of the investigational product, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer investigational product. All investigational products 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 temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All investigational products will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused investigational products are provided in the IP manual.

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

6. Investigational products should be stored in their original containers and in accordance with the labels.

7. See the IP manual for storage conditions of the investigational product once diluted.

8. Any excursions from the investigational product label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the investigational product to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

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

Investigational products will be prepared by qualified unblinded site personnel according to the IP manual. The investigational product will be administered to blinded participants.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Participants will be assigned to receive investigational product according to randomization scheme. Investigators will remain blinded to each participant's assigned investigational product throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all investigational product and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation following randomization.

This third party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the investigational product with the investigator.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded investigational product records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.2. Breaking the Blind

The interactive response technology (IRT) will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and data collection tool (DCT).

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. Investigational product Compliance

Participant compliance with investigational product will be assessed at each visit. Compliance will be assessed by the dosing schedule. Deviation(s) from the prescribed dosage regimen should be recorded in the case report form (CRF).

All study medications for this protocol are intravenous drugs administered by trained and qualified personnel. Records of each dose will be maintained and variations in doses will be managed as per Section 6.1.1. Participants who miss dosing or scheduled visits, tests or procedures for reasons other than adverse events or unavoidable administrative reasons will be reminded of the importance of maintaining the dosing schedule. Repeat non-compliance may result in withdrawal from the study in accordance with Section 7.2.

6.5. Concomitant Therapy

Medications used to prevent possible adverse events or treat adverse events are allowed at the discretion of the investigator. Use of concomitant treatments should follow the standard of care for the treating institution.

Pretreatment for bevacizumab hypersensitivity reactions should not be given unless hypersensitivity reactions have occurred with prior administration in an individual participant. The treatment regimen can produce clinically significant myelosuppression. Transfusions and growth factors are allowed and should be used according to institutional guidelines. Bisphosphonate or Rank-Ligand inhibitor therapy already given before randomization for pre-existing bone metastases or osteoporosis is allowed.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a participant receives both drugs.

Carboplatin can induce emesis, which can be more severe in participants previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics.

Participants receiving paclitaxel should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists as per the regional prescribing information or institutional guidelines.

Prior medications and non-drug treatments delivered prior to initial dosing will be recorded from 28 days prior to the start of investigational product. Concomitant Therapy, including medications and non-drug treatments will be recorded from initial dosing and monitored continuously by the investigator until at least 28 days following the last dose of investigational product or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose, to coincide with the safety evaluation period.

6.5.1. Additional Anticancer and Prohibited Treatments Including Radiotherapy

Additional anticancer treatments including, but not limited to radiotherapy are prohibited, even for palliative treatment of bone or brain metastatic lesions. The need for such additional treatments is suggestive of progressive disease and the participant should be discontinued from study medications under this study.

Participants participating in this study should discuss with their doctors the risks and benefits of immunizations (particularly live vaccine based immunizations) during this study.

No other investigational drug or treatment for benign indications may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

6.5.2. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with the investigational product; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

PF-06439535 (CN)/bevacizumab-EU, paclitaxel and carboplatin will be given as specified in Section 6.1.1. The dosing schedule may also be adjusted due to toxicity.

6.6.1. Bevacizumab Regimen Adjustments

The infusion of the investigational product should be interrupted if the participant develops dyspnea or hypotension that is deemed clinically significant by the investigator. If a participant experiences an allergic reaction, hypersensitivity, adult respiratory distress syndrome, of Grade 3 or Grade 4 according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03, they will be discontinued from treatment with the investigational product. Additionally, if a participant experiences a drug-related bronchospasm of any grade according to NCI-CTCAE, they will be discontinued from treatment with the investigational product. For participants who experience infusion-associated symptoms not previously specified, infusions should be slowed to ≤50% or interrupted.

No dose reductions from 15 mg/kg are planned for PF-06439535 (CN) or bevacizumab-EU. However, in rare cases where dose reduction is deemed necessary, the investigator can decrease the dose of PF-06439535 (CN) or bevacizumab-EU to 7.5 mg/kg with the concurrence of the sponsor (Table 5). In the event of toxicity attributed to bevacizumab, treatment should be either temporarily (up to 2 weeks) or permanently discontinued as described in Table 5. Following a temporary discontinuation, treatment may resume in accordance with local standard of care.

Table 5. Bevacizumab Dose Adjustment Guidelines

ADVERSE EVENT	ACTION
Infusion Reaction	• Mild or moderate: decrease rate of infusion. • Dyspnea or clinically significant hypotension: interrupt infusion, administer appropriate medical therapy, which may include intravenous fluids, epinephrine, corticosteroids, diphenhydramine, bronchodilators, or oxygen; monitor until complete resolution. • Severe or life-threatening: permanently discontinue therapy.
Gastrointestinal Perforations	• Therapy should be permanently discontinued in participants who develop gastrointestinal perforation.
Fistulae	• Permanently discontinue bevacizumab in participants with tracheoesophageal (TE) fistula or any Grade 4 fistula (NCI-CTCAE v.4.03). Limited information is available on the continued use of bevacizumab in participants with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of bevacizumab should be considered.
Wound Healing Complications	• Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In participants who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. • Necrotising fasciitis, including fatal cases, has rarely been reported in participants treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in participants who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
Hypertension	• Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the participant develops hypertensive crisis or hypertensive encephalopathy.
Posterior Reversible Encephalopathy Syndrome (PRES)	• In participants developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in participants previously experiencing PRES is not known.
Proteinuria/nephrotic syndrome	• Bevacizumab should be permanently discontinued in participants who develop nephrotic syndrome.

Table 5. Bevacizumab Dose Adjustment Guidelines

ADVERSE EVENT	ACTION
Arterial thromboembolism	• Therapy should be permanently discontinued in participants who develop arterial thromboembolic reactions.
Venous thromboembolism	• Bevacizumab should be discontinued in participants with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Participants with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
Haemorrhage	• Bevacizumab should be discontinued permanently in participants who experience Grade 3 or 4 bleeding during bevacizumab therapy. • Bevacizumab treatment should be discontinued in cases of intracranial bleeding.
Pulmonary haemorrhage/haemoptysis	• Participants with recent pulmonary haemorrhage/haemoptysis (>2.5 ml of red blood) should not be treated with bevacizumab.
Congestive heart failure (CHF)	• When treating participants with cardiovascular disease that has developed or worsened after the initiation of the investigational products, the investigator should determine the benefits and risks of continuing bevacizumab and/or paclitaxel/carboplatin.
Osteonecrosis of the jaw (ONJ)	• Caution should be exercised when bevacizumab and intravenous or oral bisphosphonates are administered simultaneously or sequentially. • In participants who have previously received or are receiving intravenous or oral bisphosphonates invasive dental procedures should be avoided, if possible.

6.6.2. Paclitaxel and Carboplatin Regimen Adjustments

All paclitaxel and/or carboplatin associated or possibly associated toxicities should be managed by standard medical practice. Participant toxicity should be clinically assessed before, during, and after each infusion. If paclitaxel and/or carboplatin cause unmanageable levels of toxicity at any time in the study, the treatment should be discontinued. Instruction for treatment delays and dosing modifications for paclitaxel and carboplatin are as follows:

- Reduced doses may not be increased.
- Dose modifications should be based on the AE that requires the largest change.
- Severity of AEs will be graded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

- Paclitaxel and/or carboplatin will be delayed until the AE is graded ≤1, except in the case of anemia, neuropathy, alopecia, proteinuria, and laboratory abnormalities that are deemed unrelated to treatment and clinically insignificant per investigator.

- If paclitaxel and/or carboplatin must be withheld due to hematologic toxicity, complete blood count (CBC) and platelet counts should be obtained weekly until the counts reach the lower acceptance limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

Once a dose of paclitaxel has been reduced for a participant, all subsequent cycles should be administered at that dose, unless further dose reduction is required. Treatment with paclitaxel will be stopped in case of RECIST defined disease progression, unacceptable toxicity, death, or withdrawal of consent occurs.

Dose delay (up to 2 weeks) and dose reduction of paclitaxel and/or carboplatin will be permitted per local guidelines. The dose adjustments for paclitaxel and carboplatin presented in Table 4 in the Administration (Section 6.1.1) are to be used as a guideline for investigators. Additional measures may be taken as necessary per investigator's medical judgment and per locally approved labels as well as local standard of care. All reductions should be considered permanent with no re-escalation permitted. All dose adjustments should be documented in the participant source notes. Missed dose(s) of paclitaxel will not be made up. If paclitaxel dosing is held at any point, study procedures should proceed on schedule without any delay; this includes tumor assessments.

Dose reduction of carboplatin for hematologic toxicity should be made based on institutional or regional standard of care guidelines. All dose reductions should be considered permanent with no re-escalation permitted. All dose adjustments should be documented in the participant source notes. Missed dose(s) of carboplatin will not be made up. If carboplatin dosing is held at any point, study procedures should proceed on schedule without any delay; this includes tumor assessments.

In cases where a delay in dosing is required for one or more of the drugs, the date of Day 1 of the next cycle should be delayed and all drugs required for that cycle be given on the new scheduled Day 1. Note that tumor assessments are calendar based and are not modified to fit a change in dosing schedule.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Investigational Product

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

7.1.1. Temporary Discontinuation

PF-06439535 (CN)/bevacizumab-EU, paclitaxel and carboplatin may be temporary discontinuation due to toxicity as specified in Section 6.6.

If one of the chemotherapeutic agents is delayed, the other agent and bevacizumab treatment should be delayed and Day 1 of the cycle should be shifted. If both chemotherapeutic agents cannot be administered within 2 weeks, they should be discontinued. If only one of the chemotherapeutic agents is discontinued, the other can continue. Similarly, if PF-06439535 (CN) or bevacizumab-EU cannot be administered for 2 weeks from scheduled time due to intolerable adverse events, bevacizumab should be discontinued. The interval between treatment cycles should be no less than 3 weeks and no more than 5 weeks in order to maintain 3 weeks per cycle with a maximum 2 week delay. Tumor assessments should not be shifted as they are calendar based. If PF-06439535 (CN) or bevacizumab-EU is held or discontinued, paclitaxel and/or carboplatin should be continued for at least 4 and no more than 6 cycles. For those participants who discontinue chemotherapy and investigational products, every effort should be made to remain on study for follow-up, at least through Week 19 and if there is a response through Week 25.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the investigational product and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial SAE Report.

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

Withdrawal of Consent:

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

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

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.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue investigational product.

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 infeasible 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.

In the screening period, demographics and medical/cancer history should be documented, include information on prior anti-tumor regimens (including chemotherapy and radiation therapy and duration of treatment), driver genetic alteration test results, if known, and progression or relapse date. Testing for driver genetic alterations is not required, however participant records are to be reviewed for known EGFR activating mutations (for example, exon 19 deletion or exon 21 L858R substitution mutations) or ALK rearrangements. If EGFR or ALK testing is performed, samples must be tested by local certificated laboratories,

and the results must be reviewed and confirmed as negative for EGFR and ALK prior to randomization.

Unless otherwise specified, Section 8.1, 8.1.1, 8.2.1, 8.2.2, 8.2.3, 8.2.4 and 8.2.5 below are primarily intended to provide instructions for completing protocol required tests and procedures relevant to the Treatment Period. Since the Extension Period is intended solely to provide access to study treatment for participants who continue to receive clinical benefit beyond the Treatment Period there are minimal protocol required tests and procedures as described in the Schedule of Activities Study Flowcharts. It is the responsibility of the investigator to perform tests and procedures necessary and according to local standard of care to ensure the safety and well-being of the participant from the time the participant enters the Extension Period.

8.1. Efficacy Assessments

Disease assessments are to be performed as scheduled according to calendar days, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays.

Failure to perform any of the required disease assessments will result in the inability to determine disease status for the impacted time point. A series of incomplete disease assessments will result in inability to determine disease response status back to the time of the last full assessment that did not show progression. Frequently off-schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

8.1.1. Imaging Assessments

Baseline assessments must include CT with contrast or MRI of head, chest, abdomen (including adrenals) and other disease sites such as pelvis if clinically indicated. Tumor assessments are NOT to be scheduled based on cycle length or number of cycles received. Assessment delay to conform to treatment delays is not permitted. The same method of tumor assessments should be used throughout the trial. A confirmatory scan is required approximately 6 weeks (+7 days) for a CR/PR.

CT and MRI are the best currently available and most reproducible methods of measuring target lesions selected for response assessment. MRI should only be used when considered more appropriate than CT or when there is a contraindication for CT with contrast.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and MRI should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not adequate for evaluation of lung parenchyma but should also be performed to evaluate all other aspects of the chest. MRI of the abdomen and pelvis should substitute for CT with contrast unless the

method does not adequately depict the individual's disease, in which case CT without contrast is preferred.

Other methods of evaluation should be used as appropriate. For participants having effusions or ascites, cases having cytological proof of malignancy should be considered non-target lesions. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be lung cancer legions.

For the purpose of study endpoint analyses, the determination of best disease response (PR or CR) and progression will be made in accordance with RECIST v1.1 in the opinion of the investigator. Responses must be confirmed by a second set of scans including head scan obtained 6 weeks (±7 days) later.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, neck, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, neurological systems, and weight. Height and weight will also be measured and recorded. Weight should be measured at the beginning of each cycle and will be used for dose calculation in accordance with Section 6.1.1. But height will be recorded at Screening only. Genitourinary examination is only required if directed by signs or symptoms.

A brief physical examination will be performed as directed by signs and symptoms on Day 1 (pre-dose) of each cycle after Screening.

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

8.2.2. Vital Signs

Oral temperature, blood pressure, pulse rate, and respiratory rate will be assessed.

Temperature should be taken using the same method throughout the study. Blood pressure, pulse rate, and respiratory rate should be taken with the participant in the supine or sitting position after the participant has been resting quietly for at least 5 minutes and prior to dosing on dosing days. On days of an infusion, vital signs should be taken within 30 minutes before the first infusion and within 30 minutes of the end of the last infusion.

8.2.3. Electrocardiograms

12-Lead electrocardiograms (ECGs) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and PR interval, QT interval, QTc, and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes.

If a postdose QTc remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc gets progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if the QTc does not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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 QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 9.

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.

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 investigational product should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. MUGA or ECHO

Multiple-gated acquisition (MUGA) or Echocardiogram (ECHO) will be used to assess left ventricular ejection fraction (LVEF) of each participant. See the SoA for the timing and frequency. The original methodology used for each participant must be used throughout the trial.

8.2.6. 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 Woman of Childbearing Potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the investigational product. 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 treatment visit. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

Medical occurrences that begin before the start of investigational product but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

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

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the investigational product or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately 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.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

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.

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/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 towards the safety of participants and the safety of a investigational product 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 investigational product under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of investigational product and until 6 months after discontinuing the investigational product.

If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

The following disease-related events (DREs) are common in participants with non-squamous NSCLC and can be serious/life threatening:

- Non-fatal progression of the malignancy under study (including signs and symptoms of progression).

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 corresponding efficacy assessment pages in the participant's CRF within the appropriate time frame.

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 investigational product.

8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product 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 investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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 immediately.

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 an AE page of the CRF.

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

8.4. Treatment of Overdose

For this study, any dose of bevacizumab (PF-06439535 (CN) or bevacizumab-EU greater than 15 mg/kg or the assigned dose according to the dose adjustment (Section 6.6 Dose Modification) within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory test abnormalities until PF-06439535 (CN) or bevacizumab-EU can no longer be detected systemically (at least 86 days).
3. Obtain a blood sample for pharmacokinetic (PK) analysis within 2 days from the date of the last dose of investigational product if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

The drug concentrations of PF-06439535 (CN) and bevacizumab-EU will be determined using serum samples collected at the time points specified in the SoA. Every effort will be made to collect these PK samples within the time window provided, as specified in the Schedule of Activities. The actual time of each sample collection will be recorded on the source document and electronic CRF (eCRF).

Details on sample collection, processing and shipment will be provided in the central laboratory manual.

The drug concentration sample analysis will be analyzed by the designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures.

CCI [redacted]

8.5.1. Analysis of Anti-drug (bevacizumab) Antibodies

Blood samples for assessment of ADA and neutralizing antibodies will be collected at time points specified on the SoA. Details on the sample collection, processing, and shipment are provided in the central laboratory manual.

The sample analysis will be conducted by the designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures.

A sensitive and specific immunoassay for detecting anti-drug antibodies in human serum will be used to analyze the ADA samples. The ADA assay uses biotinylated- and ruthenium-labeled PF-06439535 (CN) as reagents and will be validated in compliance with Good Laboratory Practice, Pfizer standard operating procedure (SOP) and regulatory guidance. Analysis of ADA samples will follow a tiered approach. Samples will first be screened for ADA; any samples that are positive in the screening assay will be further analyzed to confirm the positive result and determine the antibody titers. Samples determined to be positive for ADA may be further characterized for neutralizing antibodies (NAb) using a single validated NAb assay.

CCI [redacted]

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (ribonucleic acid [RNA]) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Testing Lung Tissue for Mutations

Testing for driver genetic alterations is not required, however participant records are to be reviewed for **known** EGFR activating mutations (for example, exon 19 deletion or exon 21 L858R substitution mutations) or ALK rearrangements. If EGFR or ALK testing is performed, samples must be tested by local certificated laboratories, and the results must be reviewed and confirmed as negative for EGFR and ALK prior to randomization.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

After all participants have completed the Week 25 visit (ie, the last participant randomized has completed the Week 25 visit) or have otherwise died, withdrawn consent or been lost to follow-up, the study will be considered to have reached primary completion. A database snapshot (containing data up to and including the Week 25 visit for every participant) will be performed after the primary completion date (PCD) and a study report will be developed to support the new drug application. Data collected after Week 25 will be summarized in a supplemental clinical study report which will describe safety results during the monotherapy extension period and will be considered as supplemental to the clinical study report for the PCD.

In general, efficacy, safety, PK and immunogenicity as of the Week 25 visit will be analyzed by treatment group in the study report for the PCD. In the supplemental clinical study report, safety will be summarized across all participants, and PK and immunogenicity (which are to be collected at end of treatment/withdrawal visit) will be listed.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary efficacy endpoint of the study is Objective Response Rate (ORR) defined as the percent of patients within each treatment group who achieved Complete Response (CR) or Partial Response (PR) by Week 19, based on best overall response and subsequently confirmed by Week 25, in accordance with the RECIST 1.1. The primary estimand is the treatment effect of PF-06439535 (CN) relative to bevacizumab-EU according to the primary endpoint without regard to discontinuation of treatment or use of concomitant therapy. If a participant takes anti-cancer medication, all responses after that timepoint are excluded from the analysis. ORR on each arm will be estimate and 2-sided 90% confidence interval for observed ORR will be provided. The risk difference and risk ratio in ORR between treatment arms will be estimated together with the 90% 2-sided confidence intervals. Objective response (CR or PR) will be derived based on investigator reported tumor assessments. At each time point, missing response data will be considered as non-evaluable; the time point response will be used to derive the best objective response in accordance with RECIST 1.1. In the best objective response rate calculation, if a patient has missing tumor outcome across all visits or if he/she had non-evaluable best overall response following RECIST 1.1, the patient will be considered as non-responder, and will be included in the denominator but will not be included in the numerator.

Safety will be characterized by type, incidence, severity, timing, seriousness, and relationship to investigational products of adverse events, including cardiotoxicity and infusion related reactions, and laboratory test abnormalities. Safety analyses will include participants who are randomized and receive at least one dose of investigational product.

PK evaluation will be summaries of the trough and apparent peak concentrations for PF-06439535 (CN) and bevacizumab-EU treatment arms for participants in the per protocol population who have at least one post dose drug concentration measurement.

Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb) will be summarized for participants who are randomized and receive at least one dose of investigational product.

CCI [redacted]

CCI [redacted]

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Defined Population for Analysis	Description
Intent-to-Treat Population	The Intent to Treat (ITT) Population is defined as all participants who are randomized to investigational product. The ITT population will be used for participant accountability and all efficacy analyses.
Per Protocol Population	The Per Protocol (PP) Population is defined as all participants who are randomized and received the investigational product (PF-06439535 (CN) or bevacizumab-EU) as planned and have no major protocol deviations. The PP population will be used for sensitivity analyses of the primary efficacy endpoint. The list of participants in PP population will be determined based on blinded data review prior to database release.
Pharmacokinetics Population	Participants in the per protocol population who have at least one post dose drug concentration measurement will be included in the PK analysis.
Safety population	The safety population is defined as all participants who are randomized and receive at least one dose of investigational product. The safety population will be used for the safety analyses including ADA and NAb analyses.

9.4. Statistical Analyses

This study is descriptive in nature, and hence no statistical hypothesis testing will be done. Efficacy, safety, PK, and immunogenicity will be summarized descriptively as outlined in the following subsections.

9.4.1. Efficacy Analyses

9.4.1.1. Analysis of the Primary Endpoint

The primary efficacy endpoint of the study is ORR defined as the percent of participants within each treatment group who achieved Complete Response (CR) or Partial Response (PR) by the time of the Week 19 efficacy analysis in accordance with the RECIST 1.1.

Confirmation of response is required by tumor assessments done approximately 6 weeks after the response. Responses that are not confirmed will not be counted in the primary analysis but may be included in a sensitivity analysis.

Descriptive statistics for CR, PR and ORR by treatment group, risk difference of ORR and risk ratio of ORR (RR) between treatment groups will be presented. The frequency, percentage and 90% confidence interval of these response rates will be constructed. The estimated risk difference and risk ratio in ORR between PF-06439535 (CN) and bevacizumab-EU will be computed, and the corresponding 90% confidence intervals will be calculated based on Miettinen and Nurminen (1985) method.

9.4.2. Safety Analyses

Safety population will be used for all safety analyses. Listings of all individual data will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Details of planned analyses will be described in the SAP.

9.4.2.1. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of adverse events will be graded according to the NCI-CTCAE version 4.03.[25]

Adverse events (treatment emergent adverse events; treatment related adverse events; adverse events classified as NCI-CTCAE Grade 3 or higher; and serious adverse events) will be summarized by body system and preferred term according to MedDRA terminology. Treatment emergent adverse event (TEAE) is defined as any adverse event that occurs after the beginning of the investigational product or any pre-existing adverse event that worsens after the beginning of the investigational product.

Adverse events leading to death or discontinuation of trial treatment will be presented by treatment group.

Adverse events recorded on the CRF as infusion related reactions (IRRs) will be summarized both as individual events and as a group for the purpose of summarizing the overall incidence of IRRs in the 2 treatment arms.

Selected adverse events and syndromes will be summarized using grouped Medical Dictionary for Regulatory Activities (MedDRA) codes in addition to presentation of individual AE preferred terms.

9.4.2.2. Laboratory Test Abnormalities

Hematology and chemistry laboratory data will be summarized by treatment and visit. The laboratory results will be graded according to NCI-CTCAE severity grade. The frequencies of the worst severity grade observed will be displayed by investigational product. Shift tables of baseline against each post baseline visit will be provided for selected laboratory

tests to examine the distribution of laboratory toxicities. For parameters for which an NCI-CTCAE scale does not exist, the frequency of participants with values below, within, and above the normal ranges will be summarized by treatment and visit.

Change from baseline will be additionally summarized by treatment group and visit. Baseline is defined as the most recent measurement prior to the beginning of the investigational product.

9.4.2.3. Prior Concomitant Medications

Collected prior and concomitant medications will be coded by the World Health Organization (WHO) medical dictionary; participants who received these medications will be listed and summarized by treatment group separately.

9.4.3. Other Analyses

Demographic and baseline characteristics such as participant age, sex, height, weight, ethnicity, prior therapy, medical history, ECOG performance status, and tumor mutations will be tabulated and summarized using descriptive statistics. Administration for each investigational product will be described in terms of the total number of cycles administered, the medium (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

9.4.3.1. Pharmacokinetics

The drug concentration-time data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum) according to treatment.

The detailed procedures for the population PK analysis, including the model implementation and evaluation, will be described in the Population Modeling Analysis Plan (PMAP). The results of the analysis, if conducted, will be summarized in a Population Modeling and Analysis Report (PMAR) separate from the clinical study report (CSR).

9.4.3.2. Biomarker Analysis

There are no biomarker assessments required for this trial.

9.4.3.3. Immunogenicity

For the immunogenicity data, the percentage of participants with positive ADA and neutralizing antibodies will be summarized for each treatment. For participants with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made, as appropriate, to examine possible correlations of the ADA response with clinical data on the PK, safety and/or efficacy of each product.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the participants, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

9.5. Interim Analyses

There will be no interim analysis in this study.

9.5.1. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and 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.

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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 investigational product, Pfizer should be informed immediately.

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

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the 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 or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

10.1.3. 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 shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or 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. 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.

10.1.4. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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 US Basic Results document is posted to www.clinicaltrials.gov.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. 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.

10.1.5. Data Quality Assurance

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

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

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 (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

Records and documents, including signed 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.

10.1.6. 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 electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Study Data Monitoring Plan.

10.1.7. Study and Site Closure

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

The investigator may initiate study-site closure at any time upon notification to the contract research organization (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 GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further investigational product development.

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

10.1.8. 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 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.

10.1.9. 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 investigator site file (ISF).

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

10.2. Appendix 2: Clinical Laboratory Tests

The 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 concerns.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	**Chemistry**	**Coagulation**	**Urinalysis**	**Other**
Hemoglobin WBC count Platelet count Absolute Neutrophil count	AST, ALT Alkaline phosphatase Total bilirubin Serum/Plasma Creatinine, Sodium Potassium Total Calcium BUN/urea Magnesium Albumin	INR/prothrombin time (or prothrombin time if INR is not available) APTT	pH Protein Glucose Ketones Bilirubin Blood Leukocyte esterase Quantitative urine protein analysis when dipstick urine protein ≥2+.	Pregnancy test (β-hCG)
Serological tests				
HBsAg Anti-HBc Anti-HCV Anti-HIV HBV DNA when 1) HBsAg-positive, or 2) HBsAg-negative, anti-HBc positive; HCV RNA when anti-HCV positive				

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen;
HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody;
anti-HCV = hepatitis C antibody; anti-HIV = human immunodeficiency virus antibody;
WBC = white blood cell; APTT = Activated Partial Thromboplastin Time; I
NR = International Normalized Ratio.

Investigators must document their review of each laboratory safety report.

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 investigational product, whether or not considered related to the investigational product. • 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 investigational product.

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 (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after investigational product 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 investigational product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

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

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

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event 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 disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Assessment of Intensity section).

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product 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 investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/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/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs,

symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will report AEs using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03, Publish Date: 14 June 2010, http://ctep.cancer.gov/reporting/ctc.html). The investigator will use the following definitions of severity in accordance with CTCAE version 4.03 to describe the maximum intensity of the adverse event.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to investigational product administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she

has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send 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 investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become

available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to 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.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

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 90 days after the last dose of investigational product, which corresponds to the time needed to eliminate investigational product(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.
    - Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.

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 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 6 months after the last dose of investigational product, which corresponds to the time needed to eliminate any investigational product(s).
- 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 investigational product.

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 Potential (WOCBP)

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 investigational product, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

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

   Note: Documentation for any of the above 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.

3. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

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

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Iinjectable.
3. 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 investigational product. 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.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes 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 investigational product.

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.

10.5. Appendix 5: 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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same 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. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (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.

10.6. Appendix 6: Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from *E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.*

CATEGORIZING LESIONS AT BASELINE

Measureable Lesions.

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter at least 10 mm or greater when assessed by CT or MRI, measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray, only if the tumor is clearly outlined by well-aerated lung.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

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

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, superficial legions, and abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions though 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 legions.

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

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 the window of time specified in the Schedule of Activities prior to treatment and all disease must be documented appropriately. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

The determination of whether lesions are measurable is performed only at baseline. "Measurable" at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the trial. Once selected as a target lesion, a lesion remains target throughout the trial.

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 bases 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 look for partial response at later assessments.

- If two target lesions coalesce the longest diameter 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-target disease is non-target. All measureable 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 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 techniques as baseline, including consistent administration of contract and timing of scanning. If not, subsequent objective statuses may be 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 measureable lesions. The short diameter is used in the sum for target nodules, while the longest diameter is used in the sum for all other target legions. 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 Progressive Disease (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 assessed.

    - One or more target lesions have not been assessed.

    - Or assessment methods used were inconsistent with those used at baseline and impaired assessment.

    - Or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure).

    - Or one of 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 stable disease (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 one 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 that 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 Determination of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 7 demonstrates how the objective response status is determined from the assessment of target, non-target, and new lesions at each evaluation.

Table 7. Objective Response Status at Each Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, 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

Response (partial or complete) must be confirmed by tumor assessments conducted 6 weeks (±7 days) after the response was noted.

10.7. Appendix 7: American Joint Committee on Cancer (AJCC) Definitions of Tumor, Node, Metastases (TNM) and Prognostic Stage Groups

Excerpts from the AJCC Staging Manual, 8th Edition, last updated 05 June 2018, to ensure consistency and appropriate documentation of staging.

Definitions of AJCC TNM

Definition of primary tumor (T)

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
	T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
	T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
	T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
	T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

✓	*T Suffix*	*Definition*
	(m)	Select if synchronous primary tumors are found in single organ.

Definition of Regional Lymph Node (N)

✓	*N Category*	*N Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
	N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
	N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

✓	*N Suffix*	*Definition*
	(sn)	Select if regional lymph node metastasis identified by SLN biopsy only.
	(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only.

Definition of Distant Metastasis (M)

✓	*M Category*	*M Criteria*
	cM0	No distant metastasis
	cM1	Distant metastasis
	cM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
	cM1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
	cM1c	Multiple extrathoracic metastases in a single organ or in multiple organs
	pM1	Distant metastasis, microscopically confirmed
	pM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion, microscopically confirmed. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
	pM1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node), microscopically confirmed
	pM1c	Multiple extrathoracic metastases in a single organ or in multiple organs, microscopically confirmed

AJCC Prognostic Stage Groups

Always refer to the specific chapter for rules on clinical and pathological classification of this disease.

✓	*When T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	TX	N0	M0	Occult carcinoma
	Tis	N0	M0	0
	T1mi	N0	M0	IA1
	T1a	N0	M0	IA1
	T1a	N1	M0	IIB
	T1a	N2	M0	IIIA
	T1a	N3	M0	IIIB
	T1b	N0	M0	IA2
	T1b	N1	M0	IIB
	T1b	N2	M0	IIIA
	T1b	N3	M0	IIIB
	T1c	N0	M0	IA3
	T1c	N1	M0	IIB
	T1c	N2	M0	IIIA
	T1c	N3	M0	IIIB
	T2a	N0	M0	IB
	T2a	N1	M0	IIB
	T2a	N2	M0	IIIA
	T2a	N3	M0	IIIB
	T2b	N0	M0	IIA
	T2b	N1	M0	IIB
	T2b	N2	M0	IIIA
	T2b	N3	M0	IIIB
	T3	N0	M0	IIB
	T3	N1	M0	IIIA
	T3	N2	M0	IIIB
	T3	N3	M0	IIIC
	T4	N0	M0	IIIA
	T4	N1	M0	IIIA
	T4	N2	M0	IIIB
	T4	N3	M0	IIIC
	Any T	Any N	M1	IV
	Any T	Any N	M1a	IVA
	Any T	Any N	M1b	IVA
	Any T	Any N	M1c	IVB

10.8. Appendix 8: ECOG Performance Status

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

10.9. Appendix 9: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)

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

ECG Findings That May Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients 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 patients 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 (rate

<40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

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

ECG Findings That Qualify as Serious Adverse Events

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

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

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti- HBc	hepatitis B core antibody
Anti-HCV	hepatitis C antibody
AST	aspartate aminotransferase
ATE	arterial thromboembolism
AUC	area under the concentration versus time curve
AUC_T	area under the curve (0 to last quantifiable time point)
$AUC_{inf,}$	area under the curve (0 to time infinity)
AV	atrioventricular
BSA	body surface area
CBC	complete blood count
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
Cmax	maximum serum concentration
CN	China
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related events
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EGFR	epidermal growth factor rector
EMA	European Medicines Authority
EML4-ALK	echinoderm microtubule-associated protein like 4- anaplastic lymphoma kinase
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRR	infusion related reaction
IRT	interactive response technology
ISF	investigator site file
ITT	Intent to Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KDR	kinase insert domain receptor
LVEF	left ventricular ejection fraction
LFT	liver function test
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	Multiple-gated acquisition

Abbreviation	Term
N/A	not applicable
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCD	primary completion date
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PMAP	Population Modeling Analysis Plan
PMAR	Population Modeling and Analysis Report
PR	partial response
PT	prothrombin time
PVC	polyvinylchloride
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	risk ratio (relative risk)
QTc	Q-T Corrected
QTcF	QT interval corrected by the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SMQs	standardised Medical Dictionary for Regulatory Activities queries
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitors
TNM	Tumor, Node, Metastases
ULN	upper limit of normal
UPC	urine protein to creatinine ratio
US	United States
VTE	venous thromboembolic events
VEGF	vascular endothelial growth factor
WHO	World Health Organization

Abbreviation	Term
WOCBP	Woman of Childbearing Potential

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