



Title Page

AN INTERVENTIONAL SAFETY AND EFFICACY PHASE 1B/2, OPEN-LABEL STUDY TO INVESTIGATE TOLERABILITY, PK, AND ANTITUMOR ACTIVITY OF VEPDEGESTRANT (ARV-471/PF-07850327), AN ORAL PROTEOLYSIS TARGETING CHIMERA, IN COMBINATION WITH PF-07220060 IN PARTICIPANTS AGED 18 YEARS AND OLDER WITH ER+/HER2- ADVANCED OR METASTATIC BREAST CANCER

Study Intervention Number:	PF-07850327, PF-07220060
Study Intervention Name:	vepdegestrant (ARV-471)
US IND Number:	168576
EU CT Number:	2023-508130-33-00
ClinicalTrials.gov ID:	NCT06206837
Pediatric Investigational Plan Number	Not Applicable
Protocol Number:	C4891026
Phase:	1b/2
Sponsor Legal Address (Outside US):	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Sponsor Legal Address (In US):	Arvinas Estrogen Receptor, Inc. 5 Science Park 395 Winchester Ave. New Haven, CT 06511

Brief Title: A Study to Investigate the Safety and Antitumor Activity of Vepdegestrant (ARV-471) in Combination With PF-07220060 in Adults With ER+/HER2- Advanced or Metastatic Breast Cancer

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Document History

Document	Version Date
Amendment 3	20 October 2025
Amendment 2	11 April 2024
Amendment 1	20 November 2023
Original protocol	12 September 2023

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

Protocol Amendment Summary of Changes Table

Amendment 3 (20 October 2025)

Overall Rationale for the Amendment: The main purpose of the amendment is to indicate that participants benefitting from treatment (defined as complete/partial response or stable disease as per RECIST v1.1) will continue to have access to the study intervention as part of the study. This amendment also introduces a reduced Schedule of Activities (SoA) allowing most clinical assessments per standard of care or clinical judgment of the treating physician. Reduced data recording will maintain safety and tumor assessment (performed as per standard of care).

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Added rationale for Protocol Amendment 3.	A simplified Schedule of Activities has been implemented upon study completion as per protocol design and permanent closure of participants enrollment in Phase 2.	Section 1.1 Synopsis Section 4.2 Scientific Rationale for Study Design
Summary of Data for the “QTc Prolongation” potential risk has been modified.	Summary of Data and Rationale for Risk have been updated in alignment with 2025 IB	Section 2.3.1 Risk Assessment
Clarify/Updated text to indicate that participants benefitting from the treatment (defined as complete/partial response or stable disease by RECIST v1.1) at the time of implementing Amendment 3 will continue treatment with study intervention per the SoA as part of the study until treatment discontinuation.	To fulfill the obligation to provide study treatment to participants currently on treatment still receiving a benefit from the study intervention	Section 1.1 Synopsis Section 4.1. Overall Design Section 4.4 End of Study Definition Section 6.7 Continued Access to Study Intervention After the End of the Study

Description of Change	Brief Rationale	Section # and Name
Updated SoA and added a statement that it will be reduced after implementation of Amendment 3: concomitant medications collection in eCRF no longer required; PE / vital signs / blood samples collection/ ECG performed as per clinical standard of care at the discretion of the investigator	To reduce current requirements and allow several procedures to be performed as per local practice	Section 1.3 Schedule of Activities Section 6.9 Prior and Concomitant Therapy Section 8 Study Assessments and Procedures Section 8.1.2.1 Telehealth visits Section 8.2 Efficacy Assessments Section 8.2.2 Patient-Reported Outcomes (Phase 2 Only) Section 8.3.1 Physical Examinations Section 8.3.2 Vital Signs; Section 8.3.3 Electrocardiograms Section 8.3.4 Clinical Safety Laboratory Assessments Section 8.5 Pharmacokinetics Section 8.7 Biomarkers and Pharmacodynamics Section 10.2 Clinical Laboratory Tests
Non-substantial Modifications		
Reduced content in synopsis.	To comply with new EU Clinical Trials Regulation	Section 1.1 Synopsis
Text amended for clarity and Contraception period edited from “30 days” to “2 weeks” Vepdegestrant.	To be consistent with new data reported into IB 2025 regarding the timing after the last dose of vepdegestrant for required use of highly effective contraceptives	Section 10.4.1 Male Participant Reproductive Inclusion Criteria Section 10.4.2 Female Participant Reproductive Inclusion Criteria
SoA table from Amendment 2 is moved to Section 10.14 as no longer applicable upon implementation of Protocol Amendment 3.	Previous SoA table moved to Appendix for reference purpose. To prevent sites from incorrectly referring to past SoA tables vs. current SoA tables.	Section 1.3 Schedule of Activities Section 10.14 Protocol Amendment History
Added text to indicate that dispensing will cover 2 cycles of treatment, and that drug accountability will be performed on every dispensation visit (every 2 cycles)	To be consistent with reduced SoA and timing of dispensing	Section 1.3 Schedule of Activities Section 6.1.1 Administration Section 1.3 Schedule of Activities Section 6.5 Study Intervention Compliance

Description of Change	Brief Rationale	Section # and Name
Updated the term (AESI for ARV-471) venous embolism to venous thromboembolism (VTE).	To consistently use the term VTE	Section 2.3.1 Risk Assessment Section 8.4.8 Adverse Events of Special Interest
Delete text 'or their legally authorized representative's.	To comply with sponsor protocol template guidelines. The inclusion of incapacitated adult individuals for whom a legally authorized representative may provide consent is not an option in this study.	Section 1.1 Synopsis Section 9.2 Analysis Sets Section 8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting Section 10.1.3 Informed Consent Process
Details added for the evaluation of cases of acute kidney injury	To comply with sponsor protocol template guidelines	Section 7.1.1 Potential Cases of Acute Kidney Injury Section 10.7.1 Kidney Safety Monitoring Guidelines
Revised language for the reporting of AEs and SAEs to Pfizer Safety	To comply with sponsor protocol template guidelines and align with Safety reporting process.	Section 8.4.1.1 Reporting Nonserious AEs and SAEs to Pfizer Safety Section 8.4.3. Follow-up of AEs and SAEs Section 10.3.3 Recording /Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period Section 10.3.4 Reporting of SAEs
Revised language regarding exposure during pregnancy and added information on environmental and occupational exposure as well as exposure during breastfeeding.	To comply with sponsor protocol template guidelines	Section 8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
Revised language on AESI reporting	To comply with sponsor protocol template guidelines and align with Safety reporting process.	Section 8.4.8 Adverse Events of Special Interest
Removed language regarding Lack of Efficacy	To comply with sponsor protocol template guidelines	Section 8.4.8.1 Lack of Efficacy
Revised language about reporting of medication errors	To comply with sponsor protocol template guidelines and align with Safety reporting process.	Section 8.4.10 Medication Errors
Language on Investigator's responsibility, informed consent, data protection, committees structure, public disclosure of study results, publication policy, medical	To comply with sponsor protocol template guidelines	Section 10.1.3 Informed Consent Process Section 10.1.6 Dissemination of Clinical Study Data

Description of Change	Brief Rationale	Section # and Name
records, study and site start and closure, and medically qualified individual added.		Section 10.1.9 Use of Medical Records Section 10.1.11 Publication Policy
To specify in the Appendix that clinical laboratory tests may be performed as clinically indicated and documented in site source but not in the eCRF upon implementation of Amendment	In alignment with the updated SoA	Section 10.2 Appendix 2: Clinical Laboratory Tests
Language for Country Specific Requirements for Europe has been amended	To comply with sponsor protocol template guidelines The single global version of the protocol details specific local requirements into Appendix	Appendix 12 Section 10.12.1 European Union
The term “WOCBP ” has been updated to “ IOCBP”	To comply with sponsor protocol template guidelines	Section 1.3 Schedule of Activities Section 2.3.1 Risk Assessment Section 4.2.4. Choice of Contraception/Barrier Requirements Section 8.3.5 Pregnancy Testing Section 10.2 – Table 12 - Laboratory Tests Section 10.4. Contraceptive and Barrier Guidance
Editorial changes / table numbering update	To correct grammatical errors, to maintain consistency, and/or to increase clarity	Throughout the protocol
China-Specific Requirements for sample collection and analysis were added to the protocol. These changes incorporate the PACL dated 09-May-2024	To ensure China sample collection, analysis and disposal are consistent with local policy.	Appendix 12, Section 10.12.- Country Specific Requirements
Paragraphs referring to administration of CCI have been modified. These changes incorporate the PACL dated 21-May-2024	To provide additional details and align content between protocol section and Appendix referring to concomitant medications and provide the full list of CCI that can be used during the study as concomitant medications. in addition, it was clarified that the DDI list can be revised over time and sites be informed by written notification.	Section CCI and Appendix 9, Section 10.9 “Prohibited Concomitant Medications That May Result in DDI”

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Interventional Safety and Efficacy Phase 1b/2, Open-Label Study to Investigate Tolerability, PK, and Antitumor Activity of Vepdegestrant (ARV-471/PF-07850327), an Oral Proteolysis Targeting Chimera, in Combination with PF-07220060 in Participants Aged 18 Years and Older with ER+/HER2- Advanced or Metastatic Breast Cancer

Brief Title: A Study to Investigate the Safety and Antitumor Activity of Vepdegestrant (ARV-471) in Combination With PF-07220060 in Adults With ER+/HER2- Advanced or Metastatic Breast Cancer

Regulatory Agency Identification Number(s):

US IND Number:	168576
EU Clinical Trial (CT) Number:	2023-508130-33-00
ClinicalTrials.gov ID:	NCT06206837
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4891026
Phase:	1b/2

Rationale:

The purpose of Study C4891026 is to evaluate the safety, antitumor activity, and PK of vepdegestrant in combination with PF-07220060 in the treatment of participants with estrogen receptor-positive human epidermal growth factor receptor-negative (ER+/HER2-) advanced or metastatic breast cancer (A/MBC).

Rationale for Protocol Amendment 3

The main purpose of the amendment is to introduce a reduced Schedule of Activities (SoA) with clinical assessments per standard of care or clinical judgment of the treating physician. Reduced data recording will maintain safety and tumor assessment (performed as per standard of care). In addition, this amendment is to update the end of study definition and the section regarding continued access to study intervention after the end of the study.

Objectives, Endpoints, and Estimands:

Phase 1b

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To assess safety and tolerability of vepdegestrant in combination with PF-07220060 in participants with ER+/HER2- A/MBC to select up to 2 RDEs for the combination.	DLTs during DLT observation period (Cycle 1).	DLT rate estimated based on data from DLT-evaluable participants during the DLT observation period (Cycle 1).
Secondary:	Secondary:	Secondary:
To evaluate the overall safety profile.	- AEs as characterized by type, frequency, intensity (as graded by NCI CTCAE version 5.0), seriousness, and relationship to vepdegestrant in combination with PF-07220060 - Incidence of laboratory abnormalities. - Incidence of ECG abnormalities.	Not applicable.
To evaluate antitumor activity of vepdegestrant in combination with PF-07220060.	- Confirmed OR (CR or PR) by investigator assessment. - DoR by investigator assessment. - CBR (confirmed CR or PR at any time, or SD ≥ 24 weeks) by investigator assessment. - PFS by investigator assessment.	Not applicable.
To evaluate the plasma exposure of vepdegestrant, ARV-473, and PF-07220060 when vepdegestrant and PF-07220060 are given in combination.	- Plasma concentrations of vepdegestrant, ARV-473, and PF-07220060. - Steady-state C_{max}, T_{max}, and AUC_{last} of vepdegestrant, ARV-473, and PF-07220060. - If data permit CL/F, V_z/F, and $t_{1/2}$ of vepdegestrant,	Not applicable.

Objectives	Endpoints	Estimands
	ARV-473, and PF-07220060.	

AE: adverse event; A/MBC: advanced or metastatic breast cancer; AUC: area under curve; CBR: clinical benefit response; CL: clearance; C_{max}: maximum observed concentration CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DLT: dose limiting toxicity; DoR: duration of response; ECG: electrocardiogram; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NCI: National Cancer Institute; OR: objective response; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; SD: stable disease; T_{max}: time to maximum concentration.

Phase 2

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To assess the clinical antitumor activity of vepdegestrant in combination with PF-07220060.	Confirmed OR (CR or PR) determined by investigator assessment.	The treatment effect of vepdegestrant in combination with PF-07220060 assessed by the OR rate based on Investigator assessment per RECIST v1.1 in the analysis population. Participants who do not have a post-baseline disease assessment due to early PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience documented PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as non-responders.
Secondary:	Secondary:	Secondary:
To determine additional antitumor activity outcomes of vepdegestrant in combination with PF-07220060.	- DoR by investigator assessment. - CBR (confirmed CR or PR at any time or SD $\geq$ 24 weeks) by investigator assessment. - PFS by investigator assessment. - OS.	Not applicable.
To further characterize the overall safety profile and tolerability of vepdegestrant in combination with PF-07220060.	- AEs as characterized by type, frequency, intensity (as graded by NCI CTCAE version 5.0), seriousness, and relationship to vepdegestrant in combination with PF-07220060. - Incidence of laboratory abnormalities.	Not applicable.

Objectives	Endpoints	Estimands
	Incidence of ECG abnormalities	
To evaluate the plasma exposure of vepdegestrant, ARV-473 and PF-07220060 when vepdegestrant and PF-07220060 are given in combination.	Plasma concentrations of vepdegestrant, ARV-473, and PF-07220060.	Not applicable.
To assess changes from baseline levels in plasma ctDNA with treatment.	ctDNA plasma quantitative changes from pre-treatment to evaluate potential predictability of their associations with clinical outcomes.	Not applicable.

CBR: clinical benefit response; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: circulating tumor deoxyribonucleic acid; DoR: duration of response; NCI: National Cancer Institute; OR: objective response; OS: overall survival; PD: pharmacodynamics(s), progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Overall Design

C4891026 is a prospective, open-label, multicenter, Phase 1b/2 study to evaluate the safety, antitumor activity, and PK of vepdegestrant in combination with PF-07220060 in the treatment of participants with ER+/HER2- A/MBC.

The combination will be assessed in 2 parts in C4891026:

- Phase 1b:** dose escalation/de-escalation phase to evaluate the safety and tolerability of vepdegestrant in combination with PF-07220060 and select up to 2 recommended doses for dose expansion for the combination (combination recommended doses for expansion [RDEs]) via the modified toxicity probability interval (mTPI)-2 dose-finding design.
- Phase 2:** if at least 2 dose levels from Phase 1b (eg, two combination RDEs) are considered tolerable, a randomized dose optimization Phase 2 will be conducted to further evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of vepdegestrant in combination with PF-07220060 to determine the recommended Phase 2 dose (RP2D) of the combination. If only one dose level from Phase 1b is considered tolerable, a single arm Phase 2 dose expansion will be conducted.

Phase 1b: In Phase 1b the starting dose level (DL1) of vepdegestrant will be 200 mg once daily (QD) and the starting dose level of PF-07220060 will be 100 mg twice daily (BID). The decision to escalate the starting dose level of PF-07220060 will be using mTPI-2 decision criteria based on the number of DLT-evaluable participants and the number of DLTs in those participants during the DLT observation period. DL2 will be the combination of vepdegestrant 200 mg QD and PF-07220060 300 mg BID. Based on the mTPI-2 decision criteria and depending on the occurrence of DLTs and need for dose reduction, two

additional dose levels may be investigated: vepdegestrant **CCI** mg QD in combination with PF-07220060 **CCI** mg BID and/or vepdegestrant **CCI** mg QD in combination with PF-07220060 **CCI** mg BID.

A minimum of 3 DLT-evaluable participants will be required in each cohort at a given dose level before a decision is made to de-escalate, escalate, or remain at the current dose level. Additional participants will be enrolled in a specific cohort to replace participants who are not considered DLT-evaluable. Once the first dose level is cleared and the slots for the first 3 participants at the second dose level are filled, backfill will commence at the lower dose level to enable better characterization of PK, safety, and efficacy. These participants will be considered in the overall assessment of PK, safety, efficacy, and selection of RDE.

Phase 2: In the Phase 2 portion of the study up to two RDEs will be further explored.

The RP2D of vepdegestrant and PF-07220060, identified as the dose that can be used in further large-scale testing, will be determined based on an overall assessment of safety, tolerability, PK and early signals of efficacy. The RP2D may be the same as the maximum tolerated dose (MTD) or RDE, or may be lower. The RP2D will be determined in this study after the Phase 2 expansion cohort(s) have provided sufficient data on which to make such a determination.

Dose escalation/de-escalation decisions, RDE and RP2D of the combination will be determined by the Dose Level Review Committee, composed of sponsor representatives and the study investigators, at the dose level review meeting (DLRM).

A Steering Committee has been established at the vepdegestrant program level, and it will be involved in scientific discussions involving C4891026 but not in the detailed dose discussions or decisions for this study.

Number of Participants

The total sample size is estimated to be approximately 65 participants for C4891026 Phase 1b and Phase 2. The sample size is estimated to be approximately 15 participants for Phase 1b and 50 participants (approximately 25 per dose level for Phase 2).

The number of participants to be enrolled in Phase 1b will depend on the observed safety profile, which will determine the number of participants at each dose level and the number of dose levels explored. Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-4 participants during the DLT observation period (Cycle 1). At least 6 DLT-evaluable participants in Phase 1b will be treated at each dose level to be explored in the Phase 2, before proceeding to Phase 2. If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in Phase 1b.

In Phase 2, approximately 50 participants will be enrolled. If at least 2 dose levels from Phase 1b are considered tolerable, a randomized 1:1 dose optimization Phase 2 will be conducted, approximately 25 participants for each arm will be enrolled and treated. If only

one dose level from Phase 1b is considered tolerable, a single arm Phase 2 will be conducted in approximately 25 participants.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention (vepdegestrant and PF-07220060).

Study Population

Inclusion and exclusion criteria are listed below:

Key Inclusion Criteria

Participants with ER+/HER2- A/MBC, who have been previously treated with up to 2 lines of prior therapies for advanced/metastatic disease. Phase 2 participants must have at least 1 measurable lesion as per RECIST v1.1 and must have received 1 line of any prior CDK4/6 inhibitor-based regimen.

Key Exclusion Criteria

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

- Participants in visceral crisis at risk of life-threatening complications in the short term.
- Participants with newly diagnosed or symptomatic brain metastases.
- Refractory nausea and vomiting and other gastrointestinal (GI) conditions precluding adequate absorption of study interventions.
- History of any other malignancies within the past three years, except for (1) adequately treated basal or squamous cell carcinoma of the skin and (2) curatively treated in situ carcinoma of the cervix.
- Impaired cardiovascular function or clinically significant cardiovascular diseases.

Study Arms and Duration:

The screening period will occur within 28 days prior to first dose. Study intervention will be administered in 28-day cycles.

The starting dose level of vepdegestrant will be 200 mg QD and the starting dose level of PF-07220060 will be 100 mg BID. Vepdegestrant and PF-07220060 must be taken with food. Vepdegestrant and the first of two daily doses of PF-07220060 should preferably be taken in the morning at approximately the same time.

Ethical Considerations:

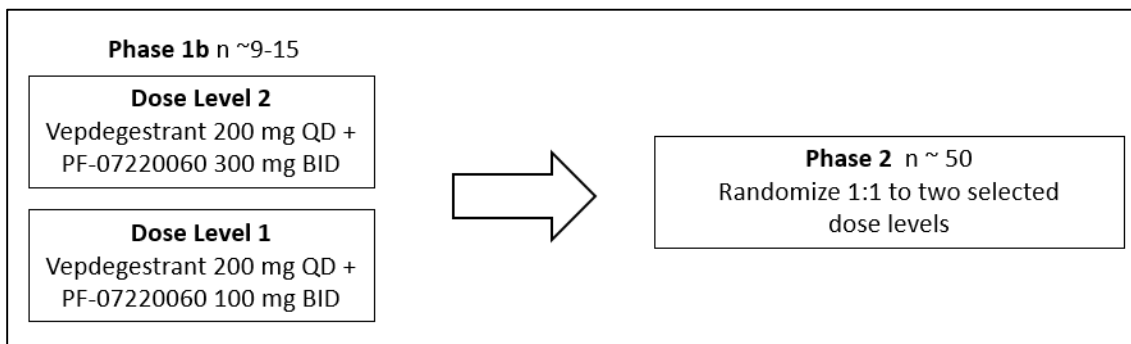
The combination of PF-07220060 with vepdegestrant is expected to provide benefit to pretreated participants with ER+/HER2- A/MBC.

In combination with letrozole or fulvestrant in participants with HR+/HER2- MBC who progressed on prior CDK4/6 inhibitor + ET, PF-07220060 demonstrated early signs of antitumor activity. This suggests combination with vepdegestrant, an agent that also targets the ER, has potential to benefit participants.

Vepdegestrant showed preclinical activity against wild-type tumors, as well as tumors with ESR1 mutations (one of the mechanisms of resistance to ET), and demonstrated activity as an ET backbone in combination with other targeted agents in BC tumor models. The administration of vepdegestrant in combination with the CDK4 inhibitor PF-07220060, could therefore represent an important therapeutic option in participants with ER+/HER2- A/MBC.

Considering the measures taken to minimize risk to study participants, the potential risks identified in association with vepdegestrant in combination with PF07220060 are justified by the anticipated benefits that may be afforded to participants with ER+/HER2 A/MBC.

1.2. Schema



In the Phase 1b, based on the mTPI-2 decision criteria and depending on the occurrence of DLTs and need for dose reduction, two additional dose levels may be investigated: vepdegestrant CC1 mg QD in combination with PF-07220060 CC1 mg BID and/or vepdegestrant CC1 mg QD in combination with PF-07220060 CC1 mg BID.

In Phase 2, approximately 50 participants will be enrolled. If at least 2 dose levels from Phase 1b are considered tolerable, a randomized 1:1 dose optimization Phase 2 will be conducted and approximately 25 participants for each arm will be enrolled and treated. If only one dose level from Phase 1b is considered tolerable, a single arm Phase 2 will be conducted.

1.3. Schedule of Activities (After Implementation of Amendment 3)

The SoA table provides an overview of the protocol visits and procedures. After implementation of Protocol Amendment 3, Table 1 supersedes the prior SoA tables (available in Section 10.14). This table is applicable to both Phase 1b and Phase 2 participants. Refer to the [STUDY ASSESSMENTS AND PROCEDURES](#) section of the protocol for detailed information on each assessment required for compliance with the protocol.

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

Table 1. Study Schedule of Assessments - (Applicable to both Phase 1b And Phase 2 Participants after Implementation of Amendment 3)

Protocol Activity	Combination Treatment Phase 1 Cycle = 28 days	EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
	Visits on Day 1 of every 2 cycles (1 cycle = 28 days)			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Visit Window	±4d		+7d	
Physical Examination/Vital Signs	As per clinical standard of care at the discretion of the investigator.			To be performed as clinically indicated per PI/site standard of care and documented in site source only. Any observed AE must be reported in the eCRF. See Sections 8.3.1 and 8.3.2 .
Clinical Laboratory Assessments				
Hematology ^c	As per clinical standard of care at the discretion of the investigator.			To be performed as clinically indicated per PI/site standard of care and documented in site source only. Any AE resulting from an abnormal test result must be reported in the eCRF. See Section 8.4.1 .
Blood Chemistry ^c	As per clinical standard of care at the discretion of the investigator.			
Pregnancy test ^c	X (to be performed every cycle)	X	X ^d	To be documented in site source; only a positive test result must be recorded in the eCRF. See Section 8.3.5 and 10.2 .

Table 1. Study Schedule of Assessments - (Applicable to both Phase 1b And Phase 2 Participants after Implementation of Amendment 3)

Protocol Activity	Combination Treatment Phase 1 Cycle = 28 days	EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
	Visits on Day 1 of every 2 cycles (1 cycle = 28 days)			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Visit Window	±4d		+7d	
12-Lead ECG	As per clinical standard of care at the discretion of the investigator.			To be performed as clinically indicated per PI/site standard of care and documented in site source and in the eCRF. Any AE resulting from an abnormal ECG must be reported in the eCRF See Section 8.3.3.
Disease Assessment				
CT/MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease (Other Than Bone Scan)	As per clinical standard of care at the discretion of the investigator.			Treatment beyond progression is not permitted. See Section 8.2.1.2 As per Amendment 3, no post-treatment disease assessments are required for participants who discontinued study intervention for reasons other than documented PD as per RECIST v1.1 criteria. See Section 8.2 Efficacy Assessments
Clinical Evaluation of Superficial Disease	As per clinical standard of care at the discretion of the investigator.			
Radionuclide Bone Scan, Whole Body	As per clinical standard of care at the discretion of the investigator.			
Other Clinical Assessments				
Contraception Check for IOCBP and males ^c	X (every cycle)	X	X	See Section 5.3.1 Contraception and Section 10.4.
AE Reporting ^c	X	X	X	Any observed AEs must be reported in the eCRF. See Section 8.4.
Review Concomitant Medications/ Treatments ^c	X	X	X	To be recorded in site source only (and on SAE form if applicable) but not in the eCRF. See Section 6.9 Prior and Concomitant Therapy.

Table 1. Study Schedule of Assessments - (Applicable to both Phase 1b And Phase 2 Participants after Implementation of Amendment 3)

Protocol Activity	Combination Treatment Phase 1 Cycle = 28 days	EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
	Visits on Day 1 of every 2 cycles (1 cycle = 28 days)			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Visit Window	±4d		+7d	
Subsequent Anticancer Therapy			X	First subsequent anticancer therapy data to be collected. See Section 7.1 Discontinuation of Study Intervention.
Study Intervention and GnRH/LHRH Agonist				
Vepdegestrant	QD			See Section 6.1 Study Intervention Administered.
PF-07220060	BID			See Section 6.1 Study Intervention Administered.
Drug Compliance ^c	X			Drug accountability will be performed prior to dispensing drug for the following interval of every 2 cycles. See Sections 6.1.1 Administration and 6.5 Study Intervention Compliance.
GnRH or LHRH Agonist (for Men and Pre-/Peri-menopausal Participants) ^c	As per local package insert		X	Treatment should start at minimum on C1D1 if not before and be administered as per local package insert, irrespective of cycle duration and up to 28 days after the last dose of study intervention. Treatment continuation after post-treatment follow-up is at the discretion of the investigator. See Section 6.9.2 GnRH or LHRH agonist

a. End of Treatment/Withdrawal: As soon as study intervention is permanently discontinued and no more than 28 calendar days after last dose of oral study intervention.

b. Post Treatment Follow-up: Follow up visit will be performed at least 28 days (+7 days) from last dose of study intervention OR prior to the initiation of any new anticancer therapy whichever comes first. The SAE reporting period is 28 days from last dose regardless of the initiation of a new anticancer therapy (see [Section 8.4.1](#)).

c. Assessments may be performed during home health visits that will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.

d. If the participant permanently discontinues treatment, the pregnancy test must be performed as per timelines available in [Appendix 4](#) or according to local regulations.

Abbreviations used in the SoA table are provided in [Appendix 15](#).

2. INTRODUCTION

Vepdegestrant (ARV-471; PF-07850327) is a potent, selective, orally bioavailable, PROTAC[®] small molecule that directly induces the degradation of the ER. Vepdegestrant is being developed for the treatment of participants with ER+ BC. PF-07220060 is a small molecule potent inhibitor of CDK4 which differs from currently approved dual CDK4/6 inhibitors in that it displays greater CDK4-over-CDK6 selectivity. PF-07220060 is being developed for the treatment of participants with BC.

In study C4891026, vepdegestrant is being investigated in combination with PF-07220060 for the treatment of participants with ER+/HER2- A/MBC.

The investigational drug vepdegestrant (ARV-471; PF-07850327) will be identified throughout the protocol as vepdegestrant.

2.1. Study Rationale

The purpose of Study C4891026 is to evaluate the safety, antitumor activity, and PK of vepdegestrant in combination with PF-07220060 in the treatment of participants with ER+/HER2- A/MBC.

2.2. Background

2.2.1. Breast Cancer

Female BC has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. BC is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths and the second leading cause of cancer death in women ([Sung et al, 2021](#)). By 2040, new breast cancer cases and deaths attributed to BC are expected to increase to 3 million cases and 1 million deaths worldwide ([Arnold et al, 2022](#)).

In the United States, there are predicted to be a total of 300,590 incident cases of BC in 2023 ([Siegel et al, 2023](#)), with the vast majority (approximately 73%) of cases being HR-positive, HER2-negative ([Howlader et al, 2014](#)). Additionally, BC is the second leading cause of cancer death in women in the US, with 43,170 women expected to die from the disease in 2023 ([Siegel et al, 2023](#)). While BC is less common in men, men account for approximately 1% of all newly diagnosed cases in the US and almost 530 men are projected to die from their disease in 2023 ([Siegel et al, 2023](#)).

The number of people living with MBC is increasing globally, primarily because of improvements in available treatment options. Expanded targeted therapies, especially in HR-positive disease, have improved survival for MBC in recent decades ([Giaquinto et al, 2022](#)). The estimated number of women living with MBC (de novo and recurrence) in the US is projected to reach 169,347 by 2025 ([Gallicchio et al, 2022](#)). Median survival among patients diagnosed with de novo metastatic disease between 2010-2016 in the US was recently estimated to be 25 months ([Taskindoust et al, 2021](#)). However, the medical need for more active agents in the advanced setting persists.

2.2.2. Overview of Current Therapy Space

Treatment options for A/MBC depend on many different factors, including whether the tumors express hormone receptors (ER and/or progesterone receptor) or HER2. The standards of care for people with ER+/HER2- A/MBC are ET, chemotherapy, and/or targeted therapy alone or in combination. Endocrine therapies include ovarian ablation or suppression (for pre-menopausal women), tamoxifen (a SERM), AIs, fulvestrant (a SERD) and elacestrant (oral SERD for *ESR1* *mut* patients). The addition of CDK4/6 inhibitors to ET, either in the first-line setting or after progression on an AI, improves PFS and OS compared to endocrine therapy alone in the treatment of patients with HR+/HER2- A/MBC. Currently, CDK4/6 inhibitors have been incorporated and established as standard treatment options for HR+/HER2- A/MBC.

While many patients derive benefit from standards of care such as CDK4/6 inhibitors and/or hormonal therapy in frontline ER+/HER2- MBC, standard treatment options upon disease progression are less clearly defined and are generally associated with shorter mPFS. While targeted therapy choices exist for some patients, such as those with a *PIK3CA* mutation or *BRCA* mutation, there is a need for more effective therapies for many patients. Novel treatments have the potential to prolong progression-free survival, offer potentially more tolerable side effects, improve patient experience on drug, or prolong survival.

Endocrine resistance is a clinical challenge and can present at diagnosis (de novo/intrinsic resistance) or after treatment with endocrine therapy (acquired resistance). Intrinsic resistance is thought to be present in up to 30% of patients and due to lack of expression of ER (Belachew & Sewasew, 2021). Approximately 50% of patients will develop SERM/AI/SERD-resistant ER-positive metastatic lesions after an average of 5 years (Fanning & Greene, 2019; Rozeboom et al, 2019). The development of ET-resistant phenotypes involves multiple mechanisms, including (a) ER α mutations (where *ESR1* gene mutations are one of the most studied) that lead to ligand-independent constitutive activation of ER; (b) in the absence of estradiol, the activation of ER α because of signaling pathway activation; and (c) variation in the expression of ER α cofactors responsible for the ER α modulator activity. Investigation of potential mutations is highly recommended after progression, especially for *PIK3CA* and *ESR1* mutations, the most common mechanisms of acquired resistance to ET. *ESR1* mutation may occur with an approximate 20%-40% prevalence after progression on an AI (Brett et al, 2021).

Fulvestrant, an approved SERD, is given as an intramuscular injection in a clinical setting, inhibits estrogen signaling through the ER primarily in 2 ways: competitive inhibition of estradiol binding to the ER to block nuclear localization, and accelerated degradation of the ER protein due to the instability of the fulvestrant-ER complex. Fulvestrant's destabilizing mechanism has validated the importance of ER degradation as a therapeutic approach. After fulvestrant treatment, ER declined significantly compared to pre-treatment reaching its lowest levels at 6 months (6-months median ER Hscore of 48 [2-135] versus pretreatment median ER Hscore of 130 [60-190]). This ER level was generally maintained at time of fulvestrant progression (median ER Hscore of 50 [8-130]) showing that no patient had lost all ER at relapse even in the longest interval between treatment and progression of 60.7 months, indicating a need for more effective ER-degrading molecules (Agrawal et al, 2016).

Fulvestrant has demonstrated activity in patients with both wild-type and *ESR1* mutant tumors in the second-line treatment setting with mPFS of 4.1 months (95% CI: 3.6, 5.5) in patients with *ESR1* wild type tumors and 3.9 months (95% CI: 3.0, 6.0) in patients with *ESR1* mutant tumors (Turner et al, 2020). However, the clinical benefit reported in participants whose disease progressed after CDK4/6 inhibitor + ET therapy treated with fulvestrant (1.94 months mPFS [95% CI: 1.84, 3.55] in the VERONICA study) (Lindeman et al, 2021) or with physician choice (1.9 months mPFS by BICR, in all patients and in patients with *ESR1* mutation, in the EMERALD study) (Bidard et al, 2022) did not show robust enhancement and needs to be further improved.

Oral SERDs are currently in research and development. Recent investigational advances have allowed the development of new orally bioavailable SERDs with encouraging results. In a Phase 3 study, elacestrant, an investigational oral SERD, has demonstrated a statistically significant and clinically meaningful improvement in PFS over standard of care ET (ie, AIs or fulvestrant) in patients with ER+/HER2- A/MBC in the second- and third-line settings following prior treatment with CDK4/6 inhibitor-based therapy (EMERALD study) (Bidard et al, 2022). Approximately half of the patients enrolled harbored *ESR1* mutations. The study results showed a statistically significant improvement in PFS in the elacestrant arm compared to the standard of care ET arm, with a mPFS of 2.79 (95% CI: 1.94, 3.78) vs 1.91 (95% CI: 1.87, 2.10) months in all patients (HR=0.697 [95% CI: 0.55, 0.88]; p=0.002) and 3.78 (95% CI: 2.17, 7.26) vs 1.87 (95% CI: 1.87, 2.14) months in patients with *ESR1* mutation (HR=0.55 [95% CI: 0.39, 0.77]; p=0.0005). The OS data showed HR=0.91 (95% CI: 0.71, 1.18) in all patients, and HR=0.90 (95% CI: 0.63, 1.30) in patients with *ESR1* mutation (FDA, 2023; ORSERDU_USPI, 2023). Elacestrant was approved by FDA in January 2023 for the treatment of postmenopausal women or adult men, with ER+/HER2-, *ESR1*-mutated A/MBC with disease progression following at least one line of ET.

Clinical data regarding expected outcomes for subsequent treatments in patients who progressed after CDK4/6 inhibitor therapy plus AI or fulvestrant are very limited. There is a gap in high-level evidence on the optimal sequencing of agents after progression on CDK4/6 inhibitor-based treatment in the frontline setting. Unanswered questions include the use of CDK4/6 inhibitors beyond progression and what is the efficacy of other therapies after progression, given the fact that most of the data generated with older regimens occurred in the era before CDK4/6 inhibitors were broadly used (McAndrew & Finn, 2021).

The past decade has seen significant improvements in the treatment options for patients with ER+/HER2- A/MBC. However, there is still an unmet need to improve clinical outcomes after progression with existing ET therapies, particularly for the second- and third-line patients where the desire is to delay treatment with chemotherapy. Novel mechanisms of action and combinations of agents that can address the mechanisms of intrinsic or acquired resistance could lead to greater benefit in terms of depth and/or durability of antitumor responses for patients with ER+ A/MBC.

2.2.3. Vepdegestrant

For more information, refer to the Vepdegestrant IB.

2.2.3.1. Drug Mechanism of Action

Vepdegestrant is a potent, selective, orally bioavailable PROTAC small molecule that directly induces degradation of the ER. Vepdegestrant is a heterobifunctional PROTAC molecule that simultaneously binds the ER and the cereblon E3 ligase complex, enabling protein-protein interactions between the ER and the ligase complex. As a result, the ER becomes poly-ubiquitinated on accessible lysine residues and subsequently undergoes targeted degradation by the proteasome leading to its elimination from cells. This direct recruitment of the Ubiquitin-Proteasome System and subsequent degradation results in improved elimination of the ER in preclinical models; therefore vepdegestrant may offer advantages to AIs or fulvestrant in patients who received prior ET.

2.2.3.2. Nonclinical Pharmacology

In vitro vepdegestrant demonstrated potent (<1 nM) and robust (>90%) ER degradation even in the presence of clinically relevant, mutated (Y537S and D538G) forms of ER. Further, based on nonclinical studies, vepdegestrant demonstrated greater ER degradation compared to fulvestrant (Flanagan et al, 2018). While SERDs destabilize ER and indirectly lead to ER degradation, vepdegestrant degrades ER through direct recruitment of the UPS, which may lead to less drug resistance. In addition to vepdegestrant, its epimer ARV-473, was assessed for ER degradation activity. While both vepdegestrant and fulvestrant reduced ER levels, ARV-473 did not reduce ER levels, even when tested at 1 μ M. In an ER-dependent gene reporter assay, vepdegestrant and ARV-473 had similar antagonist activity, indicating that vepdegestrant has both antagonist and degradation activities against ER, whereas ARV-473 displays only antagonist activity.

In vivo, vepdegestrant inhibits tumor growth in a dose-dependent manner in xenograft mouse models. In the MCF7-xenograft mouse model, 3 to 30 mg/kg vepdegestrant, orally administered to mice once daily for 28 days, displayed dose-dependent efficacy with doses of 3 and 10 mg/kg/day inhibiting tumor growth by 85% and 94%, respectively, relative to vehicle and 30 mg/kg/day leading to tumor shrinkage (up to 124% TGI). At study termination, the tumor ER levels were reduced by $\geq$ 94% compared to mice administered vehicle only, suggesting that higher doses are required for maximal efficacy than for maximal ER degradation. To explore in vivo activity of vepdegestrant against a clinically relevant ER mutation, TGI studies were performed in a patient-derived xenograft model, ST941/HI, which harbors a Y537S mutation. vepdegestrant at both 10 and 30 mg/kg/day demonstrated superior tumor growth inhibition (99% and 106% TGI, respectively) in the ST941/HI PDX model when compared to fulvestrant (62% TGI). The dose and schedule of fulvestrant used in these models led to higher plasma levels of fulvestrant than what can be clinically achieved. Regarding degradation of ER in this model: both compounds tested reduced ER levels, with 30 mg/kg vepdegestrant lowering ER by 88%, and fulvestrant reducing ER levels by 63%. These data demonstrate that vepdegestrant is more active in an ER+ BC PDX model than fulvestrant.

2.2.3.3. Nonclinical Pharmacokinetics and Metabolism

The PK profile of vepdegestrant in the nonclinical species (mouse, rat, dog, and monkey) was characterized by a CCI % of hepatic blood flow),

CCI tissue distribution (CCI L/kg), CCI half-life of elimination ($t_{1/2}$ CCI hours), and CCI oral bioavailability (CCI %). CCI

CCI in vepdegestrant exposure was observed when vepdegestrant was administered as an oral solution in the mouse (CCI mg/kg), rat (CCI mg/kg), dog (CCI mg/kg), and monkey (CCI mg/kg).

CCI

CCI is the main isoform contributing to vepdegestrant CYP metabolism (accounting for CCI % of CYP metabolism).

2.2.3.4. Potential Drug-Drug Interactions

Drugs that are inhibitors of CYP3A4 may increase the exposure of vepdegestrant, whereas drugs that are inducers of CYP3A4 may reduce the exposure of vepdegestrant. A Phase 1, open-label, fixed-sequence, 2-period study (C4891009) was conducted to estimate the effect of multiple doses of a strong CYP3A inhibitor itraconazole on the single-dose PK of vepdegestrant in 12 healthy participants. Administration with multiple doses of itraconazole (200 mg) increased vepdegestrant (200 mg) plasma exposure C_{max} by 52% and AUC_{inf} by 69% (Vepdegestrant IB).

The effect of co-administering a strong CYP3A inducer on vepdegestrant exposure has not been studied. Therefore, co-administration with a strong CYP3A inducer should be avoided

Vepdegestrant is an inhibitor of CCI in vitro. Mechanistic static modeling indicated a low potential for DDI due to vepdegestrant-mediated reversible inhibition of CCI (using CCI as the probe CCI substrate drug). Since CCI is the only known sensitive CCI substrate, participants enrolled in clinical trials are allowed to receive CCI substrates or CCI substrates with narrow therapeutic indices.

Vepdegestrant is an in vitro inhibitor of P-gp transporter. An interventional Phase 1, open-label, fixed-sequence, 2-period DDI study (C4891008) was conducted to evaluate the effect of a single oral dose of vepdegestrant on the single dose PK of dabigatran (probe substrate of P-gp) in 24 healthy participants. Co-administration with a single dose of vepdegestrant (200 mg) increased dabigatran (75 mg) plasma exposure C_{max} by 92% and AUC_{inf} by 98%. Depending on the indication of P-gp substrates, use P-gp substrates with caution, reduce the dose or avoid concomitant use per respective local product label.

Vepdegestrant is an in vitro inhibitor of BCRP transporter. An interventional, Phase 1, open-label, fixed-sequence, 2-period DDI study (C4891029) was conducted to evaluate the effect of a single dose of vepdegestrant on the single dose PK of rosuvastatin (probe substrate of BCRP) in 12 healthy participants. Co-administration with a single dose of vepdegestrant (200 mg) increased rosuvastatin (10 mg) plasma exposure AUC_{last} by 21% and C_{max} by 11%. Dose modification of BCRP substrates is not needed when administered with vepdegestrant .

Studies conducted in fasted rats and dogs showed a pH effect on absorption when administered with CCI (lowered PK at neutral pH). A PPI Cohort was conducted as part of CCI to evaluate the effect of multiple doses of esomeprazole 40 mg on the single dose PK of vepdegestrant 200 mg under fed conditions with a CCI. C_{max} by CCI% and AUC_{inf} by CCI%. These results indicated that under fed conditions with a CCI (approximately 700 calories with a fat content of approximately 35%), CCI.

Administer vepdegestrant ≥ 2 hours before or after CCI. Administer vepdegestrant ≥ 2 hours before or 10-12 hours after CCI. Alternatively, CCI can be administered anytime when vepdegestrant is taken with a CCI.

2.2.3.5. Safety Pharmacology and Toxicology

CCI

CCI

2.2.4. PF-07220060

2.2.4.1. Drug Mechanism of Action

PF-07220060 is a small molecule potent inhibitor of CDK4 which differs from currently approved dual CDK4/6 inhibitors (eg, palbociclib) in that it displays greater CDK4-over-CDK6 selectivity. In humans, this greater CDK4 selectivity is hypothesized to lessen the incidence of neutropenia and allow PF-07220060 to attain higher tolerated plasma concentrations and better target coverage, potentially allowing greater inhibition of the CDK4 in tumors.

2.2.4.2. Nonclinical Pharmacology

CDK4 and the closely related CDK6 functionally link mitogenic signaling pathways, including signaling from receptor tyrosine kinases and hormone receptors, to the cell cycle machinery (Sherr & Bartek, 2017). Mitogenic signals increase expression of D-type cyclins (cyclin D1, D2, and D3), which act as positive regulatory subunits for both kinases. INK4 proteins, including p16, form a second class of regulatory subunits, which, contrary to D-type cyclins, inhibit activation of both kinases. The cell cycle consists of a DNA synthesis, or S phase, and a M phase, preceded by G1 and G2 phases, respectively (Choi & Anders, 2014). Cyclin D-CDK4/6 activity peaks in the G1 phase to initiate G1/S cell cycle phase transition. CDK4/6 are fastidious kinases that phosphorylate relatively few substrates, including RB proteins [RB1, RBL1 (p107) and RBL2 (p130)] and the transcription factor FOXM1 (Anders et al, 2011). Phosphorylation of RB proteins allow for the E2F-mediated transcription of a suite of genes, including cyclin E, that execute orderly transition of cells across the G1-S border of the cell cycle and initiate DNA synthesis.

It is well established that CDK4 is overexpressed in a broad variety of human cancers (Choi & Anders, 2014). For example, cyclin D1 is one of the most frequently amplified genes across human cancers, while the gene encoding the CDK4/6 inhibitor p16 is more frequently deleted than any other recessive cancer gene (Beroukhi et al, 2010; Bignell et al, 2010). The cyclin D1 gene is amplified in 20% of human breast cancers (Choi & Anders, 2014). Chromosomal translocations of cyclin D1 are prevalent in specific malignancies, resulting in overexpression of cyclin D1 (Jares & Campo, 2008). Amplifications of CDK4 are frequently found in sarcomas and other malignancies (Lee et al, 2014). CDK4 activating mutations are observed in melanoma (Zuo et al, 1996). This firmly establishes CDK4 as an oncogene. In addition, numerous oncogenic pathways can activate cyclin D-CDK4, such as the ER or HER2 in BC, KRAS in NSCLC, and AR in prostate cancer (Puyol et al, 2010; Casimiro et al, 2013).

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By contrast, CDK6 has not been implicated in driving breast cancer cell proliferation, despite the close homology between both kinases (Lucas et al, 2004; Tsherniak et al, 2017). Rather, CDK6, or its cyclin subunit cyclin D3, are involved in promoting proliferation of many hematopoietic cell lineages, including hematopoietic stem and precursor cells (Malumbres et al, 2004; Sicinska et al, 2006; Laurenti et al, 2015; Scheicher et al, 2015). Therefore, for CDK4/6 inhibitors with strong inhibition of CDK6, hematologic AEs are frequently observed in the clinic (Laurenti et al, 2015; Scheicher et al, 2015).

CDK4/6 inhibition has emerged as a promising strategy for cancer therapy, especially for the treatment of endocrine resistant BC (Rani et al, 2019). The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib have been approved for the treatment of HR+, HER2- mBC in combination with ET, and these compounds have demonstrated a clinically meaningful and statistically significant increase in PFS compared to ET alone (Serra et al, 2019). CDK4/6 inhibition plus ER blockade was shown to elicit additive anti-proliferative effects against HR+, HER2- BC cells in vitro (Finn et al, 2009). Therefore, the combinatorial benefit may be attributed, at least in part, to convergent inhibitory effects of CDK4/6 and ER inhibitors on the cyclin D-CDK4/6 complex in BC cells (VanArsdale et al, 2015). Although CDK4/6 inhibitors increase response rates and prolong disease control in patients with HR+, HER2- BC, they are associated with dose-limiting hematologic toxicities, primarily neutropenia. PF-07220060 differs from currently approved dual CDK4/6 inhibitors in that it displays greater CDK4-over-CDK6 selectivity. In in vivo models, PF-07220060 reduces dose-limiting neutropenia and is projected to potentially attain higher tolerated plasma concentrations than dual CDK4/6 inhibitors, thus potentially enabling increased inhibition of the CDK4 oncogene in tumors. In addition, PF-07220060 in combination with the CDK2 inhibitor PF-07104091 resulted in significant combinatorial benefit versus single agent treatment in the HR+, HER2- HCC1428 and T47D breast cancer models, as well as in the palbociclib-resistant PDX ST941 PBR model.

2.2.4.3. Nonclinical Pharmacokinetics and Metabolism

The nonclinical PK/TK, ADME properties of PF-07220060 have been evaluated in vitro and in vivo to support nonclinical safety evaluations and to assess the potential relevance to humans. The PK of PF-07220060 after oral administration in nonclinical species (mouse, rat and dog) indicated CCI bioavailability (CCI %). Following IV dosing in these species, PF-07220060 demonstrated CCI plasma CL (CCI % of hepatic blood flow) (Davies & Morris, 1993), CCI V_{ss} (CCI L/kg), and $t_{1/2}$ values ranging from CCI h. In 1-month toxicity studies, systemic exposure (C_{max} and AUC_{24}) of PF-07220060 CCI with increasing dose over the ranges evaluated and CCI was observed in rats and dogs. PF-07220060 was CCI bound to plasma proteins across species and demonstrated CCI into CCI over CCI. In vitro studies suggest PF-07220060 may CCI for the CCI such as CCI. The CCI bioavailability observed in nonclinical species indicate that CCI CCI.

The primary clearance mechanisms of PF-07220060 were UGT2B7- and CYP3A4-mediated metabolism (CCI, respectively), with CCI renal excretion. Consequently, CCI changes in PF-07220060 exposure are anticipated following co-administration

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with CCI UGT2B7 inhibitors or inducers. Additionally, changes in PF-07220060 exposure may be observed with CCI inhibitors or inducers of CYP3A4. CCI were observed in vitro compared to metabolite profiling in mouse, rat or dog.

PF-07220060 has the potential for CCI in the gut and liver, CCI in the gut and liver and to CCI using the clinical exposure at the monotherapy dose of CCI mg BID. Overall, there is CCI which indicates a CCI DDI risk when PF-07220060 is co-administered with fulvestrant.

Due to CCI observed in vitro, changes in CCI or co-administration with CCI may CCI the absorption of PF-07220060. A dose response relationship was established between plasma exposure of PF-07220060 and the proximal CCI in the tumor. A human efficacious dose of CCI is predicted to maintain the C_{eff} at approximately CCI % of the dosing interval based on a ZR-75-1 xenograft tumor model (HR-positive BC). PF-07220060 was also tested across a range of other ER-positive BC tumors and PDX models. These models indicate that concentrations CCI clinical dose may be required for CCI

2.2.4.4. Potential Drug-Drug Interaction

In vitro studies indicated the metabolism of PF-07220060 was primarily UGT2B7-mediated (CCI %) with the remaining metabolism via CYP3A4 (CCI %). There is a potential that inhibitors and inducers of CYP3A4 and UGT2B7 may alter the PK of PF-07220060.

Investigations in human liver microsomes, along with basic and mechanistic static modeling (Fahmi et al, 2009) using the clinical exposure at the monotherapy dose of CCI indicate a potential for DDI due to PF-07220060-mediated CCI Impact of PF-07220060 on CCI Depending on the outcome of that portion of the study, the potential impact of PF-07220060 on the PK of vepdegestrant may be need to be evaluated.

In vitro studies showed that PF-07220060 may cause CCI mediated DDIs in the gut and systemically, and CCI mediated DDIs in the CCI-mediated DDIs in the CCI with concomitant medication of CCI substrates.

Use of moderate inhibitors/inducers of CYP3A4 or UGT2B7 should be avoided if possible and any use needs to be reviewed and approved by the Sponsor. Caution is warranted for co-administration of PF-07220060 with CCI substrates with a narrow therapeutic index.

CCI PF-07220060 absorption and systemic exposure. The potential impact to absorption and exposure may be the CCI If needed, administer CCI with a staggered dosing regimen (BID). Administer PF-07220060 ≥ 2 hours before or after CCI Administer PF-

07220060 ≥ 2 hours before the CCI morning dose and at least 10 hours after CCI evening dose.

2.2.4.5. Nonclinical Safety

The toxicity profile of PF-07220060 was assessed in exploratory and 1-month pivotal GLP toxicity studies rats and dogs. The HNSTD/NOAEL in dogs was CCI mg/kg/day, while the STD10 and NOAEL in rats were CCI mg/kg/day, respectively. The primary target organs identified were the CCI

PF-07220060 was assessed in a series of genetic toxicity assays. All in vitro tests were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity, insolubility, or the acceptable limits of the test system. PF-07220060 was negative for mutagenicity in both the presence and absence of metabolic activation in the GLP microbial reverse mutation assays. Additionally, PF-07220060 was negative in the exploratory in vitro micronucleus assay in TK6 cells under all test conditions. In the GLP in vivo micronucleus assessment, PF-07220060 did not induce structural chromosome aberrations or polyploidy in nucleated cells from the bone marrow of male and female rats at 30, 60, 100, or 200 mg/kg/day, and was therefore, not considered clastogenic in that assay. However, PF-07220060 induced small but statistically significant increases in micronucleus formation in polychromatic erythrocytes from bone marrow in male rats ≥ 60 mg/kg/day and in female rats at 200 mg/kg/day.

CCI studies have not been conducted with PF-07220060, however, based on the mechanism of action, and the results in the 1-month toxicity studies, CCI are potential risks in humans.

PF-07220060 had minimal activity in secondary pharmacology and ex vivo safety pharmacology assays, including weak activity ($IC_{50} > CCI \mu M$) toward the hERG channel. No cardiovascular effects (ECG or histopathology) were observed up to the highest dose tested (CCI mg/kg/day) in the pivotal dog study. In a conscious-telemetered dog GLP study, CCI mg/kg/day produced CCI. CCI; no effects were seen after the first dose. Relative to the C_{max} at the human dose of CCI mg, The NOEL for cardiovascular effect is 1.64x.

In a GLP neuropulmonary safety study in rats, PF-07220060 administration did not result in any neurofunctional or pulmonary effects up to the highest dose tested. Relative to the C_{max} at the human dose of CCI mg, The NOEL for neuropulmonary safety is 3.4x.

The nonclinical safety findings related to oral administration of PF-07220060 represent toxicities that can be monitored and/or are considered clinically manageable or acceptable risks in the intended advanced cancer participant population. Additional information of the nonclinical safety of PF-07220060 is available in the current IB.

2.2.5. Clinical Overview

Refer to the Vepdegestrant and PF-07220060 IBs, respectively, for more information.

2.2.5.1. Vepdegestrant

Vepdegestrant is being developed for the treatment of patients with ER+/HER2- A/MBC. In the ongoing FIH study (ARV-471-mBC-101; also known by C4891019), vepdegestrant is being assessed as a monotherapy and in combination with palbociclib in patients with ER+/HER2- A/MBC who had previously received multiple prior therapies. The FIH study has 3 parts: Part A is a monotherapy dose escalation, Part B is a monotherapy dose expansion at two RP2Ds (200 mg QD, 500 mg QD, oral dosing), and Part C is evaluating the combination of vepdegestrant (180, 200, 400, and 500 mg QD) and palbociclib. As of 06 June 2023, 200 participants have been treated: Part A, n=83; Part B, n=71; Part C, n=46 (Vepdegestrant IB). In the monotherapy dose escalation (Part A), all participants had prior CDK4/6 inhibitors, ~87% had prior AIs and ~83% had a prior SERD/ER antagonist, primarily fulvestrant ([Hamilton et al, 2022](#)).

Based on initial safety data (data cutoff date of 06 June 2023), vepdegestrant has been well tolerated across total daily doses of 30 mg to 700 mg in participants with MBC, with no DLTs observed and most TRAE were Grade 1 or 2. In addition, evaluation of preliminary safety data from participants treated with palbociclib in combination with vepdegestrant shows TEAEs consistent with TEAEs observed after treatment with either vepdegestrant or palbociclib alone (Vepdegestrant IB).

In Part A (monotherapy dose escalation), a total of 80 out of the 83 participants (96.4%) reported at least 1 TEAE. The most common TEAEs (regardless of attribution to study intervention) observed in ≥10% of participants were: fatigue (38.6%), nausea (32.5%), constipation (32.5%), arthralgia (22.9%), headache (20.5%), vomiting (16.9%), diarrhea (16.9%), hot flush (16.9%), back pain (15.7%), decreased appetite (15.7%), AST increased (14.5%), hyperglycemia (14.5%), and pain in extremity (14.5%). Most participants experienced TEAEs reported as Grade 1 (34.9%) or Grade 2 (41.0%); 14 participants (16.9%) had Grade 3 TEAEs, 2 participants (2.4%) had Grade 4 TEAEs (of which neutrophil count decreased assessed as serious), and 1 participant (1.2%) had a Grade 5 TEAE (unrelated cardiac arrest). A total of 60 of 83 participants (72.3%) had at least 1 TEAE considered potentially related to vepdegestrant. The most frequently (≥10% participants) reported treatment-related AEs (all grades) were fatigue (26.5%), nausea (25.3%), arthralgia (14.5%), constipation (13.3%), hot flush (13.3%), headache (10.8%), decreased appetite (9.6%), and vomiting (9.6%). Most participants experienced TRAEs that were Grade 1 (41.0%) or Grade 2 (24.1%); 6 participants (7.2%) experienced Grade 3 TRAEs. There were no Grade 4 or Grade 5 TRAEs.

In Part B (monotherapy dose expansion), a total of 63 of the 71 participants (88.7%) reported at least 1 TEAE. The most commonly reported TEAEs (regardless of attribution to study intervention) observed in ≥10% of participants include fatigue (42.3%), nausea (26.8%), arthralgia (21.1%), constipation (19.7%), decreased appetite (15.5%), anemia (14.1%), hot flush (14.1%), AST increased (12.7%), headache (11.3%), and back pain (11.3%). Most

participants experienced TEAEs reported as Grade 1 (22.5%) or Grade 2 (33.8%); 20 participants (28.2%) had Grade 3 TEAEs, 2 participants (2.8%) had Grade 4 TEAEs (hyperbilirubinemia, hypercalcemia and hepatic hemorrhage), and 1 participant (1.4%) had a Grade 5 TEAE (unrelated acute respiratory failure). A total of 54 participants (76.1%) experienced at least 1 TEAE considered potentially related to vepdegestrant. The most common TRAEs, observed in $\geq 10\%$ of participants, include fatigue (36.6%), nausea (21.1%), arthralgia (14.1%), and hot flush (12.7%). Most participants experienced TRAEs of Grade 1 (29.6%) or Grade 2 (38.0%). Five participants (7.0%) experienced TRAEs with severity of Grade 3; there was 1 Grade 4 TRAE of hyperbilirubinemia. There were no Grade 5 TRAEs.

Based on preliminary safety data from 46 participants with ER+/HER2- A/MBC treated with vepdegestrant in combination with palbociclib (Part C), the combination also appears tolerable, except for Grade 4 neutropenia, that is higher than expected based on historical data of palbociclib in combination with endocrine therapy. Neutropenia was medically manageable with/or without supportive care and/or dose adjustments as per the palbociclib prescribing information. A total of 46 of 46 participants (100%) reported at least 1 TEAE. The most common TEAEs (regardless of attribution to study intervention) observed in $\geq 20\%$ of participants included neutropenia/neutrophil count decreased (100%), fatigue (63.0%), platelet count decreased (50.0%), anemia (41.3%), constipation (28.3%), nausea (28.3%), diarrhea (21.7%), WBC count decreased (28.3%), and electrocardiogram QT prolonged (21.7%).

TEAE of electrocardiogram QT prolonged has been identified to be of potential risk based on nonclinical findings, concentration-QTc modelling demonstrating concentration-dependent increases in QTcF interval, and from clinical data from Study ARV-471-mBC-101. An ECG QTc sub-study in Phase III C4891001 study is currently ongoing to further characterize this potential risk.

From the ongoing ARV-471-mBC-101 Study (data cutoff date of 06 June 2023), 12 of the 154 patients treated in the Parts A and B monotherapy cohorts [7.8%, (8 patients from part A and 4 patients from part B)] experienced electrocardiogram QT prolonged AEs. The majority of events were Grade 1. Three patients (1.9%) experienced Grade 3 electrocardiogram QT prolonged event. There was one serious, related Grade 3 electrocardiogram QT prolonged event in Part A for a patient treated at the 700 mg dose. In addition, 10 of the 46 patients (21.7%) treated in the palbociclib combination cohort of the study (Part C) experienced electrocardiogram QT prolonged events, of which majority of events were Grade 1. One patient (2.2%) experienced Grade 3 event at the 500 mg dose. An external cardiology review concluded that of the reported QTc prolonged events, only 2 patients (from Part A and B) had a true diagnosis of QTc prolongation, of which low potassium and concomitant medications were confounding factors.

There have been 52 deaths reported in the study: 33 in Part A, 14 in Part B and 5 deaths have been reported in Part C. None of these deaths were attributable to vepdegestrant. Of the 52 deaths, 4 occurred within 30 days of study intervention discontinuation.

Based on a 06 Jun 2023 data cutoff date, evidence of preliminary clinical activity was observed, as assessed by CBR and ORR, in the monotherapy Part A dose escalation cohort of Study ARV-471-mBC-101: CBR was 36.1% (95% CI: 25.9%, 47.4%) in 30 of 83 evaluable participants; the ORR was 11.5% (95% CI: 4.7%, 22.2%), with 7 of 61 response-evaluable participants having confirmed PR. Clinical activity was observed in Part B (cohort expansion; 06 June 2023 data cutoff date): CBR was 37.1% (95% CI: 21.5%, 55.1%) and 38.9% (95% CI: 23.1, 56.5) in the 200 mg QD and 500 mg QD cohorts, respectively. Clinical benefit was also observed in the ESR1 mutation subgroup, with CBR 47.4% (95% CI: 24.4%, 71.1%) and 54.5% (95% CI: 32.2%, 75.6%) in the 200 mg QD and 500 mg QD cohorts, respectively. Efficacy data collection is ongoing for Part C ([Hurvitz SA, 2022](#)).

Preliminary PK data of vepdegestrant (Data snapshot of 06 June 2022) from Part A monotherapy dose escalation of Study ARV-471-mBC-101 are available from dose levels ranging from 30 to 700 mg administered either as QD or BID. Preliminary results indicate dose-dependent increases in C_{max} and AUC_{tau} for vepdegestrant and ARV-473 up to 500 mg total daily dose administered either as 250 mg- BID or 500 mg QD on both Cycle 1 Day 1 and Day 15. The median T_{max} ranged from CCI across the dose levels. The mean effective $T_{1/2}$ at steady state ranged from CCI. Geometric mean vepdegestrant exposure (AUC_{tau}) on Day 15 at 60 mg QD CCI the nonclinical efficacious range associated with CCI mg/kg in mice). Following 200 mg QD dosing (N=8), a geometric mean accumulation ratio based on AUC_{tau} of CCI was observed between Day 1 and Day 15. The ratio of ARV-473/vepdegestrant, based on AUC_{tau} , on Cycle 1 Day 15 is CCI%.

Safety and PK data in healthy volunteers is based on studies ARV-471-CPhm-103, C4891008, C4891009 and C4891029. All participants received either one or two single doses of 200 mg vepdegestrant alone or co-administered with a drug designated for investigating potential drug interactions (esomeprazole, dabigatran, rosuvastatin, or itraconazole). Single doses of 200 mg vepdegestrant was safe and well-tolerated in healthy participants. No death, SAE, or discontinuation due to AEs were identified except 1 participant in study ARV-471-CPhm-103 who was discontinued due to COVID-19. Study ARV-471-CPhm-103 is a Phase 1, multi-part, open-label study to evaluate the effect of food or a PPI (esomeprazole) and to evaluate the relative bioavailability of different tablet formulations on the single-dose pharmacokinetics and safety of ARV-471 in healthy postmenopausal female participants. Fourteen participants were dosed with vepdegestrant 200 mg in a CCI state CCI CCI CCI meal CCI vepdegestrant C_{max} CCI and AUC_{inf} CCI respectively. Vepdegestrant should be taken with food. PK results from other parts of Study ARV-471-CPhm-103 are summarized in [Section 2.2.3.4](#). Study C4891008 is an interventional, Phase 1, open-label, fixed sequence, 2-period study to evaluate the effect of a single oral dose vepdegestrant on the pharmacokinetics of dabigatran in healthy participants. Study C4891009 is an interventional, Phase 1, open-label, fixed sequence, 2-period study to estimate the effect of multiple doses of itraconazole on the PK of single dose vepdegestrant in the fed condition in healthy participants. Study C4891029 is an interventional, Phase 1, open-label, fixed sequence, 2-period study to evaluate the effect of a single oral dose of vepdegestrant on the pharmacokinetics of rosuvastatin in healthy participants. PK data from the 3 studies are summarized in [Section 2.2.3.4](#).

Analysis of 14 paired biopsies from participants treated with vepdegestrant monotherapy suggested robust ER degradation (up to 89%, observed at doses up to 500 mg daily; median ER degradation across dose levels was 67% [range: CCI%, 89%]), regardless of ESR1 mutation status with CCI and ER degradation in participants with WT or mutant ER (Hamilton et al, 2022).

2.2.5.2. PF-07220060

A Phase 1/2a dose escalation, dose-finding and expansion study (C4391001) evaluating the safety, tolerability, PK, PD and anti-tumor activity of PF-07220060 administered as a single agent and as part of combination therapy in participants with advanced solid tumors, including combination with letrozole or fulvestrant in participants with HR-positive, HER2-negative advanced or MBC, and in combination with enzalutamide in participants with prostate cancer, is ongoing.

Study participants in Part 1A with advanced solid tumors were given single escalating doses of PF-07220060 as monotherapy from 100 mg BID up to 500 mg BID on a continuous basis to determine the MTD and inform the RP3D.

A total of 67 participants with breast cancer metastatic/advanced, prostate cancer, colorectal cancer, endometrial cancer, HNSCC, liposarcoma, melanoma, NSCLC, small intestine cancer, have received PF-07220060 in Part 1 as of the 01 November 2022 data cutoff date. Specifically, 34 participants have been treated with 100, 200, 300, 400, and 500 mg BID single agent PF-07220060 (Part 1A), 13 participants have been treated with 300 mg BID, and 400 mg BID PF-07220060 in combination with letrozole (Part 1B), 13 participants have been treated with 300 mg BID and 400 mg BID PF-07220060 in combination with fulvestrant (Part 1C), and 6 participants have been treated in Part 1D with 400 mg BID single agent evaluating food effect on PF-07220060. One participant has enrolled in Part 1F, which will determine the MTD/RDE of PF-07220060 in combination with enzalutamide in men with prostate cancer who have received $\geq 2L$ of prior therapy. Part 1E will assess the effect of repeated administration of PF-07220060 at the monotherapy MTD on the PK of oral midazolam in participants with advanced solid tumors. For the C4391001 study, the monotherapy MTD for PF-07220060 was determined to be 400 mg BID. The RDE for monotherapy and in combination with ET was determined to be 300 mg BID.

In Part 1, as of the data cut-off date 01 November 2022, of the 61 DLT evaluable participants, 3 (5.6%) participants experienced DLTs. Two participants in the single agent 500 mg BID cohort experienced DLTs of Grade 3 thrombocytopenia. In Part 1C, 1 participant in the 400 mg BID with fulvestrant cohort experienced DLT of Grade 3 neutropenia ≥ 5 days

At the most recent data cut off (01 November 2022), a total of 448 all-causality TEAEs were reported in 66 (98.5%) of the 67 participants dosed with PF-07220060 in Part 1A, Part 1B, Part 1C, Part 1D and Part 1F. In Part 1 (N=67), the most frequently reported ($\geq 20\%$) all-causality TEAEs across all dose levels were neutropenia (49.3%), diarrhea (43.3%), nausea (34.3%), leukopenia (32.8%), anemia (26.9%), fatigue (23.9%), and thrombocytopenia (22.4%). A total of 27 (40.3%) participants reported all-causality TEAE of

Grade 3. Most frequently reported ($\geq 5\%$) Grade 3 or higher all-causality TEAEs were neutropenia (16.4%), and anemia, leukopenia, and thrombocytopenia (7.5% each). No Grade 4 TEAEs were reported. One participant (1.5%) in the Part 1A 400 mg BID group experienced a Grade 5 all-causality TEAE (respiratory failure; unrelated to study drug).

At the most recent data cut off (01 November 2022), PF-07220060 demonstrated early signs of anti-tumor activity in combination with letrozole (Part 1B) or fulvestrant (Part 1C) in participants with HR-positive, HER2-negative mBC who progressed on prior CDK4/6i + ET. The 1B and 1C cohorts at 300 mg BID and 400 mg BID + letrozole or fulvestrant were combined for efficacy assessment based on the lack of DDIs with ET and the comparable exposure observed at the 2 dose levels ($n = 26$). In the 21 participants with measurable disease as per RECIST 1.1 in 1B and 1C cohorts, an overall confirmed response rate of 28.6% (95% CI: 11.3, 52.2) was observed (1 CR in Part 1B, 5 PRs, of these 2 were in Part 1B and 3 were in Part 1C). Clinical benefit response (CR, PR, or stable disease ≥ 24 weeks) was observed in 11/21 (52.4%) (95% CI: 29.8, 74.3) participants (Yap et al, 2023).

In the ongoing study C4391001, as of 30 August 2022, preliminary PK data for PF-07220060 as monotherapy (Part 1A) and in combination with endocrine therapy (Part 1B and Part 1C) was available from 60 participants with advanced solid tumors. Preliminary PK results showed that PF-07220060 was rapidly absorbed following oral administration, with median T_{max} values of 1 to 4 hours. The exposure parameters of PF-07220060, including C_{max} , AUC, and C_{min} , generally increased with dose CCI mg BID for both Cycle 1 Day 1 and Cycle 1 Day 15. CCI Moderate accumulation of the AUC was observed following repeated BID dosing. In general, PF-07220060 exhibited moderate inter-subject variability in exposure parameters. PK of PF-07220060 as monotherapy and in combination with letrozole or fulvestrant were generally comparable. In Part 1B of study C4391001, as of 18 August 2023, emerging data suggested that a standard meal appeared not to affect exposure of PF-07220060 and clinical safety/tolerability were comparable between dosing with food and dosing with an empty stomach at CCI mg BID.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of vepdegestrant and PF-07220060 may be found in the corresponding IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Vepdegestrant		
QTc Prolongation	Potential risk based on nonclinical findings to date as per Section 2.2.3.5. As of data cutoff date of 06 June 2025, 32 (10.3%) participants were reported with AE of QTc interval prolongation in the ongoing Phase 3 pivotal study (C4891001). This AE was considered related in 25 (8.0%) participants. Six participants reported Grade 3 AE, while the others were reported as Grade 1 and 2. A dedicated QTc substudy was conducted in a subgroup of participants (N=88) in the vepdegestrant arm to further characterize the effect of vepdegestrant on the corrected QT (QTc) interval. On the basis of a population modeling analysis that evaluated the relationship between vepdegestrant plasma concentrations and QTc, the mean QTcF change from baseline was 11.1 msec (upper limit of the 90% confidence interval, 13.7 msec) with vepdegestrant at a dose of 200 mg once daily. The upper limit of the 90% confidence interval of the model-predicted increase in QTcF was less than 20 msec for all tested scenarios, at the recommended vepdegestrant dose of 200 mg once daily.	ECG monitoring at screening and during the Active Treatment Phase. Participants at high risk of QTcF prolongation are excluded from participation in the study (see EC #5). The starting dose level to be investigated will be 200 mg QD vepdegestrant in combination with PF-07220060 100 mg BID, which is lower than the recommended dose for expansion (300 mg BID). Concomitant drugs causing Torsade de Pointes or QTcF prolongation are excluded as per Section 10.9. Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events that occurred.
Venous Thromboembolism (VTE)	Potential risk based on metastatic cancer setting and known class effect with ET (SERM, SERD, AIs). One Grade 3 related serious VTE case, with confounding factors of obesity, diabetes and immobility due to recent biopsy procedure, and a Grade 3 serious embolism case assessed as unlikely related to vepdegestrant by the investigator, were reported from the ongoing FIH study (ARV-471-mBC-101).	Participants with a history of clinically significant thromboembolic or cerebrovascular events ≤ 6 months are excluded from participation in the study. Suspicion of VTE should be investigated per local standard practice (eg, blood tests of D-Dimer, fibrinogen; imaging). Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events occurred.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI [REDACTED]	Based on mechanism of action. The loss of estrogen signaling leads to alterations in the hormonal input and feedback loops that are necessary for the menstrual cycle (humans or estrus in animals) and for the maintenance of pregnancy. The summary of the non-clinical animal findings included: CCI [REDACTED] In 1-month CCI study: loss of ability to CCI [REDACTED] observed CCI [REDACTED] in animal studies: CCI [REDACTED] microscopic changes in CCI [REDACTED] tissues that impact CCI [REDACTED] CCI [REDACTED] changes in CCI [REDACTED] Clear impact on CCI [REDACTED] potential risk for CCI [REDACTED] Vepdegestrant may cause fetal loss or reproductive abnormalities when administered to the pregnant woman or IOCBP. The summary of the clinical finding included: CCI [REDACTED] have been reported to date.	Inclusion criteria by protocol will clarify menopausal status allowed and mitigation steps. Pregnant participants or participants <18 years are excluded in the clinical study protocols. Risk minimization measures in clinical study protocols, such as LHRH agonist administered prior to the first study drug dosing and continue for pre-/peri-menopausal women and use of highly effective contraceptive measures is required for both men and women during study. Ensure effective contraception methods are taken in IOCBP and male participants with IOCBP partners (per CTFG guidance).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07220060		
Hematologic - neutropenia - thrombocytopenia - anemia	PF-07220060 IB The primary target organs identified in exploratory and 1-month pivotal GLP toxicity studies were the gastrointestinal tract, hematolymphopoietic system, and the testes (Section 2.2.4.5).	Adequate bone marrow function is required for study inclusion (see EC #13) and participants will be monitored throughout the Active Treatment Phase (see SoA). Study intervention will be interrupted, reduced, or permanently discontinued based on severity of the toxicity as outlined in Section 6.6. Careful monitoring of CBC for any signs of infection or bleeding at each visit. Investigator will instruct participants to promptly contact the sites for any episodes of fever. More frequent monitoring will be implemented if necessary (Sections 6.5 and 8.4.8).
ILD/pneumonitis	PF-07220060 IB Although uncommon, cases of ILD/pneumonitis have been reported in patients with advanced BC receiving CDK4/6 inhibitors. In study C4391001, in the Phase 1 portion, 1 out of 66 participants (1.5%) experienced pneumonitis Grade 2. The participant was treated with PF-07220060 400 mg BID single agent.	Participants with active infections are excluded from participation in the study. Monitor participant for pulmonary symptoms indicative of ILD/pneumonitis (eg, hypoxia, cough, dyspnea). Investigator will instruct participants to promptly contact sites for any new or worsening respiratory symptoms associated with ILD/pneumonitis. Study intervention will be permanently discontinued in case of severe ILD/pneumonitis as outlined in Section 6.6.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal disorders (stomatitis, diarrhea, nausea, vomiting)	PF-07220060 IB The primary target organs identified in exploratory and 1-month pivotal GLP toxicity studies were the gastrointestinal tract, hematolymphopoietic system, and the testes (Section 2.2.4.5).	Participants with refractory nausea and vomiting, chronic GI disease, GI ulcer, and/or GI bleeding are excluded from participation in the study. Careful monitoring for GI disorders (eg, stomatitis, diarrhea, nausea, vomiting) will be conducted. Investigator will instruct participants to promptly contact sites for any new or worsening GI symptoms. Study intervention will be interrupted, reduced, or permanently discontinued based on severity of the toxicity as outlined in Section 6.6 .
Metabolism and nutrition disorders (decreased appetite)	PF-07220060 IB The primary target organs identified in exploratory and 1-month pivotal GLP toxicity studies were the gastrointestinal tract, hematolymphopoietic system, and the testes (Section 2.2.4.5).	Careful monitoring of appetite and body weight will be conducted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Testicular and embryo-fetal toxicity	PF-07220060 IB The primary target organs identified in exploratory and 1-month pivotal GLP toxicity studies were the gastrointestinal tract, hematolymphopoietic system, and the testes (Section 2.2.4.5).	Investigators will ensure effective contraception methods will be taken in IOCBP and male participants with IOCBP partners (see Section 5.3.1 and Section 10.4.4).
Study Procedures		
Tumor Biopsy	Risks associated with any tumor biopsy include the following: • Pain from local anesthetic. • Pain/discomfort from biopsy procedure. • Bleeding, swelling, scarring, pain or bruising at the biopsy site. • Infection of wound. Biopsies of certain sites may increase chances of life-threatening complications, eg, pneumothorax during biopsy of lung.	All procedures will be completed by qualified and trained medical practitioners. Local anesthetic will be administered. Sterile technique will be used. Participants will not be subjected to a significant risk procedure to obtain biopsies. The biopsy at the EOT visit is considered only for participants who discontinue treatment due to disease progression, provide the consent for the procedure, and when, in the investigator's judgment, such biopsy can be safely performed.
Blood Sample Collections	A blood draw may cause inflammation of the vein, pain, bruising, discomfort, redness, burning, or bleeding at the site where the needle is placed to draw the blood. May cause participant to feel dizzy or faint. There is a slight chance of infection.	All blood draws will be completed by qualified and trained medical personnel. Sterile technique will be used. Blood sample collections will be conducted at facilities prepared for adverse reactions related to the collection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CT/MRI Scans and Bone Scans	CT scans expose participants to a small dose of radiation. Contrast dye used for CT scans may cause pain or burning upon injection, may worsen kidney function in participants with kidney disease, and may cause allergic reactions that could be severe and life-threatening. Radioactive material for bone scan may cause pain or burning upon injection.	The radiation exposure is similar to what participant would have under standard-of-care and should not create a significant risk to health. Participants must meet renal inclusion criteria. CT scans will be conducted at facilities prepared for adverse reactions to the contrast dye. A bone scan exposes participants to a small dose of radiation that should not create a significant risk to health.

2.3.2. Benefit Assessment

Preliminary data from the ongoing FIH ARV-471-mBC-101 study (data cutoff date 06 June 2023) demonstrated that vepdegestrant administered orally daily is safe and well tolerated, showing antitumor activity in participants with A/MBC pretreated with CDK4/6 inhibitors plus ET. In this study vepdegestrant has shown robust ER degradation (up to 89%) observed across doses up to 500 mg daily, regardless of ESR1 mutation status. Preliminary evidence of clinical activity of vepdegestrant has been reported, with 7 confirmed PRs out of 61 response-evaluable participants, ORR was 11.5% (95% CI: 4.7%, 22.2%), and a CBR of 36.1% (95% CI: 25.9%, 47.4%) in 30 of 83 evaluable participants (monotherapy Part A dose escalation; see [Section 2.2.5.1](#)). In addition, preliminary safety data of vepdegestrant in combination with palbociclib suggest that vepdegestrant has the potential to offer an alternative endocrine therapy in combination with CDK4/6 inhibitors (see [Section 2.2.5](#)).

PF-07220060 has been shown to effectively suppress tumor growth with cell lines derived from the differing tumor types in non-clinical studies. PF-07220060 selectively binds to CDK4 while sparing CDK6 binding which may allow continuous higher dosing to exert a higher anti-tumor activity without inducing significant neutropenia. In participants who are refractory or intolerant of the existing standard therapies, PF-07220060 inhibition may provide an important new therapeutic strategy for those tumor types, including advanced or MBC, in which proliferation is dependent on the CDK4-Rb-axis. PF-07220060 has demonstrated early signs of anti-tumor activity in combination with ET in humans with HR+, HER2-negative MBC who progressed on prior CDK4/6i + ET (Study C4391001, Part 1B and Part 1C combined). At the data cutoff date 01 November 2022, the 1B and 1C cohorts at **CCI** mg BID and 400 mg BID + letrozole or fulvestrant (21 evaluable participants) showed an ORR of 28.6% (95% CI: 11.3, 52.2), with 1 CR and 5 PRs, and a CBR of 52.4% (95% CI: 29.8, 74.3).

2.3.3. Overall Benefit/Risk Conclusion

Based on the different mechanism of action, and considering the low risk of overlapping toxicities and the measures taken to minimize risk to study participants, the potential risks identified in association with vepdegestrant in combination with PF-07220060 are justified by the anticipated benefits that may be afforded to participants with ER+/HER2- A/MBC who have progressed after prior CDK4/6 inhibitor based therapy.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Phase 1b

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To assess safety and tolerability of vepdegestrant in combination with PF-07220060 in participants with ER+/HER2- A/MBC to select up to 2 RDEs for the combination.	DLTs during DLT observation period (Cycle 1).	DLT rate estimated based on data from DLT-evaluable participants during the DLT observation period (Cycle 1).
Secondary:	Secondary:	Secondary:
To evaluate the overall safety profile.	- AEs as characterized by type, frequency, intensity (as graded by NCI CTCAE version 5.0), seriousness, and relationship to vepdegestrant in combination with PF-07220060. - Incidence of laboratory abnormalities. - Incidence of ECG abnormalities	Not applicable.
To evaluate antitumor activity of vepdegestrant in combination with PF-07220060.	- Confirmed OR (CR or PR) by investigator assessment. - DoR by investigator assessment. - CBR (confirmed CR or PR at any time, or SD $\geq$ 24 weeks) by investigator assessment. - PFS by investigator assessment.	Not applicable.
To evaluate the plasma exposure of vepdegestrant, ARV-473, and PF-07220060 when vepdegestrant and PF-07220060 are given in combination.	- Plasma concentrations of vepdegestrant, ARV-473, and PF-07220060. - Steady-state C_{max}, T_{max}, and AUC_{last} of vepdegestrant, ARV-473, and PF-07220060. - If data permit CL/F, V_z/F, and $t_{1/2}$ of vepdegestrant, ARV-473, and PF-07220060.	Not applicable.
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To evaluate tumor biology and explore the treatment effect of vepdegestrant and PF-07220060 are given in combination.	Measurements of biomarkers (DNA, RNA, protein, or defined cell types) resulting from analyses of peripheral blood and/or tumor tissue biospecimen.	Not applicable.

Objectives	Endpoints	Estimands
To evaluate relationships between mutational status and response in molecularly-defined participant population.	Associations of tumor gene/genomic alterations with participant treatment responses and disease biology	No applicable
To explore the impact of pharmacogenomics on PF-07220060 plasma exposure.	Allelic variants of UGT2B7.	Not applicable.

3.2. Phase 2

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To assess the clinical antitumor activity of vepdegestrant in combination with PF-07220060.	Confirmed OR (CR or PR) determined by investigator assessment.	The treatment effect of vepdegestrant in combination with PF-07220060 assessed by the OR rate based on Investigator assessment per RECIST v1.1 in the analysis population. Participants who do not have a post-baseline disease assessment due to early PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience documented PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as non-responders.
Secondary:	Secondary:	Secondary:
To determine additional antitumor activity outcomes of vepdegestrant in combination with PF-07220060.	- DoR by investigator assessment. - CBR (confirmed CR or PR at any time or SD $\geq$24 weeks) by investigator assessment. - PFS by investigator assessment. - OS.	Not applicable.
To further characterize the overall safety profile and tolerability of vepdegestrant in combination with PF-07220060.	- AEs as characterized by type, frequency, intensity (as graded by NCI CTCAE version 5.0), seriousness, and relationship to vepdegestrant in combination with PF-07220060. - Incidence of laboratory abnormalities.	Not applicable.

Objectives	Endpoints	Estimands
	Incidence of ECG abnormalities.	
To evaluate the plasma exposure of vepdegestrant, ARV-473 and PF-07220060 when vepdegestrant and PF-07220060 are given in combination.	Plasma concentrations of vepdegestrant, ARV-473, and PF-07220060.	Not applicable.
To assess changes from baseline levels in plasma ctDNA with treatment.	ctDNA plasma quantitative changes from pre-treatment to evaluate potential predictability of their associations with clinical outcomes.	Not applicable.
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To explore the impact of PF-07220060 in combination with vepdegestrant on patient-reported symptoms and health-related quality of life.	- General cancer-related symptoms as measured by the EORTC QLQ-C30. - General health status as measured by the EQ-5D-5L.	Not applicable.
To understand tumor biology of breast cancer and to identify potential sensitivity and/or resistance mechanisms.	Identification of potential biomarkers which may be indicative of treatment sensitivity and/or resistance (eg, ESR1).	Not applicable.
To evaluate relationships between mutational status and response in molecularly-defined participant population.	Associations of tumor gene/genomic alterations with participant treatment responses and disease biology.	Not applicable.
To explore the impact of pharmacogenomics on PF-07220060 plasma exposure.	Allelic variants of UGT2B7.	Not applicable.

4. STUDY DESIGN

4.1. Overall Design

C4891026 is a prospective, open-label, multicenter, Phase 1b/2 study to evaluate the safety, antitumor activity, and PK of vepdegestrant in combination with PF-07220060 in the treatment of participants with ER+/HER2- A/MBC. The study schema is presented in [Section 1.2](#).

The combination will be assessed in 2 parts in C4891026:

- Phase 1b:** dose escalation/de-escalation phase to evaluate the safety and tolerability of vepdegestrant in combination with PF-07220060 and select up to two

recommended doses for dose expansion for the combination (combination RDEs) via the mTPI-2 dose-finding design.

- **Phase 2:** if at least 2 dose levels from Phase 1b (eg, two combination RDEs) are considered tolerable, a randomized dose optimization Phase 2 will be conducted to further evaluate the safety, tolerability, PK and antitumor activity of vepdegestrant in combination with PF-07220060 to determine the RP2D of the combination. If only one dose level from Phase 1b is considered tolerable, a single arm Phase 2 dose expansion will be conducted.

Phase 1b: In Phase 1b the starting dose level (DL1) of vepdegestrant will be 200 mg QD and the starting dose level of PF-07220060 will be 100 mg BID. The decision to escalate the starting dose level of PF-07220060 will be using mTPI-2 decision criteria based on the number of DLT-evaluable participants and the number of DLTs in those participants during the DLT observation period ([Section 10.10](#)). DL2 will be the combination of vepdegestrant 200 mg QD and PF-07220060 300 mg BID. Based on the mTPI-2 decision criteria and depending on the occurrence of DLTs and need for dose reduction, two additional dose levels may be investigated: vepdegestrant **CCI** mg QD in combination with PF-07220060 **CCI** mg BID and/or vepdegestrant **CCI** mg QD in combination with PF-07220060 **CCI** mg BID.

A minimum of 3 DLT-evaluable participants will be required in each cohort at a given dose level before a decision is made to de-escalate, escalate, or remain at the current dose level. Additional participants will be enrolled in a specific cohort to replace participants who are not considered DLT-evaluable. Once the first dose level is cleared and the slots for the first 3 participants at the second dose level are filled, backfill will commence at the lower dose level to enable better characterization of PK, safety, and efficacy. These participants will be considered in the overall assessment of PK, safety, efficacy, and selection of RDE.

Intraparticipant dose escalation is allowed provided all of the following parameters have been met: (a) the participant did not experience a DLT; (b) the participant did not require any dose reduction; (c) the higher dose level has been cleared for DLT. Consultation with the Sponsor must occur prior to any intraparticipant dose escalation occurring.

Phase 2: In the Phase 2 portion of the study up to two RDEs will be further explored.

The RP2D of vepdegestrant and PF-07220060, identified as the dose that can be used in further large-scale testing, will be determined based on an overall assessment of safety, tolerability, PK and early signals of efficacy. The RP2D may be the same as the MTD or RDE, or may be lower. The RP2D will be determined in this study after the Phase 2 expansion cohort(s) have provided sufficient data on which to make such a determination.

Dose escalation/de-escalation decisions, RDE and RP2D of the combination will be determined by the Dose Level Review Committee, composed of sponsor representatives and the study investigators.(see [Section 4.2.3](#)).

A Steering Committee has been established at the vepdegestrant program level, and it will be involved in scientific discussions involving C4891026 but not in the detailed dose discussions or decisions for this study (see [Section 10.1.5.2](#)).

4.2. Scientific Rationale for Study Design

In the ongoing FIH ARV-471-mBC-101 study, vepdegestrant is being assessed as a monotherapy and in combination with palbociclib in participants with ER+/HER2- A/MBC who had previously received multiple prior therapies. Vepdegestrant daily orally administered as single agent has been demonstrated to be safe and well tolerated up to a total daily dose of 700 mg with preliminary evidence of efficacy in participants pretreated with CDK4/6 inhibitors plus endocrine therapy. Vepdegestrant as a monotherapy has shown clinical activity in heavily pre-treated participants, as well as strong ER degradation in the nonclinical and clinical settings. Vepdegestrant is currently being studied in a Phase 3 study in ER+/HER2- advanced breast cancer in comparison to an approved SERD, fulvestrant. The hypothesis is that vepdegestrant is a more complete ER degrader and holds promise as an endocrine therapy.

PF-07220060 is a small molecule potent inhibitor of CDK4 which differs from currently approved CDK4/6 inhibitors (eg, palbociclib) in that it displays greater CDK4-over-CDK6 selectivity. In humans, this greater CDK4 selectivity is hypothesized to lessen the incidence of neutropenia and allow PF-07220060 to attain higher tolerated plasma concentrations and better target coverage, potentially allowing greater inhibition of the CDK4 in tumors.

In dog studies, palbociclib induced Grade 2-equivalent neutropenia at 100 nM in plasma whereas PF-07220060 induced the same level of neutropenia only at 1500 nM. Moreover, in an in vivo study in a ZR-75-1 HR-positive, HER2-negative BC xenograft model, palbociclib at 10 mg/kg (70 nM) induced 45% TGI while PF-07220060 at 5 mg/kg (70 nM), 15 mg/kg and 60 mg/kg (approximately 700 nM) demonstrated TGI at 50%, 80% and 108%, respectively, suggesting PF-07220060 has a wider safety margin for neutropenia at the expected efficacious dose. Taken together, these features of PF-07220060 may allow participants to receive higher doses that block the CDK4/6-Rb-axis continuously while maintaining neutrophil counts due to greater sparing of CDK6 inhibition.

Thus, it is postulated as an overarching hypothesis that compounds that spare CDK6 activity while maximally and continuously inhibiting CDK4 (CDK4 selective inhibitor thereafter) may provide participants with clinical activity with tumor regressions as well as increased response durability in MBC and in other tumor types relying on CDK4/6-Rb axis while maintaining a tolerable safety profile.

At the most recent data cut off (01 November 2022), PF-07220060 demonstrated early signs of anti-tumor activity in combination with ET (letrozole or fulvestrant) in participants with HR+/HER2- mBC who progressed on prior CDK4/6i+ET Study C4391001, Part 1B and Part 1C combined). At the data cutoff date 01 November 2022, the 1B and 1C cohorts at **CCI** mg BID and 400 mg BID + letrozole or fulvestrant (21 evaluable participants) showed an ORR of 28.6% (95% CI: 11.3, 52.2), with 1 CR and 5 PRs, and a CBR of 52.4% (95% CI: 29.8, 74.3) (see [Section 2.2.5.2](#)).

The hypothesis is that the signs of anti-tumor activity can be replicated with PF-07220060 in combination with the novel ER targeting agent vepdegestrant.

Rationale for Protocol Amendment 3

The main purpose of the amendment is to introduce a reduced SoA with clinical assessments per standard of care or clinical judgment of the treating physician. Reduced data recording will maintain safety and tumor assessment (performed as per standard of care). In addition, this amendment is to update the end of study definition and the section regarding continued access to study intervention after the end of the study.

4.2.1. Participant Input Into Design

Patient Insight surveys have been conducted in several countries via interviews through a third party. The team gathered qualitative insights to develop a deeper understanding of the breast cancer patient journey, uncover their views on clinical trials and options on certain aspects of the protocol assessments including home health visits and telemedicine. No significant findings preventing study participation have been identified.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with different characteristics to ensure the study population is representative of the patient population that will use the study intervention in clinical practice.

The diversity strategy will include sites with the potential to support the recruitment of diverse and under-represented populations in the US. The strategy to ensure diversity includes recognition that the presentation of A/MBC varies by gender, age, race, and geographic location; inclusion of diverse principal investigators; site-level training on clinical study diversity; creation of diverse recruitment materials and advertising; and accelerating an education campaign to community oncologists, patient advocacy groups, and breast cancer social media sites to increase awareness about this clinical study.

4.2.3. Dose Level Review Meeting

Dose escalation/de-escalation decisions and RDE will be determined by the Dose Level Review Committee, composed of sponsor representatives and the investigators. During the DLRM, the Committee will consider all relevant clinical data, including safety, PK, and antitumor activity if available in making decisions such as whether to dose de-escalate, dose escalate, expand cohorts, temporarily halt enrollment, and/or declare MTD. An ad hoc DLRM will be held, and enrollment may be temporarily halted, in case of any death or ≥ 2 Grade 4 events not definitely related to underlying disease, progression of disease or intercurrent illness.

4.2.4. Choice of Contraception/Barrier Requirements

Vepdegestrant is known [REDACTED] in the [REDACTED] organs of [REDACTED] which may be regarded as [REDACTED] [REDACTED] and which are considered related to the pharmacologic activity of [REDACTED]

vepdegestrant. CCI

However, based on mechanism of action, vepdegestrant may cause fetal harm when administered to the pregnant woman. Therefore, the use of a highly effective method of contraception is required for IOCBP and males (see [Appendix 4](#)).

Studies to evaluate the CCI of PF-07220060 have not been conducted. Therefore, the use of a highly effective method of contraception is required for IOCBP and males (see [Appendix 4](#)).

4.3. Justification for Dose

In the FIH ARV-471-mBC-101 study, vepdegestrant was safe and well-tolerated across total daily doses of 30 mg to 700 mg (N=78), without any DLTs observed as of 06 June 2022. Dose dependent increases of AUC₀₋₂₄ and C_{max} on C1D1 and C1D15 were observed from 30 mg to 500 mg total daily doses for vepdegestrant, with no further increase in exposure seen at 700 mg. CCI

Robust ER degradation (n=14, median decrease of 67% [range: CCI%, 89%]) was observed at all doses up to 500 mg QD in paired biopsy samples from participants with A/MBC treated in the FIH ARV-471-mBC-101 study.

Evidence of preliminary efficacy data in participants with ER+/HER2- A/MBC have been reported, in the monotherapy Part A dose escalation cohort of Study ARV-471 mBC-101. As of 06 June 2023, in Part A, monotherapy dose escalation, the CBR was 36.1% (95% CI: 25.9%, 47.4%) in 30 of 83 evaluable participants. ORR was 11.5% (95% CI: 4.7%, 22.2%), with 7 of 61 response-evaluable participants having confirmed PR. Clinical benefit (by CBR) was observed in CDK4/6 inhibitor-pretreated participants with ER+/HER2- BC in all Part A dose cohorts. So far, CCI for safety (ie, TEAEs of Grade ≥3, TRAEs of any Grade, or selected AEs of any Grade) and efficacy (CBR).

Vepdegestrant 200 mg QD is currently being tested as the RP3D in the monotherapy Phase 3 C4891001 study, as well as in combination with palbociclib in the study lead-in for the Phase 3 study C4891002, with abemaciclib in the Phase 1b/2 C4891006 study, and with everolimus in the Phase 1b ARV-471-mBC-102.

In Study C4391001, PF-07220060 was well tolerated as monotherapy (Part 1A) and in combination (Parts 1B and 1C) with ET at doses up to CCI mg BID. Confirmed PR/CR (6/21, ORR= 28.6% [95% CI: 11.3, 52.2]) were observed in participants with HR-positive, HER2-negative MBC who received CCI mg or CCI mg BID in combination with letrozole or fulvestrant (see [Section 2.2.5.2](#)). Preliminary PK showed that PF-07220060 exposure increased with increasing dose from CCI mg BID. CCI

CCI The Cycle 1 Day 15 mean exposure at CCI mg BID appears to be slightly higher; however, the sample size is limited to have a definite comparison. No pharmacokinetic drug-drug interaction was observed between PF-07220060 and letrozole or fulvestrant. Exposure of PF-07220060 at CCI mg and CCI mg

BID were comparable across monotherapy, in combination with letrozole, and in combination with fulvestrant. Steady state C_{trough} at doses greater than **CC1** mg BID exceeded the predicted efficacious concentration (ie, 70-92 nM [136-179 ng/mL]) based on preclinical tumor model (ZR-75). However, higher concentrations may be required to exceed the predicted efficacious concentrations based on other tumor models.

The good tolerability observed with each compound and the low risk of clinically significant overlapping toxicities support the investigation of vepdegestrant in combination with PF-07220060 at the tolerated and efficacious starting dose of, respectively, 200 mg QD (vepdegestrant) and 100 mg BID (PF-07220060).

4.3.1. Dose Limiting Toxicity Definition

A participant is classified as DLT-evaluable if they either 1) receive at least **CC1**% of the planned doses of each study intervention and have received all scheduled significant safety assessments during the DLT observation period or 2) have experienced a DLT. The percentage of drug received is calculated as the percentage of the actual total amount of drugs administered during the DLT observation period in relation to the planned total amount of drugs to be administered for the DLT observation period. If a participant fails to meet these criteria, they may be replaced. The sole exception to criterion (1) is if the participant has missed a minority of safety assessments due to emergency situations (eg, site accessibility issues, inability to go to an external laboratory). In such cases, the sponsor and investigators will have regular teleconferences to evaluate the participant evaluability for DLT, depending on the abundance of the available data.

For dose-finding, the DLT observation period will be the first cycle of treatment with the combination regimen in each participant. Participants who withdraw for any reason after Cycle 1 will not be replaced.

For dose-finding, any of the AEs listed in Section 4.3.1.2 through Section 4.3.1.4 occurring in the first cycle of treatment are considered DLTs unless incontrovertibly attributable to underlying disease or an extraneous cause in the opinion of the investigator. Intensity of AEs will be graded according to NCI CTCAE version 5.0. For those events involving a worsening of a baseline abnormality, a DLT must represent a clinically significant (in the opinion of the investigator after discussion with the sponsor) shift from baseline.

4.3.1.1. Criteria for Dose Finding

The provisional dose levels to be evaluated are listed in Table 2. Alternate doses may be evaluated based on clinical findings from this study as well as other studies. See Section 10.10 for more details on the mTPI-2 design and decision rules.

Table 2. Provisional Dose Levels

Dose level	Vepdegestrant	PF-07220060
Dose Level 1	200 mg QD	100 mg BID
Dose Level 2	200 mg QD	300 mg BID

When a higher dose cohort has enrolled the planned number of participants and the DLT safety monitoring period is still ongoing, new eligible participants may be enrolled into the lower dose cohorts. The dose-finding at higher dose(s) will proceed per mTPI-2 decision-rules and will not be guided by the additional participants who have been enrolled at lower doses.

4.3.1.2. Hematological DLTs

- Neutropenic fever
- Grade ≥ 3 thrombocytopenia associated with Grade ≥ 2 (clinically significant) bleeding
- Grade 4 neutropenia or thrombocytopenia lasting more than 7 days

4.3.1.3. Non-Hematological DLTs

- Non-hematological DLTs are Grade ≥ 3 toxicities that are considered clinically significant, except those that have not been maximally treated.

CCI

- For participants with Grade 2 AST, ALT or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, AST, ALT and alkaline phosphatase level $> 8 \times$ baseline or AST or ALT $> 5 \times$ baseline for ≥ 14 days will be considered as a DLT.
- Hy's Law (concomitant ALT or AST elevation of $\geq 3 \times$ ULN and total bilirubin elevation of $\geq 2 \times$ ULN without a clear alternative etiology) is considered a DLT.

CCI

- Grade ≥ 3 amylase or lipase elevation in the absence of associated symptoms or clinical or radiographic evidence of pancreatitis is NOT considered a DLT.
- QTcF prolongation: any Grade ≥ 3 QT prolongation without a clear alternative etiology is considered a DLT.

CCI

- Any death not clearly due to the underlying disease or extraneous causes.

4.3.1.4. Other DLTs

Clinically important, persistent toxicities that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor.

4.3.2. Late Toxicity Definition and Management

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

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

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

4.3.3. Maximum Tolerated Dose Definition

MTD is defined as the dose that meets the following criteria:

- Yields approximately CCI% probability of DLT and considers equivalent doses that yield a probability of DLT in the interval (Equivalence Interval) of CCI% to CCI%. The CCI% target and the Equivalence Interval are chosen based on safety considerations.
- ≥6 participants have been treated at that dose.

As described in [Section 4.2.3](#), the safety of each cohort will be assessed by a DLRM to make decisions, including the declaration of MTD.

4.3.4. Recommended Dose for Expansion

The MTD is identified based on toxicities observed during the DLT observation period (Cycle 1) and defines the limit of acceptable dose escalation in a small sample size. The combination RDE is the dose(s) chosen for further investigations in the Expansion Phase (Phase 2), based on the Phase 1b results. Safety, PK and efficacy (as data permit) data will be considered in identifying the RDEs.

4.3.5. Recommended Phase 2 Dose for Combination Therapy Definition

The RP2D identifies a dose that can be used in further large-scale testing and its determination will be based on an overall assessment of feasibility, tolerability and efficacy, based on a larger patient exposure (both in number and duration) to the combination of vepdegestrant with PF-07220060, and may be the same as the MTD or RDE, or may be lower. The RP2D will be determined in this study after the expansion cohort(s) have provided sufficient data on which to make such a determination.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if they have completed all periods of the study, or if criteria for study discontinuation have been met or at sponsor discretion if the data support ending the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. 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 this study only if all of the following criteria apply:

Age and Sex:

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.
 - Refer to [Section 10.4](#) for reproductive criteria for male ([Section 10.4.1](#)) and female ([Section 10.4.2](#)) participants.

Disease Characteristics:

2. Histological or cytological diagnosis of breast cancer. At time of enrollment this must not be amenable to surgical resection with curative intent ($\geq 1\%$ ER+ stained

cells as per local practice ([Allison et al, 2020](#)) on the most recent tumor biopsy HER2- tumor by IHC or in-situ hybridization per ASCO/CAP) ([Wolff et al, 2018](#)).

- Participants who have bilateral breast cancers that are both ER+/HER2- are eligible.
- Tumor block collected at the time of diagnosis with local recurrent or metastatic disease or archival tumor tissue is required for inclusion (Phase 1b and Phase 2). Refer to [Section 8.7.1.1](#) and [SoA](#).

3. Prior anticancer therapies:

Phase 1b:

- Participants should have received at least 1 line of SOC for A/MBC.
- Prior fulvestrant allowed.
- ≤1 prior chemotherapy line (no antibody-drug conjugates permitted) for A/MBC setting allowed.

Phase 2:

- At least one and maximum 2 lines of ET in A/MBC setting and most recent ET-based regimen for >6 months.
- 1, and only 1, prior CDK4/6 inhibitor-based regimen required (independent of the setting eg, adjuvant or advanced/metastatic).
- Up to 1 prior regimen of cytotoxic chemotherapy (no antibody-drug conjugates permitted) in the A/MBC setting.
- Prior fulvestrant allowed.

4. Lesions at study entry:

Phase 1b:

- Participant with only non-measurable lesion (including skin or bone lesion only) are eligible.

Phase 2:

- Participants must have at least 1 measurable lesion as defined by RECIST v1.1. Participants with bone lesions only can be included if at least one bone lesion has a measurable component as for RECIST v1.1 (see [Section 10.11](#)).

Other Inclusion criteria:

5. Phase 1b: ECOG PS 0 or 1
Phase 2: ECOG PS $\leq$ 2

5.2. Exclusion Criteria

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

Medical Conditions:

1. Participants in visceral crisis at risk of life-threatening complications in the short term, including participants with massive uncontrolled effusions (pleural, pericardial, and/or peritoneal), pulmonary lymphangitis, and liver involvement $>50\%$.
2. Participants with newly diagnosed brain metastases, or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Participants with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and clinically stable (including participants with residual CNS symptoms/deficits) and discontinued anti-seizure medications and corticosteroids for at least 28 days prior to first dose of IMP.
3. Refractory nausea and vomiting, chronic GI disease, GI ulcer, GI bleeding, active inflammatory bowel disease, inability to swallow the formulated product, or previous, significant gastric-bowel resection that would preclude adequate absorption of study interventions.
4. History of any other malignancies within the past three years, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated in situ carcinoma of the cervix. All other malignancies must have been curatively treated with no evidence of disease for >3 years. Participants with inflammatory breast cancer are excluded.
5. Impaired cardiovascular function or clinically significant cardiovascular diseases, as defined as:
 - Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease.

- Symptomatic cardiac valve disease. Participants with mitral valve prolapse that is asymptomatic or not associated with clinically significant sequelae (eg, mitral regurgitation) are eligible.
 - QTcF >470 msec (for women) or CCI [REDACTED] at screening, participants with risk factors for QT prolongation (eg, electrolyte abnormalities) unless mitigated or corrected prior to enrollment, or any of the following in the previous 6 months: congenital long QT syndrome, Torsade de Pointes, clinically important arrhythmias, left anterior hemiblock (bifascicular block), ongoing cardiac dysrhythmias of Grade ≥ 2 , atrial fibrillation of any grade.
6. The following prior procedures and treatment are not permitted:
- Anticancer systemic therapies:
Phase 1b and Phase 2:
 - Prior therapy with SERDs (fulvestrant is allowed), SERMs (tamoxifen is allowed), SERCAs, CERANs, and PROTACs (approved or experimental), or elacestrant.
 - Major surgery, radiotherapy, prior endocrine therapy, CDK4/6 inhibitors, or other anticancer treatments within ≤ 14 days prior to first dose of IMP (for anticancer therapy containing an antibody-based agents, approved or investigational, 28 days or 5 half-lives, whichever is shorter).
 - Participants who received: prior radiotherapy to $\geq 25\%$ of bone marrow, or prior hematopoietic stem cell, or bone marrow transplantation are not eligible independent of when it was received.
7. Any unresolved toxicities from prior surgeries or therapies Grade >1 at the time of study enrollment except for Grade 2 alopecia, peripheral neuropathy, arthralgia, or other toxicities not considered a safety risk for the participant per the investigator's judgment.
8. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study, or any social situations that would limit study compliance.

Prior/Concurrent Clinical Study Experience:

9. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.

Prior/Concomitant Therapy:

10. Concurrent administration of medications, food, or herb supplements that are strong inhibitors/inducers of CYP3A or UGT2B7, moderate inducers of CYP3A (Phase 1b only), and drugs known to predispose to Torsade de Pointes or QT interval prolongation. Prior use of strong inhibitors of CYP3A or UGT2B7 must be stopped 7 days, strong inducers of CYP3A or UGT2B7, and moderate inducers of CYP3A (Phase 1b only) must be stopped 14 days before enrollment in the study. Refer to [Sections 6.9.3](#) and [10.9](#) for the list of examples of prohibited drugs.

Diagnostic Assessments:

11. Renal impairment defined by an eGFR <50 mL/min/1.73 m². In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

* Use the 2021 CKD-EPI eGFR (serum creatinine only) equation [see [Section 10.7](#)] to calculate eGFR (in units of mL/min/1.73 m²). By multiplication of $([\text{eGFR}] \times [\text{nomogram-based participant body surface area (m}^2)]) = \text{estimated creatinine clearance (eCrCl) in mL/min.}$

12. Hepatic dysfunction defined as:

- Total bilirubin $>1.5 \times \text{ULN}$ unless the participant has documented Gilbert's syndrome (in this case total bilirubin $\geq 3 \times \text{ULN}$);
- AST $>3 \times \text{ULN}$ ($>5 \times \text{ULN}$ if attributed to liver metastases)
- ALT $>3 \times \text{ULN}$ ($>5 \times \text{ULN}$ if attributed to liver metastases)
- Alkaline phosphatase $>2.5 \times \text{ULN}$ or $>5 \times \text{ULN}$ if liver or bone metastases present.
- aPTT $>1.25 \times \text{ULN}$ and INR >1.25 unless the participant is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.

13. Hematologic abnormalities defined as:

- ANC $<1,500/\text{mm}^3$ or $1.5 \times 10^9/\text{L}$;
- Platelets $<100,000/\text{mm}^3$ or $100 \times 10^9/\text{L}$;
- Hemoglobin <9 g/dL. Receipt of a blood transfusion (blood or blood products) within 14 days before the first dose is allowed.

14. Known active infection including hepatitis B virus, hepatitis C virus, and HIV or AIDS-related illness (screening for chronic conditions is not required). A participant who has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2, is not eligible for the study, except in case SARS-CoV-2 infection occurring during the screening period is resolved at least 14 days prior to enrollment.

Note: active viral hepatitis infection is defined as untreated/uncontrolled hepatitis (eg, hepatitis B patients who are treated and whose LFTs meet eligibility are not considered to have active hepatitis B).

For HIV infection, the study participant is eligible if the disease is controlled with treatment, and the therapy does not exclude the participant as per Exclusion criterion #10.

Other Exclusion Criteria:

15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Specific for France: please refer to Section 10.12.2.1.1 Appendix 12 for additional exclusion criteria.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

Participants should take PF-07220060 and vepdegestrant with food (see [Section 6.1.1.1](#) and [Section 6.1.1.2](#)).

Participants should refrain from consuming grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos) during treatment with PF-07220060 as listed in [Section 6.1.1.2](#).

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once (for a total of 2 screenings). Rescreened participants must be assigned a unique participant number that is different from the participant number used for the initial screening.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to vepdegestrant and PF-07220060.

6.1. Study Intervention(s) Administered

Study Interventions		
Intervention Name	Vepdegestrant	PF-07220060
Type	Drug	Drug
Use	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	100 mg	100 mg
Dosage Level(s)	200 mg QD, 100 mg QD	100 mg BID, 300 mg BID Refer to Section 6.1.1.1 .
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.

Study Interventions		
Intervention Name	Vepdegestrant	PF-07220060
Packaging and Labeling	Study intervention will be provided in a high-density polyethylene bottle with child-resistant cap. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in a high-density polyethylene bottle with child-resistant cap. Each bottle will be labeled as required per country requirement.
SRSD	IB	IB
Current/Formal Name(s) or Alias(es)	ARV-471, PF-07850327, vepdegestrant	PF-07220060

6.1.1. Administration

A cycle is defined as 28 days, regardless of missed doses or dose delays.

During the combination treatment period, participants will receive vepdegestrant in combination with PF-07220060 in the 28-day cycle. After implementation of Amendment 3, a sufficient supply of study intervention will be provided to the participants to cover an interval of every 2 cycles.

PF-07220060 and vepdegestrant will be self-administered outside of the study site, except on study visit days. On study visit days, participants must be instructed to bring their study intervention to the investigational site, and to withhold their daily doses until assessment as per [SoA](#) (Section 1.3) have been completed. On these days, administration of study interventions will be performed at the site by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for approximately 30 minutes or per standard of care by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

PF-07220060 and vepdegestrant will be administered as tablets. Participants will be instructed to swallow oral study interventions whole and not manipulate or chew the study intervention prior to swallowing. Participants should be encouraged to take their doses at approximately the same time each day, and to not take more than the prescribed dose at any time. Participants will be instructed to record their daily administration in the participant diary provided by the site.

If a participant misses a day of treatment, he/she must be instructed not to double-up or “make up the dose”, but to resume dosing on the next day of the dosing cycle as prescribed.

If a participant vomits any time after taking a dose, he/she must be instructed not to “make it up”, but to resume dosing on the next day of the dosing cycle as prescribed.

If a participant inadvertently takes 1 extra dose (vepdegestrant and/or PF-07220060) during a single dosing day, the participant must be instructed to inform the investigator. The investigator should contact the study medical monitor and closely monitor the participant for any AEs. Any decision regarding next dose modifications should be made by the investigator in consultation with study medical monitor as needed.

Vepdegestrant and PF-07220060 must be taken with food.

The administration of vepdegestrant and the first of two daily doses of PF-07220060 should preferably happen in the morning at approximately the same time. The second of the two daily doses of PF-07220060 must be administered in an approximately 12-hours interval.

6.1.1.1. PF-07220060 Administration

PF-07220060 will be administered as 100 mg tablets (CCI [REDACTED]). PF-07220060 will be administered with food orally BID on a continuous basis without adjustment for body size at every cycle.

For the BID dosing regimen of PF-07220060, The two daily doses should be administered approximately 12 hours apart at approximately the same times of each day. If a participant misses a morning or evening dose by more than 6 hours, they will be instructed not to “make it up” but to resume subsequent doses at the next scheduled dose as prescribed.

Recommended dose modifications for toxicity related to study intervention are presented in [Section 6.6.1.3](#).

6.1.1.2. Vepdegestrant Administration

Vepdegestrant will be administered as 100 mg tablets (dose level CCI mg or 200 mg QD) to participants. Vepdegestrant will be administered orally, continuously on 28-day cycles according to the [SoA](#). Recommended dose modifications for toxicity related to study intervention are presented in [Section 6.6.1.3](#).

Vepdegestrant must be administered with food.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must

indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
6. Study interventions should be stored in their original containers.
7. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study interventions that are taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**
8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

Site personnel must ensure that participants clearly understand the directions for self-medication of PF-07220060 and vepdegestrant. Participants will be given a dosing diary and should be instructed to record their daily administration in the participant dosing diary.

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

Refer to the IPM manual for detailed administration instructions for all the study interventions administered in this study.

A qualified staff member will dispense the study interventions using unique container numbers via an IRT system in the bottles provided, in quantities appropriate according to the [SoA](#). A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

6.3. Assignment to Study Intervention

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

Study intervention will be dispensed at the study visits summarized in the [SoA](#).

Returned study intervention must not be redispensed to the participants.

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable eCRF, if required.

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. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants and their caregivers will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

6.5. Study Intervention Compliance

Participants will be required to return all bottles of vepdegestrant and PF-07220060, as well as the completed participant diary at every visit for drug accountability. After implementation of Amendment 3, drug accountability may be performed on Day 1 of every other cycle, prior to the dispensing of drug supply for the next two cycles (see 1.3 SoA, Section 1.3 -after implementation of Amendment 3 for details). The number of remaining tablets will be documented and recorded in the medical chart. Study interventions administration start and stop dates, including dates for study interventions interruptions and/or dose reductions, will also be recorded in the eCRF.

In absence of toxicity requiring dose modification/interruption (or dose delay), each study participant is considered underdosed if less than ccc% of the prescribed dose for a given cycle has been administered. Dose adjustments must follow instructions provided in the dose adjustment guidelines section.

6.6. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study intervention may need to be adjusted based on the toxicity observed. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Depending on the nature of the toxicity observed, dosing modifications may be required for just one or both study interventions in the combination. In the event treatment interruption is deemed necessary for just one of the study interventions, treatment with the other study intervention will continue as planned.

Dose modifications may occur in 1 of 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

6.6.1. Dose Reductions

Following dosing interruption due to toxicity, the vepdegestrant and/or PF-07220060 dose may need to be reduced when treatment is resumed.

Investigators should always manage their participants according to their medical judgment based on the clinical circumstances.

All dose modifications/adjustments must be clearly documented in the participant's source notes and IP administration CRF.

6.6.1.1. Vepdegestrant Dose Reductions

Dose reduction of vepdegestrant to 100 mg QD (see Table 3) will be allowed depending on the type and severity of toxicity encountered. Vepdegestrant dose reduction below **CCI** mg QD is not allowed and the participant will be permanently discontinued from vepdegestrant if deemed necessary due to toxicity.

Participants permanently discontinuing vepdegestrant treatment may continue receiving PF-07220060 monotherapy at investigator's discretion. If PF-07220060 is also permanently discontinued, participants enter the Post-treatment Follow-up Phase.

Table 3. Vepdegestrant Available Doses

Dose Level	Vepdegestrant Available Doses	Administration Dose
Starting	200 mg/day	Two 100 mg tablets QD
-1	100 mg/day*	One 100 mg tablet QD

* Vepdegestrant dose reduction below 100 mg/day is not allowed.

Once the dose of vepdegestrant has been reduced for a given participant, all subsequent cycles will be administered at that dose level.

If the participant has demonstrated significant benefit, dose re-escalation of vepdegestrant may be considered after consultation with the sponsor medical monitor, if the AE resolves rapidly, and re-escalation is not expected to pose a significant risk to the participant.

6.6.1.2. PF-07220060 Dose Reductions

Following dosing interruption due to toxicity, the PF-07220060 dose may remain at the same dose level or be reduced by 1 dose level (Table 4) when treatment is resumed. PF-07220060 dose reduction below **CCI** mg QD is not allowed and the participant will be permanently discontinued from PF-07220060 if deemed necessary due to toxicity.

If PF-07220060 is discontinued, vepdegestrant treatment as monotherapy may continue at investigator's discretion. If vepdegestrant is also permanently discontinued, participants enter the Post treatment Follow up Phase.

Table 4. PF-07220060 Available Doses

CCI

Once a dose has been reduced for a given participant, all subsequent cycles will be administered at that dose level. Intraparticipant dose reescalation is not allowed.

6.6.1.3. Recommended Vepdegestrant and PF-07220060 Dose Modifications

Recommended vepdegestrant and PF-07220060 dose modification for study intervention are outlined in [Table 5](#).

Table 5. Vepdegestrant and PF-07220060 Recommended Dose Modifications for Investigational Product-Related Toxicity

Toxicity ^{a,b}	NCI CTCAE Severity Grade	Vepdegestrant Dose Modifications	PF-07220060 Dose Modifications
Non-Hematological Toxicities	Grade 1	Continue at the same dose.	Continue at the same dose.
	Grade 2	Continue at the same dose.	Continue at the same dose.
	Grade 3	CCI	Persistent/intolerable: Withhold dose until toxicity is Grade ≤ 1 , or has returned to baseline, then resume treatment at the same dose level or the next lower dose level at the discretion of the investigator.
	Grade 4	CCI	Withhold dose until toxicity is Grade ≤ 1 , or has returned to baseline, then resume treatment at the same dose level or the next lower dose level at the discretion of the investigator.
Hematological Toxicities ^e	Grade 1	Continue at the same dose.	Continue at the same dose level.
	Grade 2	Continue at the same dose.	Continue at the same dose level.
	Grade 3	CCI	Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the same dose level.
		Exceptions: Laboratory values that do not have any clinical correlate. CCI	ILD/pneumonitis requires permanent discontinuation of PF-07220060.

Table 5. Vepdegestrant and PF-07220060 Recommended Dose Modifications for Investigational Product-Related Toxicity

Toxicity ^{a,b}	NCI CTCAE Severity Grade	Vepdegestrant Dose Modifications	PF-07220060 Dose Modifications
		CCI	Recurrent Grade 3: Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the next lower dose level.
	Grade 4		Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the next lower dose level.

Table 5. Vepdegestrant and PF-07220060 Recommended Dose Modifications for Investigational Product-Related Toxicity

Toxicity ^{a,b}	NCI CTCAE Severity Grade	Vepdegestrant Dose Modifications	PF-07220060 Dose Modifications
Grade 3 neutropenia^f with fever ≥ 38.5 °C and/or infection	Grade 3	CCI	Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the same dose level.
Grade 4 neutropenia^f with fever ≥ 38.5 °C and/or infection	Grade 4		Recurrent Grade 3: Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the next lower dose level. Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the next lower dose level.

a. Recurrent toxicity is defined as the same event reoccurring within the next 8 weeks as measured from the stop date of the preceding event.

b. Persistent toxicity is defined as toxicity that does not resolve despite supportive measures within 7 days to Grade ≤ 1 or to baseline.

c. Grade 3 fatigue lasting < 7 days, Grade 3 nausea/vomiting/diarrhea lasting < 72 hours in the absence of maximal medical therapy do not require dose reduction.

d. CCI

e. Recommendation applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, eg, opportunistic infections). Participant requiring administration of blood cell growth factors: suspend PF-07220060 dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade ≤ 2 . Resume PF-07220060 at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

f. Neutropenia = Grade 1: ANC below LLN and up to $1500/\text{mm}^3$; Grade 2: ANC up to 1000 to less than $1500/\text{mm}^3$; Grade 3: ANC up to 500 to less than $1000/\text{mm}^3$; Grade 4: ANC less than $500/\text{mm}^3$.

6.6.2. Dosing Interruptions

With respect to study intervention, participants experiencing AEs may have their treatment interrupted as described in [Section 6.6.1](#).

Treatment interruption for drug-related toxicities will be performed as per the investigator's best medical judgment.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in [Section 6.6.1](#).

Doses may be held up to 28 days until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even in the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity will not be replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria reported in [Section 6.6.1](#) (see [Table 5](#)), unless expressly agreed otherwise following discussion between the investigator and the study medical monitor.

In the event of a treatment interruption for reasons other than treatment related toxicity (eg, elective surgery) lasting **CCI** days, treatment resumption will be decided in consultation with the study medical monitor. Retreatment following treatment interruption for treatment-related toxicity may not occur until all of the following parameters have been met:

- $ANC \geq \text{CCI} / \text{mm}^3$.
- Platelets count $\geq \text{CCI} / \text{mm}^3$.
- Grade **CCI** nonhematologic toxicities have returned to Grade **CCI** severity.
- QTcF $< \text{CCI}$ ms and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTcF remains above **CCI** ms, ECG should be monitored more frequently as per the investigator's best medical judgement until QTcF $\leq \text{CCI}$ ms.

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

If these conditions are met within **CCI** days of treatment interruption, study intervention may be resumed. Refer to the [Table 5](#) for recommended dose modification for vepdegestrant and PF-07220060.

If participants require discontinuation of study intervention for more than **CCI** days at any time during the study, then study intervention should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the study medical monitor.

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

Enrollment in C4891026 has been completed as per protocol design and permanently closed upon enrolling 55 participants in Phase 2.

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

The sponsor reserves the right to terminate access to the supplied study intervention treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the drugs is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives. In all cases, the sponsor will follow local regulations. Therefore, if the study intervention is not available as an approved treatment in the local country at the time of study termination, participants still demonstrating clinical benefit as per RECIST v1.1 (defined as complete or partial response or stable disease) may be eligible to receive Sponsor-supplied study intervention through different modalities (eg: expanded access/continued use mechanism/rollover) if the investigator and participant desire to continue treatment and at the discretion of the sponsor and subject to local conditions and regulations.

In case a rollover study is implemented, written notification would be provided to investigational sites, and participants from the current trial could be consented and entered into the rollover study, if eligible.

6.8. Treatment of Overdose

For this study, any dose of vepdegestrant greater than the intended dose in a day will be considered an overdose. Any dose of PF-07220060 greater than the intended dose within a 24-hour time period (± 5 hours) will be considered an overdose.

There is no specific treatment for an overdose.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)). If the overdose involves both study interventions, the monitoring period should be based on the study intervention with the longest half-life.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

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

6.9. Prior and Concomitant Therapy

Participants must be instructed not to take any additional medications (over the counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the participant from the signature of the ICD and up to 28 days following the last dose of study intervention will be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The study medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician. All concomitant treatments, including authorized/approved COVID-19 vaccines, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from the signature of the ICD and up to 28 days following the last dose of study intervention will be recorded on the eCRF. Upon Amendment 3 implementation, concomitant therapy is to be recorded in site source only, and not in the eCRF. SAE forms still require concomitant therapy reporting.

6.9.1. Anticancer Therapy

No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study. This does not apply to the GnRH/LHRH agonists (Section 6.9.2).

6.9.2. GnRH or LHRH Agonist

Treatment with a GnRH or LHRH agonist (eg, goserelin and leuprolide acetate or equivalent agents) should be used according to the prescribing information for all men and women who are pre or peri-menopausal at study entry. Participants must have commenced treatment with a GnRH or LHRH agonist at least on Cycle 1 Day 1 for Phase 1b and for Phase 2, and continue administration as for local product prescribing information irrespectively of cycle duration and up to 28 days after the last dose of study intervention. Treatment continuation during survival follow-up is at the discretion of the investigator. A participant who is receiving an LHRH agonist dosed every 3 months may continue with the same formulation for the duration of the study as described above; however, in all circumstances the

investigator will determine and supply the appropriate GnRH or LHRH agonist locally approved for use in breast cancer considering any potential drug-drug interaction based on the product prescribing information. If required by local regulations, GnRH or LHRH may be provided by the sponsor if available to source in the country.

6.9.3. Prohibited Inhibitors/Inducers

The following treatments are prohibited throughout the duration of the Active Treatment Phase in Phase 1b and Phase 2:

- **Strong CYP3A inhibitors/inducers:** Co-administration with drugs that are strong CYP3A inhibitors and inducers may change the plasma concentrations of vepdegestrant and PF-07220060 in humans. The concurrent use of strong CYP3A inhibitors or inducers are prohibited in this study. Refer to [Section 10.9](#) for examples of drugs that are strong inhibitors/inducers of CYP3A.
- **Strong UGT2B7 inhibitors/inducers:** Co-administration with drugs that are strong UGT2B7 inhibitors and inducers may change the plasma concentrations of PF-07220060 in humans. The concurrent use of strong UGT2B7 inhibitors or inducers are prohibited in the Phase 1b and 2 portions of the study. Refer to [Section 10.9](#) for additional information.
- **Moderate CYP3A inducers are prohibited in the dose escalation Phase 1b portion** of the study. Refer to [Section 10.9](#) for examples of drugs.

6.9.3.1. Other Prohibited Drugs or Procedures

The following treatments are also prohibited throughout the duration of the Active Treatment Phase:

- **CCI** [REDACTED] and the drug is not included as a prohibited medication in [Section 10.9](#). See [Section 6.9.3.2](#) for instruction on use **CCI** [REDACTED] during the study.
- **Hormone replacement therapy**, topical estrogens (including any intravaginal preparations), megestrol acetate, and selective estrogen receptor modulators (eg, raloxifene) are prohibited during the Active Treatment Phase.
- **Drugs known to predispose to Torsade de Pointes or QT interval prolongation:** refer to [Section 10.9](#) for a list of drugs. Exception: sevoflurane, azithromycin, ondansetron, chloroquine may be used **with caution** during the active treatment.

- Live vaccines (where the vaccine is of a ‘live-attenuated’ virus/bacteria rather than a viral/bacterial-vector approach) virus or bacterial vaccines (eg, yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis [BCG], Yersinia pestis [EV] vaccines).
- An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with PF-07220060 in combination with vepdegestrant are unknown.
- Administration of the live flu vaccine is allowed if given at least 28 days prior to start of screening.
- The administration of killed vaccines (eg, cholera, bubonic plague, non-live influenza, non-live covid, polio, hepatitis A, and rabies vaccine) is allowed.

6.9.3.2. Concomitant Treatments to be Used with Caution or Not Recommended

The concurrent use of the following treatments is strongly discouraged throughout the duration of the Active Treatment Phase:

- **P-gp sensitive substrates:** based on in vitro data vepdegestrant may inhibit P-gp substrates. Drugs that are P-gp sensitive substrates should be used with caution as vepdegestrant may increase the drug exposure. Refer to [Section 10.9](#) for examples of drugs that are sensitive substrates of P-gp.
- **CCI** may be used, but should be staggered. Administer vepdegestrant ≥ 2 hours before or 10-12 hours after **CCI**. Administer PF-07220060 at least 10 hours after the **CCI** evening dose and 2 hours before the **CCI** morning dose.
- **CCI**: If needed, administer **CCI** at least 2 hours before or at least 2 hours after vepdegestrant and/or PF-07220060 administration.
- **CCI sensitive substrates** **CCI**: Based on in vitro studies, PF-07220060 has potential for **CCI** of intestinal and hepatic **CCI** which may be clinically significant for **CCI** substrates. No clinical data is currently available to confirm interaction with **CCI** sensitive substrates. **CCI** sensitive substrates should be used with caution.
- **Moderate CYP3A inhibitors** should be avoided if possible (for non-Phase 1b portion of the study), and any use needs to be reviewed and approved by the sponsor.
- **Other known UGT2B7 inhibitors or inducers** should be avoided if possible, and any use needs to be reviewed and approved by the sponsor

The following treatments are NOT recommended throughout the duration of the Active Treatment Phase:

- **Herbal medicines**
- **Transporter Substrates:** Concomitant use of PF-07220060 and a substrate of the CCI transporter may CCI the exposure of CCI but the extract risk is uncertain at this time. Therefore, caution is warranted for the co-administration of PF-07220060 with CCI

Consider, whenever possible, to replace the concomitant treatments to be used with caution or not recommended with other drugs with the same indication for use. If one of the treatments to be used with caution or not recommended is deemed necessary, consultation and agreement with the sponsor is encouraged prior to treatment initiation.

CCI

Due to the potential inhibition of CCI by PF-07220060 based on in vitro data, CCI are prohibited as listed in [Section 10.9](#). CCI is permitted with caution and with additional CCI. Stable dose CCI for at least 2 weeks before the first dose of PF-07220060 is required for participants who have been CCI before enrollment.

CCI

PF-07220060 is a potential CCI and potential CCI therefore, recommendations of avoiding the use of certain statins or limiting the daily dose of certain CCI are provided in [Section 10.9](#).

6.9.4. Supportive Care

Palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion and according to the specific supportive care product prescribing information or the current ASCO guidelines.

Participants should receive appropriate supportive care measures throughout the duration of the Active Treatment Phase as deemed necessary by the treating investigator including, but not limited to, the items outlined below:

- Standard therapies for preexisting medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medication should be recorded.
- Bisphosphonates and RANKL inhibitors for the treatment of osteoporosis or management of existing bone metastases may be continued for participants who have been receiving them at a stable dose for at least 2 weeks prior to enrollment. However, the need to initiate or increase the dose of these therapies during the study

will be considered as indicative of disease progression leading to participant discontinuation from the Active Treatment Phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the participant's source documentation.

- Vaccines: locally approved vaccinations and booster doses are allowed as appropriate. Refer to [Section 6.9.3.1](#) for live vaccines.
- Transfusion: RBC and PLT transfusion may be used as per investigator's discretion.
- Anti-infectives may also be used at the investigator's discretion. Before administration verify any potential drug-drug interaction with the study interventions as per [Section 10.9](#).

6.9.5. Hematopoietic Growth Factors

Hematopoietic growth factors (eg, G-CSF, GM-CSF) may be used as indicated by the current ASCO guidelines ([Smith et al, 2015](#)). During the screening window (ie, 14 days prior to Day 1), Granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. For those countries where the indication and dosage of G-CSF compounds may differ from ASCO guidelines, refer to the local product prescribing information or follow the country's clinical practice ([Smith et al, 2015](#)).

6.9.6. Antidiarrheal, Antiemetic Therapy

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

Antidiarrheal: All participants who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Anti-diarrheal agents should be administered as needed.

Antiemetic Therapy: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

The choice of the drug as well as the duration of treatment is at the investigator's discretion assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy [Section 6.9](#).

6.9.7. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Steroids given as hormonal replacement (prednisone ≤10 mg/day or equivalents) is allowed. Acute emergency administration, topical applications,

inhaled sprays, eye drops, or local injections of corticosteroids as premedication prior to contrast media administration as per local guidelines is allowed.

6.9.8. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included as a prohibited medication in the Concomitant Therapy [Section 6.9](#).

6.9.9. Surgery and Radiotherapy

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

Any concurrent radiotherapy (excluding palliative radiotherapy as per specifications below) are prohibited throughout the duration of the Active Treatment Phase of the study. Participants requiring any of these procedures will be discontinued from the Active Treatment Phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions providing the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

Palliative radiotherapy to specific sites of disease will be permitted if considered medically necessary by the treating physician. All attempts will be made to rule out PD in the event of increased localized pain.

In view of the current lack of data about the interaction of vepdegestrant with radiotherapy, vepdegestrant and PF-07220060 treatment should be interrupted 7 days before initiation of palliative radiotherapy and restarted after recovery of any radiotherapy associated signs and symptoms.

For participants with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Information related to the administration of palliative radiotherapy (date and site of radiotherapy) should be recorded on the appropriate CRFs.

6.9.10. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with vepdegestrant or PF-07220060. Standard medical supportive care should be provided to manage any AEs, and data collected in the eCRF accordingly.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and survival. See the [SoA](#) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

Follow-Up:

At least 28 calendar days (+7 days) after discontinuation of study intervention or prior if a new anticancer therapy is initiated (whichever comes first), participants will return to site to undergo the safety follow-up assessments as reported in the [SoA](#). See [Section 8.4.1](#) for details about AE/SAE reporting requirements. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every

4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

Participants who have already demonstrated objective disease progression as per RECIST v1.1 do not need to have scans repeated at the end of treatment visit or during the post-treatment follow-up. Participants who have been discontinued for reasons other than disease progression as per RECIST v1.1 will continue to repeat the oncological assessments as detailed in the [SoA](#). (No longer required upon Amendment 3 implementation).

For Phase 2 as reported in the [SoA](#), survival status will be collected in the CRF every 3 months (± 7 days) from the last dose of study treatment, including subsequent anticancer therapies (eg, start and stop dates, BOR and date of PD of the subsequent therapy), until death, withdrawal of consent, lost to follow-up, or end of study, whichever occurs first. Telephone contact is acceptable. As permitted by local regulations, study site staff may use alternative sources (ie, public database) to retrieve the date of death. Participants may be contacted for survival information at additional time points. (Survival follow-up is no longer required upon Amendment 3 implementation).

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) may require expedited evaluation to differentiate DIKI from other causes of AKI.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

AKI (including DIKI) is associated with (i) confirmed Screat increase and confirmed decrease in Screat-based eGFR or eCrCl OR (ii) confirmed new-onset or increased proteinuria (or albuminuria).

Assessments of urine protein-to-creatinine ratio, urine volume or urine protein may also be performed as appropriate.

Confirmed postbaseline decrease in kidney function should be assessed individually based on clinical judgment. Cases wherein uncertainty remains, the investigator can review the case with the sponsor, which may consult the Pfizer Kidney Safety Council if such a situation occurs during the study for support, if necessary.

The investigator should consult with the sponsor for any suspected cases of kidney injury.

In the event of new changes in kidney function $\geq 30\%$ increase in serum creatinine from baseline, decrease $\geq 30\%$ in eGFR, there should be further evaluation to rule out acute kidney injury. Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and herbal supplements), family history, sexual history, travel history, blood transfusion, and potential

occupational exposure to chemicals. If there is a reason to expect obstruction of the urinary tract as a cause of the changes in kidney function, evaluation for obstruction should be considered, and additional assessments such as renal ultrasound may also be obtained if appropriate. Other assessments that may be performed include urine protein excretion [UACr, UPCr, urine protein (spot or 24 hour)], urine volume, and urine microscopic examination. A nephrology consult may be requested for further clarification. If decreased kidney function is suspected, participants should return to the clinic as soon as possible to confirm abnormal results and to conduct additional assessments if needed.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of drug-induced kidney injury if no other reason for the kidney function abnormalities is identified.

7.1.2. ECG Changes

Refer to [Section 6.6](#) for details on dose modifications due to ECG changes.

The ECG must be reviewed by qualified personnel at the site as soon as any abnormality is observed, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. In some cases, it may be appropriate to repeat abnormal ECGs (ie, at least 2 times approximately 2 minutes apart) 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 to achieve precise ECG recordings.

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

7.1.3. COVID-19

While SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if they have a positive test result for SARS-CoV-2 infection, are known to have asymptomatic infection, or are suspected of having SARS-CoV-2. When the infection resolves, the participant may be considered for screening. In case SARS-CoV-2 infection occurs during the screening period, the active infections must be resolved at least 14 days prior to enrollment.

If a participant has symptomatic COVID-19 during the Active Treatment Phase, this should be reported as an AE or SAE (as appropriate), and appropriate medical intervention provided considering potential DDIs for any concomitant medication administered for treatment of SARS-CoV-2 infection. Study treatment should be temporarily interrupted/delayed to allow the symptoms to recover to Grade ≤ 1 for a minimum of 72 hours, and the participant should be afebrile for a minimum of 72 hours. The study team should be notified when treatment is restarted.

If the investigator/treating physician is concerned about the safety of the participant, it is recommended that he/she discuss any permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Significant protocol deviation;
- Lost to follow-up;
- Withdrawal by participant;
- Study terminated by sponsor;
- Death.

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

After implementation of Amendment 3, the [SoA](#) will be reduced, as per Section 1.3.

8.1. Administrative and Baseline Procedures

The investigator or qualified designee 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.

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.

Radiographic assessments conducted as part of the participant's standard of care and obtained before signing of the ICD may be utilized for eligibility provided the procedures meet the protocol specified criteria and were performed within the time frame defined in the [SoA](#) (Section 1.3).

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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that they have taken to ensure that required processes are adhered to as soon as possible. The Pfizer 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.

The total blood sampling volume for individual participants in this C4891026 is approximately 12 mL up to 60 mL per study visit. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Baseline Procedures

Medical history will be recorded at screening for each participant. Medical history includes any signs, symptoms, and history not associated to the disease under study before informed consent.

Oncological history will be recorded at screening for each participant and includes details regarding the disease under study, including tumor histology (eg, ER, progesterone, HER2 receptor status as per local assessments), relevant disease characteristics, TNM staging ([Giuliano et al, 2018](#)), and all prior treatments including prior systemic therapies, radiation, and surgical procedures.

8.1.2. Telehealth and Home Health Visits

Under some circumstances (eg, public emergencies), telehealth and/or home health visits may be performed **upon sponsor approval**.

8.1.2.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the [SoA](#), including:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to [Section 8.4](#).
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol (as applicable). Refer to [Appendix 4](#).
- Review GnRH/LHRH compliance as applicable.
- Review the laboratory and tumor assessments results as applicable.

Any telehealth visit may be changed to an in-person visit based on participant preference or investigator discretion.

Participants must be reminded to promptly notify site staff about any change in their health status. Participants may request an unscheduled telehealth or in-person visit with site staff.

8.1.2.2. Home Health Visits

A home health visit may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. Assessments that may be performed during a home health visit are described in the [SoA](#), including:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to [Section 8.4](#).
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol (as applicable). Refer to [Appendix 4](#).
- Review GnRH/LHRH compliance as applicable.
- Review the laboratory and tumor assessments results as applicable.
- Physical examinations and vital sign collection.
- PRO assessments, if appropriate.
- Blood samples collection.

The investigator must review the reports from healthcare professionals conducting home health visits and follow up with the participant as appropriate.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

8.2. Efficacy Assessments

After implementation of Amendment 3, the frequency of efficacy assessments will be performed as per clinical standard of care at the discretion of the investigator. Assessments will be performed according to RECIST v1.1.

8.2.1. Tumor Response Assessments

The [SoA](#) should be fixed according to the calendar, regardless of treatment delays and/or interruptions. Imaging assessments are to be scheduled using the date of first dose of study treatments combination as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique/modality MUST be used throughout the study for a given lesion/participant.

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced chest, abdomen, and pelvis computed tomography or MRI scans; MRI (gadolinium contrast-enhanced) as the preferred technique for assessments of brain lesions (enhanced CT scan is also acceptable). All 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. Contrast enhanced CT scans of the chest are the preferred modality and should not be substituted by chest MRI even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF). Clinical assessment of superficial lesions will include photographs with caliper of all superficial metastatic lesions identified.

All primary and secondary endpoints based on radiological (and photographic when applicable) assessments of tumor burden (ie, PFS, OR, DoR, CBR) will be based on programmatically derived version of local radiologist's/investigator's assessment (the target lesion measurements, non-target lesion status, and new lesions status recorded on the CRF) according to RECIST v1.1.

Tumor assessment requirements are summarized in Table 6.

Table 6. Tumor Assessment Requirements

	Screening	Active Treatment Phase	EOT/Withdrawal Visit
CT or MRI of chest, abdomen, and pelvis (CAP)	Required	Required	Required
CT or MRI of any other site of disease (including brain)	Required for suspected disease site.	Required for other disease sites identified at screening	Required for other disease sites identified at screening and/or suspected disease site.

Table 6. Tumor Assessment Requirements

	Screening	Active Treatment Phase	EOT/Withdrawal Visit
	CT scan with bone windows OR MRI is required to confirm bone lesions identified by bone scans.	and/or suspected disease site. CT scan with bone windows OR MRI is required for follow-up of bone lesions identified at screening. May also be used to confirm any abnormalities found on subsequent bone scans.	
X-Ray (bone lesions only)	Required ONLY if any abnormality was found via the baseline bone scan and X-ray is the preferred technique to monitor bone lesions.	Required for follow-up of bone lesions identified at screening ONLY if X-ray is the preferred technique. May also be used to confirm any abnormalities found on subsequent bone scans.	Required only if it is the X-ray is the preferred technique to follow bone lesions, unless disease progression has been confirmed elsewhere.
Radionuclide bone scan (whole body).	Required. Any abnormality identified by bone scan must also be confirmed by X-ray, OR CT scan with bone windows, OR MRI.	Required Any abnormality identified by bone scan on treatment must also be confirmed by X-ray OR CT-scan with bone windows, OR MRI. Also requires at the time of confirmation of CR.	Required, unless disease progression has been confirmed elsewhere
Clinical Evaluation of Superficial Disease	Required	Required	Required

Screening (Baseline) Assessments

Radiographic assessments obtained per the participant's standard-of-care prior to signing the informed consent do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days prior to first dose of study treatment (see below exceptions for brain scans and bone scans), (2) they were performed using the method requirements outlined in RECIST v1.1, (3) the same technique/modality can be used to follow identified lesions throughout the study for a given participant, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard-of-care is available in the participant's source notes.

Baseline contrast enhanced chest, abdomen, and pelvis computed tomography or MRI scans are mandatory (details are listed above).

Baseline brain scans are only required if signs and symptoms indicate presence of metastatic brain disease. Brain scans obtained per the participant's standard-of-care before signing the informed consent do not need to be repeated if obtained within 6 weeks prior to first dose of study intervention. If brain metastases are identified at screening, post-baseline brain scans are required.

Baseline bone scans are mandatory to detect bony sites of disease. Bone scans obtained per the participant's standard-of-care before signing the informed consent do not need to be repeated if obtained within 12 weeks prior to first dose of study treatment. Any suspicious abnormalities (ie, hotspots) identified on the screening bone scans, **MUST** be confirmed by X-ray or CT scan with bone windows or MRI. The tumor assessment technique/modality selected at screening **MUST** be used throughout the study for the evaluation of the bone lesions identified at screening. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.

Baseline clinical assessment of superficial lesions (if any): it will include assessments with caliper of all superficial metastatic lesions identified. For skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Active Treatment Phase Assessments

Tumor assessments during the Active Treatment Phase will be performed as specified in the [SoA](#) until radiographically and/or clinically (ie, for photographed lesions) documented PD as per RECIST v1.1, initiation of new anticancer therapy or discontinuation of participant from overall study participation (eg, death, withdrawal of consent, lost to follow-up), or defined end of study (whichever occurs first).

Bone lesion(s) assessed at screening by CT with bone windows or MRI will be subsequently re-assessed on treatment by CT with bone windows or MRI (consistently with the technique used at screening) as specified in the [SoA](#). Subsequent bone scans are mandatory as specified in [SoA](#).

Active Treatment Phase brain scans will be performed if brain lesions were present at baseline or if brain metastases are suspected.

Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v1.1, participants are expected to discontinue study therapy and begin the follow-up phase of the study.

Participants who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed lesions) documented PD as per RECIST v1.1 criteria will continue to have tumor assessments performed as specified in the [SoA](#) until disease progression as per RECIST v1.1 definitions, initiation of new anticancer therapy or

discontinuation of participant from overall study participation (eg, death, withdrawal of consent, lost to follow-up), or defined end of study (whichever occurs first). After implementation of Amendment 3, participants who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed lesions) documented PD as per RECIST v1.1 will not be required to have tumor assessments performed after permanent treatment discontinuation.

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

CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response.

Clinical assessment of superficial disease should be carried out preferably on the same date as the imaging studies and will include assessments with caliper of all superficial metastatic lesions. For skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Further imaging assessments may be performed at any time if clinically indicated (eg, suspect PD, symptomatic deterioration).

For participants having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment eCRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion eCRF.

Objective tumor response will be measured using RECIST v1.1 (see [Section 10.11](#)).

8.2.1.1. Alternative Facilities for Tumor Assessments

Tumor assessment may be performed upon sponsor approval at an alternative facility as long the equipment is adequate (eg, qualification, calibration, maintenance) and the images are available at the investigative site for overall tumor response assessments and for submission to ICR (if using ICR).

8.2.1.2. Treatment Continuation Beyond Disease Progression By Imaging

Participants must be discontinued from study intervention as soon as objective progressive disease per RECIST v1.1 is reported. Treatment continuation beyond disease progression by imaging is not permitted.

8.2.2. Patient-Reported Outcomes (Phase 2 Only)

Patient-Reported Outcomes are no longer required as part of Amendment 3.

PROs will be assessed using both a general cancer scale and a general health status scale. The EORTC QLQ-C30 will capture general cancer symptoms and the EQ-5D-5L will be assessed to calculate utility values that will be necessary for early cost utility analysis

([Aaronson et al, 1993](#); [Osoba et al, 1997](#); [Rabin & de Charro, 2001](#); [Herdman et al, 2011](#); [Janssen et al, 2013](#); [Musoro et al, 2019](#)).

All self-assessment questionnaires must be completed by the participants while in the clinic, prior to any procedures. Should a home health visit be conducted, questionnaires should be administered to the participant by the healthcare provider. Interviewer administration in clinic may be used under special circumstances.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in [SoA](#). Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

At screening, a complete PE should include the examination of general appearance (head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, abdominal cavity, neurologic, and skeletal). Sites of disease identified by physical examination will be recorded on the tumor assessment pages and recorded as Target or Non-target disease. Height (at screening only) and body weight will also be measured and recorded.

Symptom-directed PEs may be performed at subsequent visits as clinically indicated as per Amendment 3. Additional PEs and body weight may also be performed if clinically indicated.

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

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

PE findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE ([Appendix 3](#)) must be reported according to the processes in [Section 8.4.1](#) to [8.4.3](#).

When should it be done:

All PEs occurring on dosing days must be performed prior to study intervention administration. The PE should precede blood collection.

8.3.2. Vital Signs

Per Amendment 3, vital signs will be collected as clinically indicated. Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE ([Appendix 3](#)) must be reported according to the processes in [Sections 8.4.1](#) to [8.4.3](#).

Vital signs should be measured per institutional standards and will include systolic and diastolic blood pressure and pulse rate.

Vital signs should be assessed while the participant is in a sitting position. The same position and same arm should be used consistently throughout the duration unless circumstances, eg, hospitalization, dictate otherwise.

Vital signs should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Abnormal readings as per clinical judgment should be repeated and confirmed.

When should it be done:

All vital sign measurements as per the [SoA](#) should be performed prior to study intervention administration and should precede blood collection.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the [SoA](#) (Per Amendment 3, ECG tests will be performed as clinically indicated at Investigator's discretion) using an ECG machine that automatically calculates the heart rate and measures PR interval, QT interval, QTcF values, and QRS complex. For ECG machines that do not report QTcF, calculation of QTcF from QT and heart rate, for example using online tools, is required. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. Triplicate ECGs are defined as 3 consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 measurements.

If readings confirm a QTcF value ≥ 501 msec or >60 msec change from baseline, immediate search for reversible causes (including electrolyte abnormalities, hypoxia, and concomitant medications for drugs that may potentially prolong the QT interval) should be performed.

If a) a post dose change in QTcF values remains >60 ms from the baseline **and/or** is >480 msec; or b) an absolute QT value is ≥ 501 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF values get progressively longer, the participant should repeat the ECG. A cardiologist should be consulted if QTcF values do not return to less than the criteria 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 QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in [Appendix 8](#).

When should it be done:

When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

8.3.3.1. Alternative Facilities for Electrocardiograms

The participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. ECGs can also be performed at home through home health vendors or through remote device collection if standard specifications outlined above are being met.

8.3.4. Clinical Safety Laboratory Assessments

Per Amendment 3, clinical safety laboratory tests will be performed as clinically indicated. Laboratory results are to be documented in site source only. See [Appendix 2](#) for the list of clinical safety laboratory tests to be performed and the [SoA](#) for the timing and frequency. All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory guidance (eg. Manual) and the [SoA](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

See [Appendix 6](#) for suggested actions and follow-up assessments in the event of potential DILI.

See [Appendix 7](#) for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital.

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

8.3.5. Pregnancy Testing

A urine or serum pregnancy test, confirmation of childbearing potential (Section 10.4.3), and confirmation of appropriate contraception use (Section 10.4.4) are required at screening. Following screening, pregnancy tests may be urine or serum tests, unless otherwise requested by IRBs/ECs or if required by local regulations, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in IOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to starting the study treatment. Pregnancy tests will also be done whenever during the active treatment period a pregnancy is suspected and until 1 month after the last dose of study intervention. Pregnancy tests may also be repeated if requested by IRBs/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.

8.3.5.1. At-Home Pregnancy Testing

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

8.3.6. ECOG Performance Status

ECOG PS (Table 7) will be assessed at the time points specified in the SoA.

Table 7. ECOG Performance Status Scale

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.

Table 7. ECOG Performance Status Scale

2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

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

The definitions of an AE and an SAE can be found in [Appendix 3](#).

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see [Section 7.1](#)).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the applicable reporting method as described in [Appendix 3](#), Section 10.3.4.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer.

8.4.1.1. Reporting Nonserious AEs and SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of these data being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period which begins after obtaining informed consent as described in [Section 8.4.1](#), will be recorded on the AE section of the CRF.

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE leading to permanent discontinuation of study intervention that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

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

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

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

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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.

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

Further information on follow-up procedures is provided in [Appendix 3](#).

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy). For information on how to report to Pfizer Safety, refer to Section [10.3.4](#).

- If EDP occurs in a participant's partner after the start of study intervention and until 28 days after the last dose of study intervention, the investigator must report this information to Pfizer Safety, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports

breastfeeding after having been exposed to the study intervention by ingestion or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. For information on how to report to Pfizer Safety, refer to Section 10.3.4. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

CV events will be reported as AE/SAE as per Section 8.4 and Appendix 3 and as per ECG criteria in Section 8.3.3 and Section 10.8. CV events are to be managed per the dose modification/interruption guidelines in Section 6.6. AEs and SAEs that result in death are to be reported per guidelines as outlined in Section 8.4.

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

Not applicable.

8.4.8. Protocol-Specified Adverse Events of Special Interest

Protocol-Specified AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All protocol-specified AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. A protocol-specified AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported to Pfizer Safety.

Protocol-Specified AEs for vepdegestrant include QTc prolongation and venous thromboembolism.

Hematologic toxicities such as anemia, neutropenia and thrombocytopenia are considered AEs for PF-07220060. Additional laboratory tests for CBC with differentials may be required to be performed and recorded as an unscheduled visit. Hematologic toxicities should be monitored on a more frequent basis (eg, CBC with differentials performed 2 or 3 times a week) based on the discretion of the investigators. Investigators should manage these hematologic toxicities based on institution standard.

The relevant risks and mitigation strategies are summarized in [Section 2.3.1](#).

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the AE Page of the CRF	Reported to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

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

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage defined as underdose or overdose;

- The administration of a single drug, when a combination is required per protocol, for >3 consecutive days;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours **only when associated with an SAE**.

8.5. Pharmacokinetics

Pharmacokinetic assessments are no longer required as part of Amendment 3. Refer to the Laboratory Manual for detailed collection, processing, and shipping procedures previously followed.

8.5.1. Vepdegestrant and ARV-473

Blood samples for measurement of plasma concentrations of vepdegestrant (PF-07850327) and its epimer ARV-473 (PF-07850328) will be collected as specified in the [SoA](#). At each designated time point, a blood sample of approximately 3 mL whole blood to provide approximately 1.5 mL plasma will be collected into appropriately labeled tubes containing K2 EDTA for vepdegestrant and ARV-473. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in the [SoA](#) will not be considered protocol deviations as long as they have a documented actual time and date of collection and relevant time and date of dosing. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the eCRF. If the dose prior to a PK sample collection was missed or reduced, the date of the missing/reduced dose should also be recorded in the eCRF.

On the days of vepdegestrant PK sample collection, participants must be instructed not to take vepdegestrant dosing at home and to withhold their daily dose of vepdegestrant until the predose PK sample has been collected. On vepdegestrant PK sampling days, the vepdegestrant doses should be taken in the clinic under the supervision of the study site personnel.

If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be rescheduled with agreement of the clinical investigator, participant, and sponsor. In addition to samples collected at the scheduled times, every effort should be made to collect an additional blood sample from participants experiencing unexpected and/or serious AEs and to document the date and time of sample collection and of last dosing prior to PK collection on the eCRF (no longer required upon implementation of Amendment 3).

Samples collected for analyses of vepdegestrant and its epimer, ARV-473, concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of vepdegestrant and its epimer, ARV-473, will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

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

8.5.2. PF-07220060

Blood samples will be collected for measurement of plasma concentrations of PF-07220060 as specified in the [SoA](#). At each designated time point, a blood sample of approximately 3 mL whole blood to provide approximately 1.5 mL plasma will be collected into appropriately labeled tube containing K2 EDTA for PF-07220060. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in the [SoA](#) will not be considered protocol deviations as long as they have a documented actual time and date of collection and relevant time and date of dosing. The actual time of the sample collection and the most recent

dosing time before and after each collection will be recorded on the eCRF. If the dose prior to a PK sample collection was missed or reduced, the date of the missing/reduced dose should also be recorded in the eCRF.

Samples will be used to evaluate the PK of PF-07220060. Samples collected for analyses of PF-07220060 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these PK plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07220060 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

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

8.6. Genetics

8.6.1. Specified Genetics

A 4-mL blood pharmacogenomic sample for DNA isolation will be collected into plastic K2-EDTA tubes, as defined in the [SoA](#). The DNA sample will be analyzed for the purpose of assessing any relationship between allelic variants of genes encoding drug metabolizing enzymes and transporters including, but not limited to, UGT2B7. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK, biomarker response, or to explore AEs should these be observed.

See [Section 10.5](#) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the [SoA](#), as local regulations and IRBs/ECs allow.

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

See [Section 10.5](#) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in Laboratory Manual.

8.7. Biomarkers

8.7.1. Biomarkers

The collection of any sample for Biomarkers research at the End of Treatment visit listed below and described in subsection 8.7.1.1 Blood Samples are no longer required as part of Amendment 3.

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the [SoA](#):

- Tumor tissue at screening (refer to [Section 5.1](#) Inclusion Criteria #2).
- Blood samples. (no longer required)

Optional samples for biomarker research include:

- Tumor tissue sample collection at the EOT visit. (no longer required)

Tumor tissue and blood samples will be used to determine mechanisms of sensitivity or resistance to study treatment, conduct genomic and/or genetic molecular profiling analyses, which include, but not limited to, ER and/or CDK4 pathway related genes and/or their protein expression status assessment. Refer to the [SoA](#) for sample collection time points and Study/Laboratory Manual for sample processing and shipping. The biospecimen types described in Section 8.7.1.1 are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses. (no longer required)

8.7.1.1. Blood Samples

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure soluble proteins, and analyze nucleic acids to support study objectives. The following will be collected at the time points specified in the [SoA](#) (no longer required):

- ctDNA to evaluate tumor gene mutations (ie, [CCI](#) etc) and quantitative changes of ctDNA from baseline: 2 × 10 mL blood sample for each time point (C1D1, C2D1, C3D1 and EOT).
- PGx samples: 1 x 4 mL blood sample at C1D1. Germline DNA collection to evaluate [CCI](#) (and other genes if deemed relevant) allelic variants.

More details will be provided in the Laboratory Manual. Additional analyses may be warranted based on emerging data.

8.7.1.2. Retained Research Samples for Biomarkers

Retained Research Samples for Biomarkers are not included in this study.

8.8. Immunogenicity

Immunogenicity assessments are not included in this study.

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 the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

There is no formal hypothesis testing in this study.

9.1.1. Estimands

9.1.1.1. Primary Estimand

Phase 1b

Primary Estimand: DLT rate estimated based on data from DLT-evaluable participants during the DLT observation period (Cycle 1). The estimand has the following attributes:

- Population: DLT-evaluable participants with A/MBC, defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who receive at least 1 dose of the study interventions in Phase 1b and either experience DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than CC% of the planned dose of each study drug during DLT observation period for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced. See [Section 4.3.1](#) for the DLT definition.
- Endpoint: Occurrence of DLTs during the DLT observation period.
- Population-level summary measure: DLT rate defined as the number of DLT evaluable participants with DLTs in the DLT observation period divided by the number of DLT evaluable participants in the DLT observation period.

Phase 2

Primary Estimand: The treatment effect of vepdegestrant in combination with PF-07220060 on ORR per RECIST v1.1. response criteria as determined by investigator assessment. The estimand has the following attributes:

- **Population:** participants with A/MBC, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention.
- **Endpoint:** OR defined as confirmed CR or PR per RECIST v1.1. response criteria as determined by investigator, from the date of first dose until the first documentation of PD, death, or start of new anticancer therapy. Both CR and PR must be confirmed by repeat assessments performed no fewer than 28 days after the criteria for response are first met.
- **Intercurrent events:** All data collected after an intercurrent event of subsequent anticancer therapy will be excluded. All response assessments regardless of gaps in disease assessments will be considered. Participants who do not have a post-baseline disease assessment due to early PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience documented PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as non responders.
- **Population-level summary measure:** ORR defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR.

9.2. Analysis Sets

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

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention (vepdegestrant and PF-07220060).

Participant Analysis Set	Description
Safety Analysis Set (SAS)	All enrolled participants assigned to study intervention and who take at least 1 dose of study intervention.
DLT Evaluable Set	All enrolled participants who received at least 1 dose of study interventions in Phase 1b and either experienced DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than XX % of the planned dose of each study drug during the DLT observation period for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.
Biomarker Analysis Set	The biomarker analysis set for each biomarker is a subset of the Safety Analysis Set and includes all participants with at least 1 biomarker evaluated predose.

Participant Analysis Set	Description
PK Concentration Set	All participants who are in the Safety Analysis Set and have at least 1 concentration of either vepdegestrant, ARV-473, or PF-07220060 above the lower limit of quantitation.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

All antitumor activity analyses and all safety analyses will be performed using the SAS.

In general, descriptive summaries will be presented for the antitumor activity and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. For PK variables geometric mean $\pm$ standard deviation (calculated as $\exp[\mu \pm s]$) and coefficient of variation (%CV) will also be presented.

All primary and secondary endpoints based on radiological and photographic (when applicable) assessments of tumor burden (ie, PFS, ORR, DoR, CBR) will be derived using the local radiologist's/investigator's assessment according to (RECIST v1.1).

9.3.2. Primary Endpoints

9.3.2.1. Phase 1b

9.3.2.1.1. Definition of Endpoint

The primary endpoint in Phase 1b is DLT during the DLT-observation period.

9.3.2.1.2. Main Analytical Approach

Analyses of DLT are based on the DLT Evaluable Set. The occurrence of DLTs and AEs constituting DLTs during the DLT observation period will be summarized and listed by dose level for participants enrolled in Phase 1b.

9.3.2.2. Phase 2

9.3.2.2.1. Definition of Endpoint

The primary efficacy endpoint in the randomized dose optimization Phase 2 is confirmed OR defined as confirmed CR or PR, determined by investigator assessment.

9.3.2.2.2. Main Analytical Approach

ORR is defined as the proportion of participants in the SAS with a confirmed OR per RECIST v1.1 criteria assessed by investigator. Both CR and PR must be confirmed by repeat

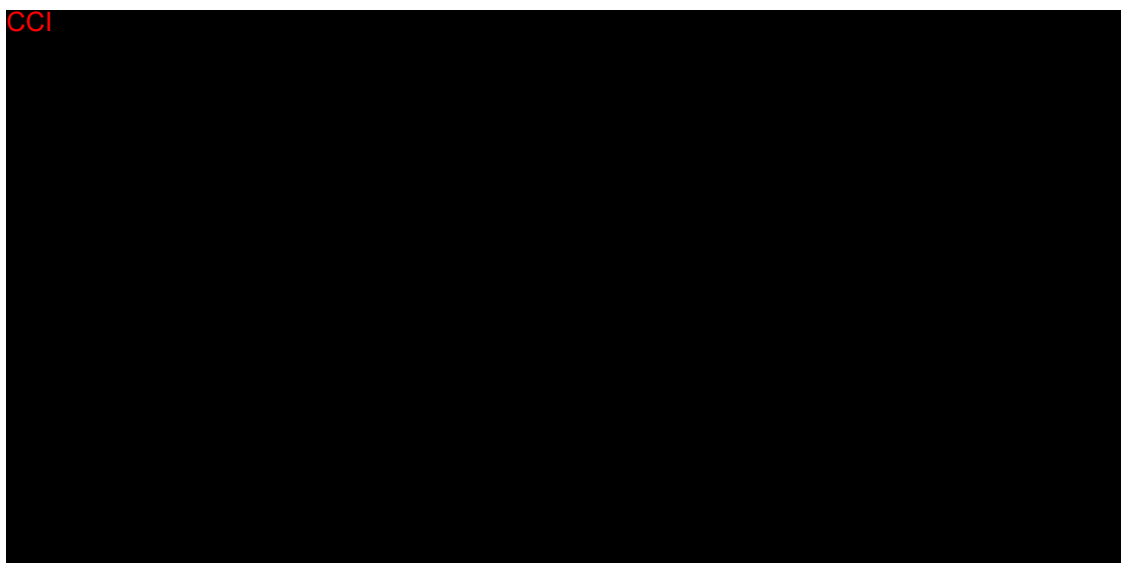
assessments performed no fewer than 28 days after the criteria for response are first met. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anticancer therapies other than the study interventions prior to reaching a CR or PR, or who die, have documented PD, or stop tumor assessments for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. ORR will be calculated along with the 2-sided 95% CI using the Wilson score method (Newcombe, 1998; Wallis, 2013). If two doses are taken into a randomized Phase 2, the point estimate of the difference of the rates between treatment arm will be provided along with corresponding approximate 2 sided 95% CIs based on normal distribution.

9.3.3. Secondary Endpoints

9.3.3.1. Secondary Efficacy Endpoint

Efficacy endpoints to evaluate antitumor activity of vepdegestrant in combination with PF-07220060:

- CBR is defined as the proportion of participants with BOR of confirmed CR or PR at any time, or SD $\geq$ 24 weeks. CBR will be summarized by frequency counts and percentages, along with 2-sided 95% CIs using the Wilson score method. If two doses are taken into a randomized Phase 2, the point estimate of the difference of the rates between treatment arm will be provided along with corresponding approximate 2-sided 95% CIs based on normal distribution.
- DoR is defined for participants with confirmed OR (CR or PR) as the time from the first documentation of OR to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. The censoring rules for DoR are as described below for PFS.
- PFS is defined as the time from the date of first dose of study interventions to the date of first documentation of PD or death due to any cause, whichever occurs first.



CCI

- OS is defined as the time from the date of first dose of study interventions to the date of death due to any cause. Participants last known to be alive will be censored at the date of last contact.

DoR, PFS, and OS will be analyzed using Kaplan-Meier methods. Point estimates will be presented with 95% CIs. The detailed analyses will be described in the SAP.

9.3.3.2. Pharmacokinetic Analysis

PK Analysis for Phase 1b and Phase 2

Plasma concentrations of vepdegestrant, ARV-473, and PF-07220060 will be listed, summarized, and plotted separately for Phase 1b and Phase 2 for all participants in the PK Concentration set as defined in [Section 9.2](#). For summary statistics and mean/median plots by collection time/day, the nominal PK sample collection time/day will be used; for individual participant plots by time/day, the actual PK collection time/day will be used. PK sampling deviations from the protocol-specified collection time/day will be listed.

Population PK analysis of samples collected in this study, if performed, will be in accordance with current regulatory guidelines. The PK concentration data set from this study may be pooled with datasets from other vepdegestrant or PF-07220060 clinical studies and modeled separately. In addition, population PK modeling may be attempted to investigate any causal relationship between vepdegestrant and/or ARV-473 and /or PF-07220060 exposure and pharmacogenomics, biomarker, safety, antitumor activity, and/or laboratory data. These modeling analyses will be reported separately from the final CSR.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Results from tertiary/exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of exploratory objectives and endpoints, the analyses may not be complete at the time of the CSR. Results from exploratory analyses that are not included in the CSR will be shared with the scientific community through publication at a scientific conference and/or in a peer-reviewed scientific journal. Detailed analysis for the tertiary and exploratory endpoints will be specified in a separate technical document outside of the SAP.

9.3.4.1. Patient-Reported Outcomes

Analyses of the PROs will be based on the SAS for the Phase 2 only. Summary statistics (mean and SD, median, range) of absolute scores over time will be reported for EORTC QLQ-C30 and the EQ-5D-5L. The mean change of absolute scores from baseline over time will also be reported. For the EQ-5D-5L health state profiles, the proportions of participants reporting having “none”, “slight”, “moderate”, “severe”, or “extreme/unable” problems at each time point will be reported.

9.3.4.2. Biomarkers

Exploratory biomarker analyses by using tumor tissue biospecimen and peripheral blood samples will be conducted, including, but not limited to, DNA, RNA, protein, or defined cell types. Their association with endpoints and other clinical parameters will be analyzed. Appropriate statistical methods may be used to investigate any possible relationship of biomarker levels with antitumor activity of vepdegestrant in combination with PF-07220060. Descriptive results will be provided if sample size is insufficient for statistical analyses.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters heart rate, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the

>500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR (QTcF) using Fridericia correction method. Data will be summarized and listed for QT interval, PR, RR interval, PR interval, QRS complex, QTcF, and by dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute value of the corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. Details of additional analysis (if any) will be specified in SAP.

9.3.5.2. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA. AE data will be reported in tables and listings. Summaries of AE by appropriate MedDRA terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present overall AEs and SAEs during the entire study period. Listings of DLTs and deaths will be provided.

9.3.5.3. Laboratory Test Abnormalities

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

9.3.6. Other Analyses

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

9.4. Interim Analyses

No interim analysis for efficacy will be conducted for this study.

As this is an open-label Phase 1b/2 study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

There will be dose level review meetings to determine dose escalation/de-escalation (see [Section 4.2.3](#) for details).

9.5. Sample Size Determination

The total sample size is estimated to be approximately 65 participants for C4891026 Phase 1b and Phase 2. The sample size is estimated to be approximately 15 participants for Phase 1b and 50 participants (approximately 25 per dose level for Phase 2).

9.5.1. Phase 1b

A sufficient number of participants will be screened to achieve approximately 15 participants enrolled to study intervention. The number of participants to be enrolled in Phase 1b will depend on the observed safety profile, which will determine the number of participants at each dose level and the number of dose levels explored. Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-4 participants during the DLT observation period (Cycle 1). At least 6 DLT-evaluable participants in Phase 1b will be treated at each dose level to be explored in the Phase 2, before proceeding to Phase 2. If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in Phase 1b. The mTPI-2 dose escalation/de-escalation recommendation will be based on the estimated toxicity rate and 3 intervals (underdosing, target toxicity, and excessive toxicity). Phase 1b will use the mTPI-2 dose finding design with the target toxicity rate of [CCI] with target toxicity interval of [CCI] shown below:

- If current dose is in the underdosing [CCI] toxicity interval: escalate to next higher dose;
- If current dose is in the target toxicity [CCI] toxicity interval: stay at current dose;
- If current dose is in the excessive toxicity or overdosing [CCI] toxicity interval: deescalate to a lower dose.

9.5.2. Phase 2

In Phase 2, approximately 50 participants will be enrolled. If at least 2 dose levels from Phase 1b are considered tolerable, a randomized 1:1 dose optimization Phase 2 will be conducted, approximately 25 participants for each arm will be enrolled and treated. If only one dose level from Phase 1b is considered tolerable, a single arm Phase 2 will be conducted.

Participants will receive the study drugs at the combination RDEs (as determined from Phase 1b) to further evaluate the safety, tolerability, PK and antitumor activity of vepdegestrant in combination with PF-07220060 so to determine the RP2D of the combination.

The sample size is not based on statistical hypothesis test; rather, it is based on clinical consideration that the stated sample size will provide sufficient evidence of preliminary antitumor activity of vepdegestrant in combination with PF-07220060. A total of 25 participants per arm will provide the specified precision of ORR estimates. Table 8 provides the 2-sided 95% CIs for ORR based on different number of observed responders.

Table 8. Exact 95% CIs for ORR for 25 Participants

N	Number of Responders	Observed ORR	95% CIs for ORR*
25	1	4%	(0.7% – 19.5%)
25	2	8%	(2.2% – 25.0%)
25	3	12%	(4.2% – 30.0%)
25	4	16%	(6.4% – 34.7%)
25	5	20%	(8.9% – 39.1%)
25	6	24%	(11.5% – 43.4%)
25	7	28%	(14.3% – 47.6%)
25	8	32%	(17.2% – 51.6%)
25	9	36%	(20.2% – 55.5%)
25	10	40%	(23.4% – 59.3%)
25	11	44%	(26.7% – 62.9%)
25	12	48%	(30.0% – 66.5%)
25	13	52%	(33.5% - 70.0%)
25	14	56%	(37.1% - 73.3%)
25	15	60%	(40.7% - 76.6%)
25	16	64%	(44.5% - 79.8%)
25	17	68%	(48.4% - 82.8%)
25	18	72%	(52.4% - 85.7%)
25	19	76%	(56.6% - 88.5%)
25	20	80%	(60.9% - 91.1%)

* Using Wilson score method (not corrected).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or qualified designee will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The investigator may not delegate obtaining consent to a local healthcare professional.

The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.5.2. Steering Committee

There will be a vepdegestrant program level Steering Committee which will be responsible for providing objective and independent strategic scientific advice and medical input on the ongoing and future clinical development plans for vepdegestrant in ER+ breast cancer. This

group will be involved in scientific discussions involving data collected from C4891026 but will not be involved in the detailed dose discussions or decisions for this study.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of “bonafide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participantlevel data will be anonymized in accordance

with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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

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

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

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for very complex cases (eg, including radiographic testing results or a hospital discharge report to better assess a potential DLT, etc) may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).
- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).
- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

- Negative benefit/risk assessment.

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

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

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the

relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

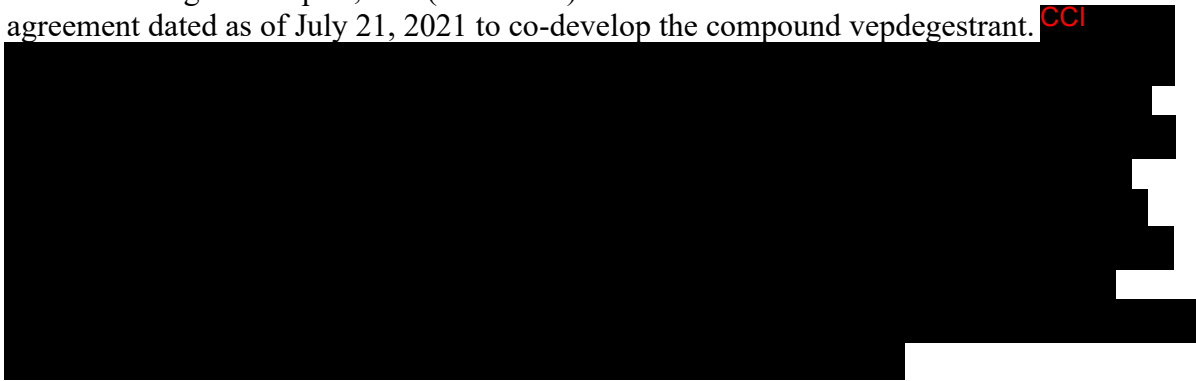
10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.1.13. Transfer of Obligations Statement

Arvinas Estrogen Receptor, Inc. ("Arvinas") and Pfizer entered into a collaboration agreement dated as of July 21, 2021 to co-develop the compound vepdegestrant. CCI



For the purposes of the protocol, sponsor here refers to Pfizer.

10.2. Appendix 2: Clinical Laboratory Tests

After implementation of Amendment 3, clinical laboratory tests may be performed as clinically indicated and documented in site source but not in the eCRF. 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 local clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 9. Laboratory Tests

	Notes
Hematology	Database should be constructed to allow capture of differential counts as percent and absolute values but only one or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria
Hemoglobin	
Platelets	
WBC	
Absolute Neutrophils	
Absolute Lymphocytes	
Absolute Monocytes	
Absolute Eosinophils	
Absolute Basophils	
Blood Chemistry	From Cycle 7 Day 1 onward, sodium, potassium, total calcium, phosphorous, and magnesium will be performed only if clinically indicated.
ALT	
AST	
Alkaline Phosphatase	
Sodium	
Potassium	
Magnesium	
Chloride	
Total Calcium	
Total Bilirubin***	
Urea or BUN	
Creatinine	
eGFR as per 2021 CKD-EPI equations	
Uric Acid (Urate)	
Glucose (fasted)	
Albumin	
Phosphorus or Phosphate	
Lipase (Cycle 1 only)	
Amylase (Cycle 1 only)	
Coagulation	
PT or INR	
aPTT	
Additional Tests	
FSH test as applicable (at screening only)	

Table 9. Laboratory Tests

Pregnancy Test	
For IOCBP participants only. Urine or Serum pregnancy test (at screening). Following screening pregnancy tests (urine or serum) must have sensitivity of least 25 mIU/mL.	

***For Hy’s law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase.

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

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

10.3.1. Definition of AE

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

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

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Events <u>NOT</u> Meeting the AE Definition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. - The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. - 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 - 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.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity - The term disability means a substantial disruption of a person’s ability to conduct normal life functions. - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.
f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
g. Other situations: - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 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, the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Severity section) if it occurs during the active collection period.

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

AE and SAE Recording/Reporting			
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure. It should be noted that reporting SAE information to Pfizer Safety is not the same as recording on the AE page of the CRF. When the same data are collected, these 2 reporting methods 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 reporting method used for reporting of SAE information to Pfizer Safety.			
Safety Event	Recorded on the CRF	Reported to Pfizer Safety	Reported Within 24 Hours of Awareness
SAE	All	All	Yes
Nonserious AE	All	None	No
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF unless the study is managed via SAE+	All instances of EDP are reported (whether or not there is an associated SAE) All instances of EDB are reported (whether or not there is an associated SAE)	Yes
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported	Yes

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- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information on the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety when the reporting method is paper (eg, in lieu of completion of the CT SAE Report Form/AE or SAE CRF page).
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to [Section 10.1.9](#) Use of Medical Records for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

If required on the AE page of the CRF, the investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the AE:

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Once the causality assessment is determined, the investigator must document it in the CRF and, for safety reporting purposes, document the relatedness as “Yes” (for related) or “No” (for unrelated).
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the selected reporting method and in accordance with the SAE reporting requirements.

Outcome Assessment

Record the appropriate outcome of the event in relation to the participant's status:

- Fatal: The termination of life as a result of an AE.

- Not Recovered/Not Resolved: One of the possible results of an AE outcome that indicates that the event has not improved or recuperated.
- Recovered/Resolved: One of the possible results of an AE outcome that indicates that the event has improved or recuperated.
- Recovered/Resolved with Sequelae: One of the possible results of an AE outcome where the participant recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering/Resolving: One of the possible results of an AE outcome that indicates that the event is improving.
- Unknown: Not known, not observed, not recorded, or refused.

Follow-Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Capture

- The primary mechanism for reporting an SAE to Pfizer Safety will be the EDC (eg, eSAE or SAE+) or PSSA.
- For studies managed via SAE+, information pertaining to EDP or EDB is collected in the EDC and sent to Pfizer via PDF file.
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the EDC or PSSA or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the EDC 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 participant or receives updated data on a previously reported SAE after the EDC 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 the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case the EDC or PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the study intervention period and for at least 2 weeks after the last dose of study intervention of vepdegestrant (ARV-471/PF-07850327), and at least 93 days after the last dose of study intervention of PF-07220060, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) **plus** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

- Be persistently abstinent from heterosexual intercourse and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
 - Agree to use a male condom when having sexual intercourse with an IOCBP who is not currently pregnant, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a IOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in IOCBP partners of male participants (refer to the list of highly effective methods below in [Section 10.4.4](#)).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion No. 1 (Age and Sex; [Section 5.1](#)) and specify the reproductive requirements for including female participants. Refer to [Section 10.4.4](#) for a complete list of contraceptive methods permitted in the study.

A participant is eligible to participate if the participant (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction for at least 2 weeks after the last dose of vepdegestrant and at least 33 days after the last dose of PF-07220060; and (c) at least 1 of the following conditions applies:

- Is not an IOCBP (see definition in [Section 10.4.3](#)).

OR

- Is an IOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at

least 2 weeks after the last dose of vepdegestrant, and at least 33 days after the last dose of PF-07220060, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should confirm the use of appropriate contraceptive method in relationship to the first dose of study intervention.

OR

- Is an IOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 2 weeks after the last dose of vepdegestrant, and at least 33 days after the last dose of PF-07220060, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to the use of the highly effective method above (with the exception of abstinence), the participant agrees to concurrently use an effective barrier method. The investigator should confirm the use of the appropriate contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Individual of Childbearing Potential

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

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

Individuals in the following categories are not considered IOCBP:

1. Premenopausal female with 1 of the following:

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

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator judgment will determine childbearing status and study eligibility.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history

interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal individual:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition,
 - FSH level in the postmenopausal range (as per the reference range used by the laboratory) must also be used to confirm a postmenopausal state in individuals under 60 years old with no alternative physiological (including drugs) or pathological cause and not using hormonal contraception or HRT.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Intrauterine device (Copper IUD).
2. IUD. Hormone based IUD is NOT allowed.
3. Bilateral tubal occlusion (eg, bilateral tubal ligation).
4. Vasectomized partner.
 - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the IOCBP 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

5. Sexual Abstinence
 - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. Compliance with sexual abstinence needs to be evaluated and confirmed in relation to the duration of the study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Further details of sample purpose(s) are given in Section 8.6. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to vepdegestrant-based combination therapies or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
 - Samples for specified genetic analysis (refer to [Section 8.6.1](#)) will be stored for up to 3 years or other period as per local requirements.
- Retained Research samples (refer to [Section 8.6.2](#)) will be stored indefinitely or for another period as per local requirements. Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values (or below) within the normal range who subsequently present with AST OR ALT values $\geq 3 \times \text{ULN}$ AND a T bili value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $< 2 \times \text{ULN}$ or not available.

For participants with baseline AST **OR** ALT **OR** T bili 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 $\geq 3 \times \text{ULN}$; or $\geq 8 \times \text{ULN}$ (whichever is smaller).
- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of $\geq 1 \times \text{ULN}$ **or** if the value reaches $\geq 3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated. Screat and reflex Scys values are needed to estimate the combined Screat-Scys eGFR calculation to ascertain whether eGFR change from baseline is comparable for 2021 CKD-EPI eGFR Screat-only and for 2021 CKD-EPI eGFR combined Screat plus Scys (for adult participants only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculations Recommendations

Adults (18 Years and Older) - 2021 CKD-EPI Equations

eGFR (mL/min/1.73 m²)

2021 CKD-EPI Screat Only	Screat (mg/dL)	Scys (mg/L)	Recommended eGFR Equation ^a
Female	if ≤0.7	NA	$eGFR = 142 \times (Screat/0.7)^{-0.241} \times (1.012)^{Age}$
Female	if >0.7	NA	$eGFR = 142 \times (Screat/0.7)^{-0.241} \times (1.012)^{Age}$
Male	if ≤0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
2021 CKD-EPI Scys	Screat (mg/dL)	Scys (mg/L)	Recommended eGFR equation
Female	any	if ≤0.8	$eGFR = 133 \times (Scys/0.8)^{-0.499} \times 0.932^{Age}$
Female	any	if >0.8	$eGFR = 133 \times (Scys/0.8)^{-1.328} \times 0.932^{Age}$
Male	any	if ≤0.8	$eGFR = 133 \times (Scys/0.8)^{-0.499} \times 0.9962^{Age}$
Male	any	if >0.8	$eGFR = 133 \times (Scys/0.8)^{-1.328} \times 0.9962^{Age}$

2021 CKD-EPI Screat-Scys Combined	Screat (mg/dL)	Scys (mg/L)	Recommended eGFR Equation
Female	if ≤0.7	if ≤0.8	$eGFR = 135 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 135 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 135 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 135 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

a. Inker et al, 2021.

10.7.3. Kidney Function Calculators

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR):
https://www.kidney.org/professionals/KDOQI/gfr_calculator

Please note that investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years) are applied. Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are

responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl or creatinine) will be according to CTCAE criteria for adult participants.

NCI CTCAE (2017) Criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute Kidney Injury (AKI)	NA	NA	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
AKI: A disorder characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction).					
Creatinine increased	>ULN to 1.5 x ULN	>1.5 to 3.0 x baseline OR >1.5 to 3.0 x ULN	>3.0 to 6.0 x baseline OR >3.0 to 6.0 x ULN	>6.0 x ULN	NA
Chronic Kidney Disease (CKD)	eGFR ≥ 60 to 89 mL/min/1.73m ² <for ADULT participants> OR eCrCl ≥ 60 to 80 mL/min <for PEDIATRIC participants>	eGFR 30 to 59 mL/min/1.73m ² <for ADULT participants> OR eCrCl 30 to 59 mL/min <for PEDIATRIC participants>	eGFR 15 to 29 mL/min/1.73m ² <for ADULT participants> OR eCrCl 15 to 29 mL/min <for PEDIATRIC participants>	eGFR <15 mL/min/1.73m ² <for ADULT participants> OR eCrCl <15 mL/min <for PEDIATRIC participants> OR dialysis indicated	Death

Proteinuria	ADULTS: Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24hr	ADULTS: Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24hr PEDIATRICS: Urine Protein- to-Creatinine Ratio (UPCR) 0.5 to 1.9	ADULTS: Proteinuria 4+ OR Proteinuria ≥3.5 g/24hr PEDIATRICS: Urine Protein- to-Creatinine Ratio (UPCR) >1.9	NA	NA
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CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.

Proteinuria: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.

Source: Extracted from CTCAE v5.0 – November 27, 2017.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
- Marked sinus bradycardia (rate <40 bpm) lasting minutes. - New PR interval prolongation >280 ms. - New prolongation of QTcF to >480 ms (absolute). - New prolongation of QTcF by ≥ 60 ms from baseline. - New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. - New-onset type I second-degree (Wenckebach) AV block of >30 second duration. - Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs
- QTcF prolongation to >500 ms. - New ST-T changes suggestive of myocardial ischemia. - New-onset LBBB (QRS complex >120 ms). - New-onset right bundle branch block (QRS complex >120 ms). - Symptomatic bradycardia. - Asystole: - In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥ 3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node; - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic 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-second duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-second 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 major events of potential clinical concern listed above 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 is to be reported as AEs/SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

The concurrent use of the following treatments is prohibited throughout the duration of the Active Treatment Phase.

- **Vepdegestrant:** CCI accounted for CCI% of the CYP metabolism of vepdegestrant based on in vitro data. Co-administration with drugs that are strong CYP3A inhibitors and inducers may change the plasma concentrations of vepdegestrant in humans and are therefore prohibited throughout the Active Treatment Phase in Phase 1b and Phase 2. Moderate CYP3A inducers are also prohibited during Active Treatment in Phase 1b.
- **PF-07220060:** In vitro studies indicated the metabolism of PF-07220060 was primarily UGT2B7-mediated (CCI%) with the remaining metabolism via CYP3A4 (CCI%). The concurrent use of strong UGT2B7 inhibitors/inducers, and strong CYP3A inhibitors/inducers is prohibited throughout the Active Treatment Phase. Moderate CYP3A inducers are also prohibited during Active Treatment in Phase 1b.

Prior use of medications, food or herb supplements that are strong inhibitors of CYP3A or UGT2B7 must be stopped 7 days before enrollment. Strong inducers of CYP3A or strong inducers of UGT2B7, and moderate inducers of CYP3A (Phase 1b only) must be stopped 14 days before enrollment.

Examples of prohibited concomitant medications are provided below. This is not an all-inclusive list (examples including, but not limited to the drugs provided below). Strong UGT2B7 inhibitors or inducers are not well defined and examples are not provided.

This list of drugs prohibited for potential DDI concerns may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the PF-07220060, availability of new information in literature on the DDI potential of other drugs), if the overall benefit: risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

Site staff should consult with the sponsor or designee with any questions regarding potential DDI. Investigators should consult the product prescribing information for any other medication used throughout the duration of the Active Treatment Phase for information regarding medication that is prohibited for concurrent use.

Drug Category	Drugs	Required Washout Period
Strong CYP3A inhibitors*	Antibiotics: clarithromycin, josamycin, telithromycin, troleandomycin Antidepressants: nefazodone Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole Antiprogestins: mifepristone	1 week

Drug Category	Drugs	Required Washout Period
	Antivirals: boceprevir, danoprevir, elvitegravir, ensitrelvir, indinavir, lopinavir, nelfinavir, and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir, telaprevir, tipranavir Calcium channel blocker: mibefradil Pharmacokinetic enhancer: cobicistat Vasopressin antagonists: conivaptan Food products: grapefruit, grapefruit juice or any product containing grapefruit Farnesyltransferase inhibitor: lonafarnib Direct oral anticoagulant: apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, ticagrelor	
Strong CYP3A inducers*	Antibiotics: rifampin, rifapentine Anticonvulsants: carbamazepine, phenytoin Cystic fibrosis treatments: lumacaftor Herbal medications: St. John's wort	2 weeks
Moderate CYP3A inducers	Alzheimer's disease treatments: semagacestat Analgesics: metamizole Antibiotics: nafcillin, rifabutin Anticonvulsants: cenobamate, phenobarbital, primidone Antidiarrheals: telotristat ethyl Antigout: lesinurad Antihypertensive: bosentan Antipsychotics: thioridazine Antivirals: efavirenz, etravirine, lersivirine, lopinavir, talviraline, tipranavir, ritonavir, asunaprevir, and beclabuvir and daclatasvir Endometriosis pain: elagolix Hemolytic anemia treatments: mitapivat Sleep disorder treatments: modafinil	2 weeks

* University of Washington Drug Interaction Database and FDA listings as sources.

10.9.1. Drugs Known to Predispose to Torsade de Pointes or QT Interval Prolongation

Concurrent use of vepdegestrant and PF-07220060 with drugs with known risk of causing Torsade de Pointes or QT interval prolongation is prohibited throughout the duration of the Active Treatment Phase.

This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Drug Category	Drugs
Drugs known to predispose to Torsade de Pointes	Anesthetic: sevoflurane*, propofol Antianginal: bepridil Antiarrhythmic: ibutilide, dofetilide, dronedarone, flecainide, nifekalant, hydroquinidine, quinidine, disopyramide, amiodarone, sotalol, procainamide Antibiotic: azithromycin*, ciprofloxacin, clarithromycin, erythromycin, gatifloxacin**, grepafloxacin**, levofloxacin, moxifloxacin, roxithromycin, sparfloxacin** Antidepressant: citalopram, escitalopram Antiemetic: domperidone, ondansetron* Antifungal: pentamidine, fluconazole Antihistamine: terfenadine**, astemizole** Antilipemic: probucol**

Drug Category	Drugs
	Antimalarial: halofantrine, chloroquine*, hydroxychloroquine Antiparasitic: meglumine antimoniate Antipsychotic: thioridazine, levomepromazine (methotrimeprazine), mesoridazine**, haloperidol, chlorprothixene, levosulpiride, pimozide Antipsychotic/antiemetic: chlorpromazine, droperidol, sertindole, sulpiride, sultopride Cholinesterase inhibitor: donepezil GI stimulant: cisapride** Muscle relaxant: terodiline Opioid agonist: methadone, levomethadyl acetate** Phosphodiesterase 3 inhibitor: anagrelide, cilostazol Psychedelic: ibogaine Vasoconstrictor: terlipressin Vasodilator: papaverine HCl (intra-coronary)

*Allowed to be used with **caution** (per USPI and SmPC) during the Active Treatment Phase.

**removed from US market

Adapted from crediblemeds.org (organization that curates the University of Arizona Cancer Center for Education and Research on Therapeutics database): “Risk Categories for Drugs that Prolong QT & induce TdP – Known Risk of TdP”. See website for current list: <https://crediblemeds.org/index.php/druglist>

10.9.2. Substrates of Transporters

vepdegestrant is an inhibitor of P-gp. Treatment with vepdegestrant has potential for increasing exposure of concomitant medications that are sensitive substrates for P-gp transporters. P-gp sensitive substrates should be used with caution.

This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Drug Category*	Drugs
P-gp sensitive substrates	Antiarrhythmics: digoxin/digitoxin Histamine H-1 receptor antagonists: fexofenadine

* University of Washington Drug Interaction Database and FDA listings as sources

10.9.3. CCI

CCI may CCI PF-07220060 absorption and systemic exposure CCI. This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Drug Category	Drugs
CCI	

*Reference corresponding concomitant drugs USPIs.

10.9.4. Recommendations for CCI Usage With PF-07220060

CCI	Recommendation*
	Avoid
	Avoid
	Avoid
	Avoid
	Limit to 20 mg BID
	Limit to 20 mg QD
	Limit to 5 mg QD

* No clinical DDI study has been conducted between PF-07220060 and CCI. Recommendations are based on DDI risk between CCI from the respective USPIs.

10.10. Appendix 10: Detailed Dose Escalation/De-Escalation Scheme for mTPI-2 Design

A safe dose will be determined using the adaptive mTPI-2 design (Guo et al, 2017). The mTPI-2 design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals (corresponding to under, proper, and overdosing in terms of toxicity) that reflect the relative difference between the toxicity rate of each dose level to the pre-specified Target (pT) rate ($pT = \frac{CCI}{N}$). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI-2 will recommend escalating the dose level; if it is close to pT, the mTPI-2 will recommend continuing at the current dose; if it is far greater than pT, the mTPI-2 will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI-2 design are based on posterior probabilities calculated under a coherent probability model. As shown by Ji and Wang, the mTPI design is more efficient and safer than the 3+3 design (Ji & Wang, 2013). They considered 42 scenarios to cover a wide range of practical dose response shapes and concluded that the 3 + 3 design was more likely to treat participants at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3 + 3 design exhibited a lower overall toxicity percentage than the mTPI design in only 1 of 42 scenarios. Sometimes the decision rules in the original mTPI can be debated in practice. The mTPI-2, an extension of the mTPI, helps to solve these undesirable issues.

Decision rules are based on calculating the UPM of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity (Table 10). Specifically, the underdosing interval is defined as $[0, pT - e1]$, the overdosing interval $[pT + e2, 1]$, and the proper-dosing interval $[pT - e1, pT + e2]$, where $e1$ and $e2$ are small fractions. Based on the projected safety profile, $e1$ is selected as $\frac{CCI}{N}$, and $e2$ is selected as $\frac{CCI}{N}$. Therefore, the target interval for the DLT rate is $[\frac{CCI}{N}, \frac{CCI}{N}]$. The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a participant belonging to that dosing interval divided by the length of the dosing interval. The mTPI-2 design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose finding decision, which is the dose level to be used for future participants. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next 3-4 participants will be treated at the next higher dose level. Simulations have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

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

With 3 participants treated at current dose level, and the current dose being the lowest dose:

- 0 DLT – escalate;

- 1-2 DLTs – new participants will be treated at the lowest dose unless the number of DLTs reaches the elimination boundary;
- 3 DLTs – consider current dose as intolerable.

With 3 participants treated at current dose level, and the current dose being the highest dose:

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

With 6 participants treated at current dose level, and the current dose being the highest dose:

- 0-1 DLT – based on the observed safety profile, Phase 1b enrollment may stop, and the highest dose will be declared as the MTD/potential RP2D;
- 2-3 DLTs – de-escalate;
- 4-6 DLTs – de-escalate; consider current dose as intolerable.

With 6 participants treated at current dose level, and the current dose being the lowest dose:

- 0-1 DLT – escalate if the higher dose has not previously been considered as intolerable;
- 2-3 DLTs – new participants will be treated at the lowest dose unless the number of DLTs reaches the elimination boundary;
- 4-6 DLTs – consider current dose as intolerable.

With 9 participants treated at current dose level, and the current dose being the highest dose:

- 0-2 DLT – based on the observed safety profile, Phase 1b enrollment may stop, and the highest dose will be declared as the MTD/potential RP2D;
- 3-4 DLTs – de-escalate;
- 5-9 DLTs – de-escalate; consider current dose as intolerable.

With 9 participants treated at current dose level, and the current dose being the lowest dose:

- 0-2 DLT – escalate if the higher dose has not previously been considered as intolerable;

- 3-4 DLTs – new participants will be treated at the lowest dose unless the number of DLTs reaches the elimination boundary;
- 5-9 DLTs – consider current dose as intolerable.

With 12 participants treated at current dose level, and the current dose being the highest dose:

- 0-2 DLTs – based on the observed safety profile, Phase 1b enrollment may stop, and the highest dose will be declared as the MTD/potential RP2D;
- 3 DLTs – remain at the same dose;
- 4-6 DLTs – de-escalate;
- 7-12 DLTs – deescalate; consider current dose as intolerable.

With 12 participants treated at current dose level, and the current dose is the lowest dose:

- 0-2 DLTs – escalate if the higher dose has not previously been considered as intolerable;
- 3 DLTs – remain at the same dose;
- 4-6 DLTs – new participants will be treated at the lowest dose unless the number of DLTs reaches the elimination boundary;
- 7-12 DLTs – consider current dose as intolerable.

Table 10. mTPI-2 Decision Rules

		Number of Participants												
Number of Participants with DLTs		3	4	5	6	7	8	9	10	11	12	13	14	15
	0	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	D	S	E	E	E	E	E	E	E	E	E	E	E
	2	D	D	D	D	S	S	E	E	E	E	E	E	E
	3	DU	DU	D	D	D	D	D	S	S	S	E	E	E
	4		DU	DU	DU	D	D	D	D	D	D	S	S	S
	5			DU	DU	DU	DU	DU	D	D	D	D	D	D
	6				DU	DU	DU	DU	DU	DU	D	D	D	D
	7					DU	DU	DU	DU	DU	DU	DU	D	D
	8						DU	DU	DU	DU	DU	DU	DU	DU
	9							DU	DU	DU	DU	DU	DU	DU
	10								DU	DU	DU	DU	DU	DU
	11									DU	DU	DU	DU	DU
	12										DU	DU	DU	DU
	13											DU	DU	DU
	14												DU	DU
	15													DU

E = Escalate to the next higher dose level

S = Stay at the current dose level

D = De-escalate to the next lower dose level

DU = The current dose level is unacceptably toxic and should be eliminated from further dose finding

10.11. Appendix 11: RECIST v1.1

Adapted from Eisenhauer et al, 2009 ([Eisenhauer et al, 2009](#))

CATEGORIZING LESIONS AT BASELINE

All sites of disease must be assessed at screening as close as possible to the start of study intervention date (≤ 28 days prior to the start of study intervention unless otherwise specified in [Section 8.2.1](#)). If screening assessment is inadequate, subsequent statuses generally should be not evaluable.

Lesions are selected at screening and followed as either target or non-target lesions. All target lesions must be measurable. Any lesions or sites of disease not classified as target lesions including those that are non-measurable are classified as non-target. Definitions of measurable, non-measurable, target, and non-target lesions are provided below.

Measurable Lesions

Measurable lesions (including both nodal and non-nodal) are lesions that can be accurately measured as follows:

- Lesions with longest diameter ≥ 10 mm in the axial plane (bone lesions are not included except for soft tissue expansile masses arising from bone) when assessed by CT or MRI
- Lesions with longest diameter ≥ 20 mm when assessed by chest X-ray.
- Superficial lesions with longest diameter ≥ 10 mm when assessed by caliper
- Malignant lymph nodes with the short axis ≥ 15 mm. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the smaller of the axial, sagittal or coronal will be considered the short axis).

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

Non-measurable disease

All other disease including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin and lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, nodes with short axis ≥ 10 mm but < 15 mm, disease documented by indirect evidence only (eg, by lab values), or previously radiated lesions that have not progressed, are considered non-measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (lesions with longest diameter for non-lymph nodes ≥ 10 mm and nodes with longest short axis ≥ 15 mm) and suitability for accurate repeated measurements. Measurements are recorded in mm and must be provided for target lesions.

Non-Target Lesions

All non-measurable lesions are non-target. All measurable lesions not identified as target lesions are also included as non-target lesions.

OBJECTIVE STATUS AT EACH EVALUATION

Response is assessed by the investigators, with objective status at each assessment recorded on the IOTA eCRF.

Objective Status is to be recorded at each post-baseline evaluation.

Sites of disease should be assessed using the same technique as baseline, including consistent administration of contrast agents (see [Section 8.2.1](#)). If a change needs to be made the case should be discussed with the radiologist and the sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

If target lesions were present at screening, screening sum of diameters is calculated as the total sum of the longest diameters for non-nodal lesions and short axis for nodal lesions. Sum of diameters at subsequent assessments can be calculated in the same manner using the same set of target lesions.

Response evaluation of target lesions

- **CR:** Complete disappearance of all target lesions, with the exception of nodal disease. All nodes must decrease to normal (short axis < 10 mm). All target lesions must be assessed.
- **PR:** At least a 30% decrease from baseline in the sum of diameters of all target lesions. The short diameter is used in the sum for nodal target lesions, while the longest diameter is used in the sum for non-nodal target lesions. All target lesions must be assessed.
- **PD:** At least a 20% increase in the sum of diameters of target measurable lesions above nadir (smallest sum observed considering baseline and all assessments prior to the time point under evaluation), with a minimum absolute increase of 5 mm relative to nadir. If only a subset of target lesions is assessed and the sum of the non-missing lesion

diameters results in an increase of at least 5 mm and at least 20% above the nadir then the progression criteria will have been met.

- **Stable Disease (SD):** Does not qualify for CR, PR, PD. All target lesions must be assessed.
- **Not Evaluable (NE):** PD has not been documented, and at least one of the following is true:
 - One or more target lesions have not been assessed.
 - Assessment methods used were inconsistent with those used at baseline (unless considered “interchangeable”).
 - One or more target lesions cannot be measured accurately unless due to being too small to measure.
 - One or more target lesions were excised or irradiated and have not reappeared or increased.

General considerations on Response Evaluation of Target lesions:

- A target lesion that is irradiated or excised post-screening is no longer measurable and generally should be assessed as Not Evaluable. Increase or reappearance of such lesions should constitute progression.
- A target lesion biopsied during the screening period will NOT be considered as a measurable lesion.
- Participants with bone disease only may have measurable disease if the following applies: lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI (ie, with soft tissue component that can be evaluated by CT or MRI and meet the definition of measurability as per RECIST v1.1).
- For lesions that become necrotic in the center, the longest diameter should still be used in the sum of diameters.
- Measurements for target lesions that become small should continue to be recorded;
 - If the lesion is considered to have disappeared, 0 mm should be recorded.
 - If a lesion is determined to be present but too small to measure (ie, lesion less than 10 mm with an exact measurement that cannot be performed), the lesion status will indicate “too small to measure” and 5 mm will be used in the calculation of the sum of the diameters.

- If 2 target lesions coalesce, the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- If a subset of the target lesions identified at baseline were not measured post-baseline, the objective status of target lesions at the visit is Not Evaluable, unless the partial sum of diameters for the subset of target lesions assessed at the visit already meets the PD criteria, ie, at least 5 mm and 20% increase above the smallest sum of diameters observed, in which case the objective status of target lesions at the visit is PD.
- If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. The patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions and previous response. For example, if the patient's tumor had reached a CR status and a non-lymph node target lesion reappeared, then the patient's response would be considered PD at the time of reappearance.
- In contrast, if the tumor status was a PR or SD and 1 lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response.

Response evaluation of non-target lesions

- **CR/Absent:** Complete disappearance of all non-target lesions. All nodes must decrease to normal (short axis <10 mm). All disease sites must be assessed.
- **Non-CR/Non-PD/Present without unequivocal progression:** Persistence of 1 or more non-target lesion(s).
- **PD/Unequivocal progression:** Unequivocal progression of existing non-target lesions.
- **Not All Evaluated/Inevaluable:** Progression has not been documented and non-target lesions are not all assessable or disease assessed with inconsistent methods (unless considered "interchangeable") or one or more target lesions were excised or irradiated and have not reappeared or increased.

Note: there is no standard RECIST method of using non-target disease assessments to determine unequivocal progression in non-target disease; by the nature of non-measurable disease, this is not possible. Unequivocal progression is based on clinical judgment. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of investigational product and initiation of a new therapy (eg, an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread). In the presence of SD or PR in target disease, overall progression due to unequivocal increase in nontarget disease should be rare.

New lesions evaluation criteria

- If a lesion is identified in a location not scanned previously, this will be considered progression of disease (new lesion).
- If a new lesion is equivocal at one assessment (classified as “Equivocal”) and verified at the next, (classified as “Unequivocal”), the earlier date is used as the progression date.

OR Status at each assessment

Assessment is based on the target and non-target lesions response as described above and in Table 11.

Table 11. Objective Response Status at Each Assessment for Patients With Measurable Disease at Baseline

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

*Non-PD includes CR and Non-CR/Non-PD

** New lesions must be unequivocal

Note: cases for which target disease is assessed as SD or better but non-target assessments are missing, must be reviewed carefully. By considering the whole sequence, it may be reasonable to assume missed non-target assessments were not progression.

Date of Response

If there are multiple scan dates associated with a tumor evaluation (ie, radiological assessments occur over a series of days rather than the same day), the earliest scan date associated with the evaluation will be used as the date of the assessment. The same convention should be used for the investigator assessment (IOTA eCRF page).

Best Overall Response (BOR)

The BOR will be assessed based on reported overall lesion responses at different evaluation time points from the start of study intervention date until the first documentation of PD. For CR and PR, the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow-up measurements must have met the SD criteria at least once after the start of study intervention at a minimum interval of 6 weeks.

10.12. Appendix 12: Country-Specific Requirements

10.12.1. European Union

This study will be conducted in compliance with Regulation (EU) CTR No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents.

The sponsor will notify EU Member States concerned of the following:

- Annual safety reports via submission to CTIS
- Any SUSAR via reporting to the EudraVigilance database no later than 7 days or 15 days for a fatal or life-threatening SUSAR or non-fatal or non-life-threatening SUSAR, respectively, after becoming aware of that event. A SUSAR is defined as a serious adverse event reaction, the nature, severity, or outcome of which is not consistent with the reference safety information.
- Any unexpected event that affects the benefit-risk profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event.
- Any serious breach, as described in Section 10.1.1.1, no later than 7 days of becoming aware of that breach.
- Any urgent safety measure, as described in Section 10.1.1.1, no later than 7 days of the measure being taken.
- Any inspection report of a third-country authority concerning the study.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

10.12.2. France

10.12.2.1. Contrat Unique

1. GCP Training

Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

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.

4. Termination Rights

Pfizer retains the right to discontinue development of vepdegestrant at any time.

10.12.2.1.1. Additional Other Exclusion Criteria

16. Participants deprived of liberty by judicial or administrative decision.

17. Participants subject to a legal protection measure (guardianship, curatorship, safeguard of justice).

18. Participants not affiliated to a social security system or equivalent.

10.12.3. China

1. The sample analysis labs and disposal vendors are added to meet the requirement outlined in the Rules for the Implementation of Regulations on Management of Human Genetic Resources, Decree No. 21 of the Ministry of Science and Technology of the People's Republic of China:

Testing Name	Testing and Analysis Unit	Destruction Unit
ctDNA	Shanghai Jince Clinical Laboratories Co., Ltd	Shanghai Chengtou Environment Group Co., Ltd.

2. The following content is added to ensure all China sample collection and analysis are consistent with HGRAC policy:

For all China participants, sample collection and testing will not be performed until approval by HGRAC (Human Genetic Resource Administration of China).

10.13. Appendix 13. Bone Marrow Reserve in Adults

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961(Ellis, 1961)

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head :			136.6		
	Cranium	165.8	0.75	124.3	13.1	13.1
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7		
	2 Humerus,	26.5	0.75	20.0	8.3	8.3
	head & neck					
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	10.2
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	36.2
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW		
VERTEBRAE	Vertebrae (Cervical):			35.8			
	1	6.6	All 0.75	5.0	3.4	28.4	
	2	8.4		6.3			
	3	5.4		4.1			
	4	5.7		4.3			
	5	5.8		4.4			
	6	7.0		5.3			
	7	8.5		6.4			
	Vertebrae (Thoracic):			147.9			
	1 pair	10.8	All 0.75	8.1	14.1		
	2	11.7		8.8			
	3	11.4		8.5			
	4	12.2		9.1			
	5	13.4		10.1			
	6	15.3		11.5			
	7	16.1		12.1			
	8	18.5		13.9			
	9	19.7		14.8			
	10	21.2		15.9			
	11	21.7		16.3			
	12	25.0		18.8			
	Vertebrae (Lumbar) :			114.1			
	1 pair	27.8	All 0.75	20.8	10.9		
	2	29.1		21.8			
	3	31.8		23.8			
	4	32.1		24.1			
	5	31.4		23.6			
TOTAL		1497.7		1045.7	100.0	100.0	

10.14. Appendix 14: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 2 (11 April 2024)

Overall Rationale for the Amendment: The protocol was amended mainly to incorporate CCI [REDACTED] such as eligibility criteria, intraparticipant dose escalation criteria, clarification to non-hematological DLTs, and country specific exclusion criteria for France.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Adding a requirement to perform a pre-dose ECG at Cycle 3.	CCI [REDACTED] to allow for increased ECG monitoring due to potential risk of QTc prolongation of vepdegestrant	Section 1.3. Table 2 and Table 4 Schedule of Activities
Adding intraparticipant dose escalation criteria for Phase 1b participants.	CCI [REDACTED] to clarify intra-patient dose escalation criteria	Section 4.1. Overall Design
Adding the radiological imaging to rule out pancreatitis for participants who experience a Grade ≥ 3 amylase or lipase.	CCI [REDACTED] to modify the definition of the non-hematological DLTs in case of Grade 3 amylase or lipase to exclude pancreatitis.	Section 4.3.1.3. Non-Hematological DLTs
Modified eligibility criteria to provide sex specific thresholds for QTcF and to exclude participants with risk factors for QT prolongation.	CCI [REDACTED] to exclude patients who present with corrected CCI [REDACTED] ECG and with risk factors for QT prolongation (eg, electrolyte abnormalities) unless mitigated or corrected prior to enrollment	Section 1.1 Synopsis and Section 5.2. Exclusion Criteria, Medical Conditions: Criterion # 5

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Description of Change	Brief Rationale	Section # and Name
Included additional country specific exclusion criteria for participants in France	CCI [REDACTED]	Section 10.12.1.1.2 Appendix 12. And Section 5.2
Non-Substantial Modification(s)		
Added ClinicalTrials.gov ID number	Study registration identifier available	Title page and Section 1.1. Synopsis
The process for contacting medically qualified individual (MQI, also known as the medical monitor) has been updated. The contact information for the study medical monitor is documented in the Study Team Contact List and the Emergency Contact Card is being replaced by a study information card.	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List. The Emergency Contact Card is being replaced by a study information card and will no longer be referenced.	Appendix 1 Section 10.1.12 Sponsor's Medically Qualified Individual; Appendix 15: Abbreviations
The number of Grade 4 events to trigger an ad hoc Dose Level Review Meeting and to temporarily halt the enrolment must be equal or greater than 2, as reported in the summary of changes table for Protocol Amendment 1.	Internal consistency	Section 4.2.3. Dose Level Review Meeting
Text corrected and aligned with Schedule of Activities and Appendix 4. Pregnancy test will be done until 1 month after last dose of study intervention.	Internal consistency	Section 8.3.5. Pregnancy Testing
Table 12 has been corrected and aligned to the Schedule of Activities to allow for serum or urine pregnancy tests at screening	Internal consistency	Appendix 2 Clinical Laboratory Test
General editorial changes	To increase clarity	9.2 Analysis Sets 10.7.3. Kidney Function Calculation Tools

Description of Change	Brief Rationale	Section # and Name

Amendment 1 (20 November 2023)

Overall Rationale for the Amendment: The protocol was amended mainly to incorporate CCI [REDACTED] such as eligibility/reproductive criteria, pharmacogenomics of UGT2B7 including the addition of an exploratory endpoint, clarification on the administration of study interventions, and clarification of stopping rules in regards to specific safety criteria.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
CCI [REDACTED] added as a potential risk for Vepdegestrant	To update the safety profile of vepdegestrant.	Section 2.3.1
Criteria for renal impairment defined by an eGFR was changed from 45 to 50 mL/min/	CCI [REDACTED]	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
An ad hoc DLRM will be held in case any stopping criteria are met.	CCI [REDACTED] to include a stopping rule that enrollment may be temporarily halted in case of any death or ≥ 2 Grade 4 events.	Section 4.2.3 Dose Level Review Meeting
Modification of the DLT threshold for participants with Grade 2 AST, ALT, or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis.	CCI [REDACTED]	Section 4.3.1.3 non-Hematological DLTs
Text updated to clarify that PF-07220060 reproductive criteria apply for at least 3 months after the last dose.	CCI [REDACTED]	Section 10.4.1 Appendix 4 Male Participant Reproductive Inclusion Criteria

Description of Change	Brief Rationale	Section # and Name
Additional blood sampling added for a new tertiary/exploratory objective of evaluating the effect of UGT2B7 gene polymorphism on PF-07220060 plasma exposure with an endpoint of UGT2B7 allelic variants from analysis of DNA and the associated methodology.	CCI [REDACTED]	Section 1.3 Tables 1, 2, 3, and 4 Section 3.1 Objectives, Endpoints, and Estimands -Phase 1b Section 3.2 Objectives, Endpoints, and Estimands - Phase 2 Section 8.6.1 Specified genetics Section 8.7.1.1 Blood samples Section 10.5 Appendix 5: Genetics
Data supporting the administration of PF-07220060 with food have been added.	To provide rationale for updating section 6.1.1.1 and 6.1.1.2.	Section 2.2.5.2 PF-07220060
Text and figure updated to indicate administration of study interventions with food and timing for BID administration of doses.	To clarify specific instructions for administration of PF-07220060 and vepdegestrant must be taken with food based on evolving PF-07220060 data and to increase participant compliance.	Section 1.1 Synopsis Section 6.1.1.1 PF-07220060 Administration Section 6.1.1.2 Vepdegestrant Administration Section 5.3.2 Meals and Dietary Restrictions
Added moderate CCI inducers to the prohibited drugs in the dose escalation Phase 1b portion of the study.	CCI [REDACTED]	Section 1.1 Synopsis Section 6.9.3 Prohibited Inhibitors/ Inducers Section 6.9.3.2. Concomitant Treatments to be Used with Caution or Not Recommended Section 10.9 Appendix 9: Prohibited Concomitant Medications That May Result in DDI
Text regarding continuing beyond progression was deleted.	CCI [REDACTED] that there are no current data to support continuing beyond progression.	Section 8.2.1 Tumor response Assessments Section 8.2.1.2 Treatment Continuation Beyond Disease Progression By Imaging

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Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Text added to clarify the escalation / de-escalation algorithm and the possibility to enroll additional participants under “backfill” enrollment.	To clarify the possible enrollment strategy for Phase 1b.	Section 1.1 Synopsis Section 4.1 Overall design
Criteria for prior treatment not permitted has been updated.	To clarify the criterion.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
Text updated to clarify that the tumor block collected at screening is the same to be used for biomarker testing.	For clarification and to ensure consistency.	Section 1.3 Tables 2 and 4 Section 5.1 Inclusion Criteria Section 8.7.1. Biomarkers
To correct escalation / de-escalation algorithm.	CCI [REDACTED]	Section 10.10 Appendix 10: Detailed Dose Escalation/De-Escalation Scheme for mTPI-2 Design
Typographical errors were corrected, and minor edits were made.	For clarification and to ensure consistency.	Throughout the protocol.

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1 *There is no window for C1D1.
Visit Window		±2d*	±1d	±1d	±2d		+7d	
Baseline Documentation								
Informed Consent Process	X							Informed consent must be obtained within 28 days of enrollment and prior to any protocol-required assessments being performed (Section 10.1.3). Procedures conducted as part of the participant’s routine clinical practice and obtained before signing of the ICD may be utilized for screening as specified in Section 8.1.
Demography and Medical/ Oncological History	X							To include information on prior anticancer treatments (Section 8.1.1).
Physical Examination/Vital Signs	X	X		X	X	X		Not required on C1D1 if acceptable screening assessment is performed within 7 days prior to first dose administered on C1D1. See Sections 8.3.1 and 8.3.2.
Height (at Screening Only) and Body Weight	X	X			X			See Section 8.3.1.
ECOG Performance Status	X							See Section 8.3.6.
Clinical Laboratory Assessments								C1D1: Hematology, blood chemistry and 12-lead ECG not required if acceptable screening assessment is performed within 7 days prior to first dose administered on C1D1.

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1 *There is no window for C1D1.
Visit Window		±2d*	±1d	±1d	±2d		+7d	
Hematology ^c	X	X	X	X	X	X	X	Coagulation assessment during treatment will be performed as clinically indicated.
Blood Chemistry ^c	X	X		X	X	X	X	
Coagulation ^c	X							Post-treatment follow-up laboratory assessments only if laboratory abnormalities not recovered from at EOT. See Appendix 2 .
Pregnancy test ^c	X	X			X	X	X	See Section 8.3.5 and Appendix 2 .
FSH test	X							FSH test must be performed as needed to confirm a postmenopausal state in women under 60 years of age with no alternative causes (eg, drugs, disease). See Appendix 2 and Appendix 4 .
12-Lead ECG	See.							ECG must be performed first, then blood collection before dosing on all visits (Section 8.3.3).

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1
Visit Window		±2d*	±1d	±1d	±2d		+7d	*There is no window for C1D1.
Disease Assessment								
CT/MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease (Other Than Bone Scan)	X	Performed every 8 weeks (±7 days) from date of first dose of the combination for the first year, followed by every 12 weeks (±7 days).				X	X	Post-Treatment disease assessments are required only for participants who discontinued study intervention for reason other than documented PD as per RECIST v1.1 criteria. See Section 8.2 and Table 6.
Clinical Evaluation of Superficial Disease	X	Performed every 8 weeks (±7 days) from date of first dose of the combination for the first year, followed by every 12 weeks (±7 days).				X	X	
Radionuclide Bone Scan, Whole Body	X	Performed every 24 weeks (±7 days) from date of first dose of the combination per Section 8.2.1.				X	X	
Other Clinical Assessments								
Contraception Check for WOCBP and males ^c	X	X			X	X	X	See Section 5.3.1 and Appendix 4.
Serious and nonserious AE Monitoring ^c	X	X		X	X	X	X	See Section 8.4.1.
Review Concomitant Medications/Treatments ^c	X	X		X	X	X	X	Recorded from 28 days prior to first dose and up to 28 days after the last dose of study intervention. See Section 6.9 and Section 10.9.

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1 *There is no window for C1D1.
Visit Window		±2d*	±1d	±1d	±2d		+7d	
Subsequent Anticancer Therapy ^c							X	First subsequent anticancer therapy data to be collected. See Section 7.1 .
Study Intervention and GnRH/LHRH Agonist								
Allocation to Study Intervention ^c	X							Allocation to study intervention must be completed after eligibility has been confirmed. Study intervention administration should start ≤3 days after assignment. See Section 6.3 .
Vepdegestrant		QD						See Section 6.1.1.2 .
PF-07220060		BID						See Section 6.1.1.1 .
Drug Compliance ^c		X			X			Drug accountability will be performed prior to dispensing drug for the following cycle. See Sections 6.2 and 6.5 .

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1
Visit Window		±2d*	±1d	±1d	±2d		+7d	*There is no window for C1D1.
GnRH or LHRH Agonist (for Men and Pre-/Peri-menopausal Participants) ^c	As per local package insert						X	Treatment should start at minimum on C1D1 if not before and be administered as per local package insert, irrespective of cycle duration and up to 28 days after the last dose of study intervention. Treatment continuation after post-treatment follow-up is at the discretion of the investigator. See Section 6.9.2 .
Pharmacokinetic Assessment								
Blood Sample for vepdegestrant and ARV-473 PK	See Section 8.5 and Table 2.							
Blood Sample for PF-07220060 PK								
Other Sample Collections								
Tumor Tissue for Biomarker	See Table 2.							
Retained Research Sample for Genetics (Prep D1)	See Table 2.							
Blood Sample for PGx	See Table 2							

Study Schedule of Assessments (Phase 1b) (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days				EOT/ Withdrawal ^a	Post- Treatment Follow-Up ^b	Notes
		Cycles 1 and 2			Cycles ≥3			All assessments should be performed prior to study intervention administration, unless otherwise specified.
Study Day	≤ 28 days prior to first dose	Day 1	Day 8 [§]	Day 15	Day 1			§ Day 8 applies only to Cycle 1
Visit Window		±2d*	±1d	±1d	±2d		+7d	*There is no window for C1D1.

- End of Treatment/Withdrawal:** These assessments are to be performed only if they have not been completed during the previous 28 days on study, or within the previous 8 weeks for disease assessments if EOT occurred during the first year of treatment, or within the previous 12 weeks if EOT visit occurred after the first year of treatment, or within the previous 24 weeks for bone scans, unless needed for monitoring of safety findings
- Post-Treatment Follow-up:** Follow-up visit will be performed at least 28 days (+7 days) after discontinuation of study intervention OR prior to the initiation of any new anticancer therapy whichever comes first. The SAE reporting period is 28 days from last dose regardless of the initiation of a new anticancer therapy (see [Section 8.4.1](#)).
- Assessments may be performed during home health visits that will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.

ECG, PK and Other Sample Collection (Phase 1b) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 Days																EOT/ Withdrawal	
		Cycle 1										Cycle 2 and 3				Cycle 4	Cycles 5 and 7		
Day		1	8	15								1		15		1	1		
Hour (pre or postdose)		Pre ^b	Pre ^b	Pre ^b	0.5 ^h	1 ^h	2 ^h	4 ^h	6 ^h	8 ^h	12 ^h	Pre ^b	Post ^b	Pre ^b	Post ^b	Pre ^b	Pre ^b		
Window (± min)					3	6	15	20	30	30	120								
Triplicate 12-lead ECG ^c	X (Single ECG only)	X	X	X				X (4-8 hrs)					X	X C2 only	X C2 only	X C2 only	X		X (Single ECG only)
Blood Samples for vepdegestrant and ARV-473 PK ^d			X	X	X	X	X	X	X	X	X	X	X	X C2 only	X C2 only	X C2 only		X	
Blood Samples for PF-07220060 PK ^e			X	X	X	X	X	X	X	X	X	X	X	X C2 only	X C2 only	X C2 only		X	
Tumor Tissue for Biomarker ^f	X																		X optional ^a
Retained Research Sample for Genetics (Prep D1) ^g		X																	
Blood Sample for PGx ⁱ		X																	

a. Biopsy at the EOT visit is considered only for participants who discontinue treatment due to disease progression, provide the consent for the procedure, and when, in the investigator's judgment, such biopsy can be safely performed.

b. Predose samples to be collected within 2 hours prior to dosing; postdose samples 4-8 hours after dosing. Assessments should be performed in the following order, as applicable: ECGs, blood samples for PK, other blood samples.

c. ECG performed immediately prior to PK blood collections. ECGs beyond C4D1 will be performed as clinically indicated. See [Section 8.3.3](#).

d. Samples should be approximately 3 mL at each time point. See [Section 8.5](#).

e. Samples should be approximately 3 mL at each time point. See [Section 8.5](#).

f. See [Section 8.7](#) and [Section 5.1 Inclusion Criteria 2](#).

g. Sample should be 4 mL. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See [Section 8.6.2](#).

h. Serial PK sampling of vepdegestrant and PF-07220060 must be done separately for each timepoint due to the dosing sequence requirement when both drugs are administered in the same period (see [Section 6.1.1](#)). Timepoint for collection of serial PK samples must be determined by the time of administration of the respective drugs.

i. A blood specimen (approximately 4 mL) will be collected for PGx analysis (see [Section 8.7.1](#)).

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2	Cycles ≥3					All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections. *There is no window for C1D1.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	
Baseline Documentation								
Informed Consent Process	X							Informed consent must be obtained within 28 days of enrollment and prior to any protocol-required assessments being performed (Section 10.1.3). Procedures conducted as part of the participant's routine clinical practice and obtained before signing of the ICD may be utilized for screening as specified in Section 8.1 .
Demography and Medical/Oncological History	X							To include information on prior anticancer treatments (Section 8.1.1).
Physical Examination/Vital Signs	X	X	X	X	X			Not required on C1D1 if acceptable screening assessment is performed within 7 days prior to first dose. See Sections 8.3.1 and 8.3.2 .
Height (at Screening Only) and Body Weight	X	X		X				See Sections 8.3.1 .
ECOG Performance Status	X							See Section 8.3.6 .

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2		Cycles ≥3				All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections. *There is no window for C1D1.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	
Clinical Laboratory Assessments								C1D1: Hematology, blood chemistry, and 12-lead ECG not required if acceptable screening assessment is performed within 7 days prior to first dose.
Hematology ^c	X	X	X	X	X	X		Post-treatment follow-up laboratory assessments only if laboratory abnormalities not recovered from at EOT. See Appendix 2 . Coagulation assessment during treatment will be performed as clinically indicated.
Blood Chemistr	X	X	X	X	X	X		
Coagulation ^c	X							
Pregnancy tes	X	X		X	X	X		See Section 8.3.5 and Appendix 2 .
FSH test	X							FSH test must be performed as needed to confirm a postmenopausal state in women under 60 years of age with no alternative causes (eg, drugs, disease). See Appendix 2 and Appendix 4 .
12-Lead ECG	See Section 8.3.3 and Table 4							

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2		Cycles ≥3				All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections. *There is no window for C1D1.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	
<i>Disease Assessment</i>								
CT/MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease (Other Than Bone Scan)	X	Performed every 8 weeks (±7 days) from date of first dose of the combination for the first year, followed by every 12 weeks (±7 days).			X	X		Post-Treatment disease assessments are required only for participants who discontinued study intervention for reason other than documented PD as per RECIST v1.1 criteria. See Section 8.2 and Table 6.
Clinical Evaluation of Superficial Disease	X	Performed every 8 weeks (±7 days) from date of first dose of the combination for the first year, followed by every 12 weeks (±7 days).			X	X		
Radionuclide Bone Scan, Whole Body	X	Performed every 24 weeks (±7 days) from date of first dose of the combination per Section 8.2.1.			X	X		
<i>Other Clinical Assessments</i>								
Contraception Check for WOCBP and males ^c	X	X		X	X	X	X	See Section 5.3.1 and Appendix 4.
Serious and nonserious AE monitoring ^c	X	X	X	X	X	X		See Section 8.4.1.
Review Concomitant Medications/Treatment	X	X	X	X	X	X		Recorded from 28 days prior to first dose and up to 28 days after the last dose of study intervention. See Section 6.9 and Appendix 9.

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2		Cycles ≥3				All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections. *There is no window for C1D1.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	
Subsequent Anticancer Therapy						X	X	All subsequent anticancer therapies data to be collected. See Section 7.1 .
PRO assessments: EuroQol; EQ-5D-5L EORTC QLQ-C30		X		X	X			To be completed prior to any study or medical procedure on Day 1 of Cycles 1, 2, and 3 and Day 1 of every other cycle thereafter starting with Cycle 5, and the EOT visit. See Section 8.2.2 .
Survival Follow-up							X	See Section 7.1 .
Study Interventions and GnRH/LHRH Agonist								
Allocation to Study Intervention ^c	X							Allocation to study intervention must be completed after eligibility has been confirmed. Study intervention administration should start ≤3 days after assignment. See Section 6.3 .
Vepdegestrant		QD						See Section 6.1.1.2 .
PF-07220060		BID						See Section 6.1.1.1 .
Drug Compliance		X		X				Drug accountability will be performed prior to dispensing drug for the following cycle. See Sections 6.2 and 6.5 .

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2		Cycles ≥3				All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections. *There is no window for C1D1.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	
GnRH or LHRH Agonist (for Men and Pre-/Perimenopausal Participants)	As per local package insert					X	X (PI discretion)	See Section 6.9.2 . Treatment should start at least on C1D1 and administered as per local package insert, irrespective of cycle duration and up to 28 days after the last dose of study intervention. Treatment continuation during survival follow-up is at the discretion of the PI.
Pharmacokinetic Assessment								
Blood Sample for vepdegestrant and ARV-473 PK	See Section 8.5 and Table 4							
Blood Sample for PF-07220060 PK								
Other Sample Collections								
Tumor Tissue for Biomarker	See Table 4							.
Blood Sample for ctDNA	See Table 4							
Retained Research Sample for Genetics (Prep D1)	See Table 4							
Blood Sample for PGx	See Table 4							

Study Schedule of Assessments (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 days			EOT / Withdrawal ^a	Post- Treatment Follow-Up ^b	Survival Follow- Up ^d	Notes
		Cycles 1 and 2		Cycles ≥3				All assessments should be performed prior to study intervention administration, unless otherwise specified. Assessments should be performed in the following order, as applicable: PROs, blood and other sample collections.
Study Day		Day 1	Day 15	Day 1			Every 3 months	
Visit Window	≤ 28 days prior to first dose	±2d*	±2d	±2d		+7d	±7d	*There is no window for C1D1.

- a. **End of Treatment/Withdrawal:** These assessments are to be performed only if they have not been completed during the previous 28 days on study, or within the previous 8 weeks for disease assessments if EOT occurred during the first year of treatment, or within the previous 12 weeks if EOT visit occurred after the first year of treatment, or within the previous 24 weeks for bone scans, unless needed for monitoring of safety findings
- b. **Post-Treatment Follow-up:** Follow-up visit will be performed at least 28 days (+7 days) after discontinuation of study intervention OR prior to the initiation of any new anticancer therapy whichever comes first. The SAE reporting period is 28 days from last dose regardless of the initiation of a new anticancer therapy (see [Section 8.4.1](#)).
- c. Assessments may be performed during home health visits that will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.
- d. **Survival Follow-up:** Survival status will be collected every 3 months starting from the last dose of study treatment. All anticancer therapy regimens taken after study treatment discontinuation will be collected. Telephone contact is acceptable.

ECG, PK and Other Sample Collection (Phase 2) - (from Amendment 2 – no longer applicable upon Amendment 3 implementation)

Protocol Activity	Screening	Combination Treatment Period 1 Cycle = 28 Days									EOT/ Withdrawal
		Cycle 1			Cycle 2 and 3				Cycle 4	Cycles 5 and 7	
Day		1	15		1		15		1	1	
Hour (pre or postdose) ^b		Pre	Pre	Post	Pre	Post	Pre	Post	Pre	Pre	
Triplicate 12-lead ECG ^c	X (Single ECG only)	X	X	X	X	X C2 only	X C2 only	X C2 only	X		X (Single ECG only)
Blood Samples for vepdegestrant and ARV-473 PK ^d			X	X	X	X C2 only	X C2 only	X C2 only		X	
Blood Samples for PF-07220060 PK ^e			X	X	X	X C2 only	X C2 only	X C2 only		X	
Tumor Tissue for Biomarker ^f	X										X (optional) ^a
Blood Samples for ctDNA ^g		X			X						X
Retained Research Sample for Genetics (Prep D1) ^h		X									
Blood sample for PGx ⁱ		X									

- a. The biopsy at the EOT visit is considered only for participants who discontinue treatment due to disease progression, provide the consent for the procedure, and when, in the investigator's judgment, such biopsy can be safely performed.
- b. Predose samples to be collected within 2 hours prior to dosing; postdose samples 4-8 hours after dosing. Assessments should be performed in the following order, as applicable: ECGs, blood samples for PK, other blood samples.
- c. ECG performed immediately prior to PK blood collections. ECGs beyond C4D1 will be performed as clinically indicated. See Section 8.3.3.
- d. Samples should be approximately 3 mL at each time point. See Section 8.5.
- e. Samples should be approximately 3 mL at each time point. See Section 8.5.
- f. See Section 8.7 and Section 5.1 Inclusion Criteria 2.
- g. Samples should be 2 × 10 mL at each time point. See Section 8.7.1.1.
- h. Sample should be 4 mL. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.6.2.
- i. A blood specimen (approximately 4 mL) will be collected for PGx analysis (see Section 8.7.1).

10.15. Appendix 15: Abbreviations

The following may be used in the protocol.

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
A/MBC	advanced/metastatic breast cancer
aPTT	activated partial thromboplastin time
AR	androgen receptor
CCI	
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC _{inf}	AUC versus time curve from time 0 extrapolated to infinity
AUC _{tau}	area under concentration-time curve over dosing interval
AUC ₀₋₂₄	AUC from time 0 to 24 hours
AUC ₂₄	AUC time 24 hours
AV	atrioventricular
AxMP	auxiliary medicinal product
BC	breast cancer
BCG vaccine	Bacille Calmette-Guérin vaccine
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BP	blood pressure
bpm	beats per minute
BRCA	BRCA gene
BUN	blood urea nitrogen
CAP	chest, abdomen, and pelvis; College of American Pathologist
CBR	clinical benefit rate
C1D1	Cycle 1 Day 1
CDK2	cyclin-dependent kinase 2
CDK4/6	cyclin-dependent kinase 4/6
CDK4/6i	CDK4/6 inhibitor
CDK4-Rb	cyclin-dependent kinase 4-Rb gene
CERAN	complete estrogen receptor antagonist
CFR	Code of Federal Regulations

Abbreviation	Term
CI	confidence interval
CK	creatinine kinase
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
CIOMS	Council for International Organizations of Medical Sciences
C _{max}	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTIS	Clinical Trials Information System.
CTFG	Clinical Trial Facilitation and Coordination Group
CTR	Clinical Trials Regulation
CV	coefficient of variation
CYP	cytochrome P450
D	de-escalate to the next lower dose level
D1	Day 1
DCT	data collection tools
DDI	drug-drug interaction
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
CCI	
DoR	duration of response
DU	dispensable unit; current dose level is unacceptably toxic and should be eliminated from further dose finding
E	escalate to the next higher dose level
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy

Abbreviation	Term
E-DMC	External Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC Quality of Life Cancer Questionnaire 30
EOT	end of treatment
EPI	epidemiology collaboration
EQ-5D-5L	European Quality of Life 5 Domain 5 Level Scale
ER	estrogen receptor
ESR1	Estrogen Receptor 1 gene
ESR1mut	Estrogen Receptor 1 mutant gene
ET	endocrine therapy/early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
GnRH	gonadotropin releasing hormone
CCI	
HCl	hydrochloride
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HRT	Hormone replacement therapy
KDOQI	Kidney Disease Outcomes Quality Initiative
IB	Investigator's Brochure
IC ₅₀	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central review
ID	identification
IHC	immunohistochemistry
ILD	interstitial lung disease

Abbreviation	Term
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IOCBP	individual of childbearing potential
IPM	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IV	intravenous
LBBS	left bundle branch block
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
MBC	metastatic breast cancer
MCF7	Michigan Cancer Foundation 7
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	median progression-free survival
MQI	medically qualified individual
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
N	total number
NA	not applicable; not available
NCI	National Cancer Institute
NE	not estimable
NIMP	non-investigational medicinal product
NSCLC	non-small-cell lung cancer
NY	New York
OR	objective response
ORR	objective response rate
OS	overall survival
PA3	protocol amendment 3
PACL	protocol administrative change letter
PD	pharmacodynamics(s)/progressive disease
PDF	Portable Document Format
PDX	patient derived xenograft
PE	physical examination
PFS	progression-free survival
P-gp	P-glycoprotein
PGx	pharmacogenomics
PI	Principal Investigator

Abbreviation	Term
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	pharmacokinetic(s)
PLT	platelets
PPI	proton pump inhibitor
PR	partial response/pulse rate
PRO	patient reported outcome
PROTAC	Proteolysis Targeting Chimera
PS	performance status
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
pT	pre-specified Target
PVC	premature ventricular contraction
QD	once daily
QTc	corrected QT interval
QTcF	QTc (Fridericia method)
QTL	quality tolerance limit
RANKL	receptor activator of nuclear factor kappa B ligand
RB	retinoblastoma
RBC	red blood cell
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RP3D	recommended phase 3 dose
RR	response rate
S	stay at the current dose level
SAE	serious adverse event
SAE+	serious adverse event reporting system
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
Screat	serum creatinine
Scys	serum cystatin C
SD	single dose, stable disease, standard deviation
SERCA	selective estrogen receptor covalent antagonist
SERD	selective estrogen receptor downregulator or degrader
SERM	selective estrogen receptor modulators
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	Single reference Safety Document
STD10	dose severely toxic to 10%
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Term
T bili	total bilirubin
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TK	toxicokinetic
T _{max}	time to maximum concentration
TNM	tumor, node and metastasis
TRAE	treatment-related adverse event
UAC _r	urine albumin-to-creatinine ratio
UPC _r	urine protein-to-creatinine ratio
ULN	upper limit of normal
UPM	unit probability mass
UPS	Ubiquitin-Proteosome System
US	United States
USPI	United State Prescribing Information
UV	ultraviolet
VTE	venous thromboembolism
WBC	white blood cell
WT	Wilde type
WOCBP	woman/women of childbearing potential

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