



## Title Page

**AN INTERVENTIONAL, OPEN-LABEL, RANDOMIZED, MULTICENTER,  
PHASE 2 STUDY OF PF-07220060 PLUS LETROZOLE COMPARED TO  
LETROZOLE ALONE IN POSTMENOPAUSAL WOMEN 18 YEARS OR OLDER  
WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER  
IN THE NEOADJUVANT SETTING**

|                                              |                                                               |
|----------------------------------------------|---------------------------------------------------------------|
| <b>Study Intervention Number:</b>            | PF-07220060                                                   |
| <b>Study Intervention Name:</b>              | NA                                                            |
| <b>US IND Number:</b>                        | 145,814                                                       |
| <b>EU CT Number:</b>                         | 2024-512848-30-00                                             |
| <b>ClinicalTrials.gov ID:</b>                | NCT06465368                                                   |
| <b>Pediatric Investigational Plan Number</b> | NA                                                            |
| <b>Protocol Number:</b>                      | C4391025                                                      |
| <b>Phase:</b>                                | 2                                                             |
| <b>Sponsor Legal Address:</b>                | Pfizer Inc.<br>66 Hudson Boulevard East<br>New York, NY 10001 |

**Brief Title:**

A Study to Learn About the Study Medicine Called PF-07220060 in Combination With Letrozole Compared to Letrozole Alone in Postmenopausal Women 18 Years or Older With HR-Positive, HER2-Negative Breast Cancer in the Neoadjuvant Setting

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## Document History

| Document                  | Version Date     |
|---------------------------|------------------|
| Amendment 2               | 25 November 2024 |
| Amendment 1 (Switzerland) | 03 October 2024  |
| Original protocol         | 27 March 2024    |

## Protocol Amendment Summary of Changes Table

This amendment incorporates all revisions to date, including amendments and protocol administration change letters made at the request of the country health authorities.

### Amendment 2, 25 November 2024

**Overall Rationale for the Amendment:** The primary rationale for this amendment is to apply to all regions the changes in the previous amendment for Switzerland and to provide clarification on key points of the study.

| Substantial Changes                                                                                                                 |                                                                                                                                                                     |                                 |
|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Change                                                                                                                              | Rationale                                                                                                                                                           | Section                         |
| Added text to clarify that prohibited drugs are prohibited throughout the conduct of the study and not just prior to the first dose | In response to a regulatory request from CHMP as updated in Protocol Amendment 1 (submitted to Switzerland), to clarify and align with Appendix 9                   | Section 6.9.1.1.1               |
| Added a new subsection to address concomitant medications which may result in DDI with letrozole                                    | In response to a regulatory request from CHMP as updated in Protocol Amendment 1 (submitted to Switzerland) to include potential DDI with letrozole                 | Section 6.9.2.1                 |
| Added list of UGT2B7 inhibitors and inducers, and modified washout period requirements for prohibited drugs                         | In response to a regulatory request from CHMP as updated in Protocol Amendment 1 (submitted to Switzerland) to include these for consistency with Section 6.9.1.1.1 | Section 10.9                    |
| Non Substantial Changes                                                                                                             |                                                                                                                                                                     |                                 |
| Added ClinicalTrials.gov ID                                                                                                         | To include regulatory agency ID number                                                                                                                              | Title Page<br>Protocol Synopsis |
| Added EU CT Number                                                                                                                  | To include regulatory agency ID number consistent with Title Page                                                                                                   | Protocol Synopsis               |
| Updated efficacy data in last paragraph                                                                                             | To provide updated data consistent with IB update                                                                                                                   | Section 2.2.1.1.1               |
| Added a statement to clarify that biopsies from multiple sites of multi-focal tumors are not required                               | To clarify that a biopsy from only one mass is required for multi-focal tumors                                                                                      | Section 8.2.1<br>Section 8.7.1  |

|                                                                                                                                                                                 |                                                                                                                                                                                      |                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Included guidelines for when there are discrepancies between central and local lab values, and provided window from Screening for when Day 1 labs would not need to be repeated | To confirm that treatment decisions and management of participants will be made at the investigator's discretion when there are discrepancies between local and central lab values   | Section 8.3.4                    |
| Added timing for when the D14 biopsy must be collected                                                                                                                          | To clarify the timing of the D14 biopsy sample in relation to the PK sample for participants in Arm A (Experimental)                                                                 | Section 8.7.1                    |
| Updated to reflect that the lab assessment analyses will summarize laboratory tests on the treatment period.                                                                    | To correct and error in the original protocol which indicated the analyses would be performed on the study period; made consistent with the SAP                                      | Section 9.3.5.3                  |
| Added clarifier to pre-dose PK sample note to indicate sample is collected in Arm A participants only                                                                           | Per PACL (July 2024)<br>To clarify that the PK samples are to be collected for those participants in Arm A only                                                                      | Section 1.3                      |
| Added clarifier to post-dose PK sample note to indicate sample is collected in Arm A participants only; added clarifier on timing of PK sample in relation to biopsy            | Per PACL (July 2024)<br>To clarify that the PK samples are to be collected for those participants in Arm A only and to clarify the timing of the biopsy in relation to the PK sample | Section 1.3                      |
| Updated use of letrozole to reflect its use as both an experimental treatment and an active comparator                                                                          | Per PACL (Sep 2024)<br>In response to a regulatory request to clarify the use of letrozole in this study                                                                             | Section 4.2.2<br>Section 6.1     |
| Revised Exclusion Criterion 9b to include correct eGFR calculation                                                                                                              | Per PACL (July 2024)<br>To correct the discrepancy between formula indicated for use in the EC versus the formula indicated for use in Appendix 7.                                   | Section 5.2                      |
| Updated to include letrozole is to be administered in the morning                                                                                                               | Per PACL (July 2024)<br>To specify time of administration to ensure there is no delay with the timing of the D14 assessments                                                         | Section 6.1.1.2                  |
| Added a statement clarify the acceptable timeframe for use of prior imaging                                                                                                     | Per PACL (July 2024)<br>To clarify the acceptable timeframe for which prior imaging can be used to confirm the primary tumor size (relative to Inclusion Criterion #4a)              | Section 8.2.1                    |
| Updated definition of "enrolled" to clarify the acceptable and intended use of a legally authorized representative in this study                                                | Per PACL (Sep 2024)<br>In response to a regulatory request to clarify the intended use of legally authorized representatives in this study                                           | Protocol Synopsis<br>Section 9.2 |
| Corrected the definition of the PK concentration analysis set                                                                                                                   | Per PACL (July 2024)<br>To clarify the PK concentration set description                                                                                                              | Section 9.2                      |

|                                                                                                  |                                                                                                                                                                                                                                          |                |
|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Added a clarifying statement that the actions taken are to mitigate the risk of reidentification | Per PACL (Oct 2024)<br>In response to a regulatory request to clarify the actions are to mitigate risks                                                                                                                                  | Section 10.1.9 |
| Updates made to address discrepancies between SoA and Appendix 2                                 | Per PACL (July 2024)<br>To correct the discrepancy between SoA and Appendix 2; to indicate that the D14 PT/INR and aPTT are assessed only if clinically indicated; to include Cystatin C as part of the chemistry panel                  | Section 10.2   |
| New section included to address country-specific requirements for the European Union             | To include a required appendix for country-specific requirements and including changes to the protocol applicable to the EU only in response to requests from the regulatory health agency (per EU-specific PACL Sept 2024 and Oct 2024) | Section 11     |

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## 1. PROTOCOL SUMMARY

### 1.1. Synopsis

#### Protocol Title:

An Interventional, Open-Label, Randomized, Multicenter Phase 2 Study of PF-07220060 Plus Letrozole Compared to Letrozole Alone in Postmenopausal Women 18 Years or Older With Hormone Receptor-Positive, HER2-Negative Breast Cancer in the Neoadjuvant Setting

**Brief Title:** A Study to Learn About the Study Medicine Called PF-07220060 in Combination With Letrozole Compared to Letrozole Alone in Postmenopausal Women 18 Years or Older With HR-Positive, HER2-Negative Breast Cancer in the Neoadjuvant Setting.

#### Regulatory Agency Identification Number(s):

|                                        |                   |
|----------------------------------------|-------------------|
| US IND Number:                         | 145,814           |
| EU CT Number:                          | 2024-512848-30-00 |
| ClinicalTrials.gov ID:                 | NCT06465368       |
| Pediatric Investigational Plan Number: | NA                |
| Protocol Number:                       | C4391025          |
| Phase:                                 | 2                 |

#### Rationale:

The purpose of this study is to evaluate the effects of PF-07220060, a small molecule highly potent cyclin-dependent kinase 4 (CDK4) inhibitor which is designed to interrupt the growth of cancer cells, plus letrozole and letrozole alone, a hormone therapy approved for the treatment of breast cancer (BC) in postmenopausal women on antigen Ki-67 (Ki-67) expression in tumors, after 2 weeks of treatment in participants with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative BC in the neoadjuvant setting, who have not been previously treated. Ki-67 is extensively used as a prognostic and predictive marker for cancer diagnosis and treatment, which may be an effective target in cancer therapy. The endpoint will further demonstrate activity of CDK4 in complete cell cycle arrest. In addition to current ongoing Phase 1/2 studies and translational work that has been done, this will inform further investigation in the early breast cancer setting.

## Objectives and Endpoints:

| Objectives                                                                                                                                                                                        | Endpoints                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary:</b>                                                                                                                                                                                   | <b>Primary:</b>                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>Evaluate the effects of PF-07220060 plus letrozole and letrozole alone, respectively, on Ki-67 expression in tumors after 2 weeks of treatment.</li> </ul> | <ul style="list-style-type: none"> <li>Complete cell cycle arrest (CCCA) (Ki-67 <math>\leq 2.7\%</math>) rates at Day 14 (centrally assessed biopsy).</li> </ul> |
| <b>Secondary:</b>                                                                                                                                                                                 | <b>Secondary:</b>                                                                                                                                                |
| <ul style="list-style-type: none"> <li>Evaluate the safety and tolerability of PF-07220060 plus letrozole and letrozole alone after 2 weeks of treatment.</li> </ul>                              | <ul style="list-style-type: none"> <li>Incidence of all adverse events (AEs), serious AEs, and AEs leading to study drug discontinuation.</li> </ul>             |
| <ul style="list-style-type: none"> <li>Evaluate ctDNA response on treatment after 2 weeks of treatment.</li> </ul>                                                                                | <ul style="list-style-type: none"> <li>ctDNA measurements at baseline and Day 14.</li> </ul>                                                                     |
| <ul style="list-style-type: none"> <li>To determine steady-state plasma concentrations of PF-07220060 in combination with letrozole.</li> </ul>                                                   | <ul style="list-style-type: none"> <li>C<sub>trough</sub> and peri-biopsy plasma concentrations of PF-07220060.</li> </ul>                                       |
| <ul style="list-style-type: none"> <li>Determine changes in Ki-67 expression.</li> </ul>                                                                                                          | <ul style="list-style-type: none"> <li>Ki-67 staining.</li> </ul>                                                                                                |

## Overall Design

This is a Phase 2 open-label, randomized, multicenter study of PF-07220060 plus letrozole compared to letrozole alone in participants with HR-positive, HER2-negative BC in the neoadjuvant setting to evaluate the biological activity of PF-07220060 plus letrozole and letrozole alone.

The study will target enrolling approximately 50 Ki-67 evaluable participants in each arm. The estimated total number of enrolled patients is 118 under the assumption that about 85% of the enrolled participants will have Ki-67 evaluable data. Participants will be randomized in a 1:1 manner to:

- Arm A (Experimental Arm; n = approximately 59): Participants will receive:
  - PF-07220060 300 mg, orally, twice daily (BID), continuously for 14 days, plus letrozole 2.5 mg, orally, once daily (QD), continuously for 14 days.
- Arm B (Control Arm; n = approximately 59): Participants will receive:
  - Letrozole 2.5 mg, orally, QD, continuously for 14 days (window of opportunity).

It is estimated that this sample size will provide approximately 50 evaluable participants with paired biopsies in the experimental arm and 50 evaluable participants with paired biopsies in the control arm (baseline, Day 14).

Participants will have both a baseline biopsy and an on-treatment biopsy (Day 14). The baseline biopsy must be de novo (newly collected fixed biopsy sample; sample collected for diagnosis is acceptable as long as it was collected within 3 months of study treatment initiation, no other treatment has occurred between biopsy and initiation of study treatment,

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and fulfills the sample collection requirements). After the 14-day treatment period, participants will come off study and continue on SOC therapy (e.g., surgery, radiotherapy, chemotherapy) per physician's choice.

### **Number of Participants**

Approximately 118 participants will be enrolled. The participants will be randomized to either the experimental arm (PF-07220060 plus letrozole) or the control arm (letrozole monotherapy) in a 1:1 ratio.

**Note:** "Enrolled" means a participant's agreement (which may include support from their legally authorized representative as permitted by local regulations) to participate in a clinical study following completion of the informed consent process and randomization to PF-07220060 plus letrozole or letrozole monotherapy. Legally authorized representatives are those who can assist a participant with the ICD process. It is not the intent of this study to include participants who are otherwise incapacitated and unable to consent for themselves.

**Study Population** Eligible participants include postmenopausal women (age  $\geq 18$  years) with histologically confirmed HR-positive and HER2-negative BC (per local assessment), documented by estrogen receptor (ER) and/or progesterone receptor (PR)-positive disease with ER or PR staining  $\geq 1\%$  of tumor cell nuclei, and documented HER2-negative disease by immunohistochemistry (IHC) or in situ hybridization (ISH). Participants must have Ki-67 score  $\geq 10\%$  with unilateral, invasive T1c-T4c, N0-N2, M0 BC. Participants must be willing and able to undergo a baseline and Day 14 biopsy, and must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Participants must be treatment naïve for the treatment of BC and cannot have had prior treatment with any systemic therapy (e.g., chemotherapy, hormonal therapy), radiation, surgery, or any investigational agents or use of hormone replacement therapy (HRT) or any other estrogen-containing medication (including vaginal estrogen) within 2 weeks prior to diagnostic tissue sample taken.

### **Study Arms and Duration:**

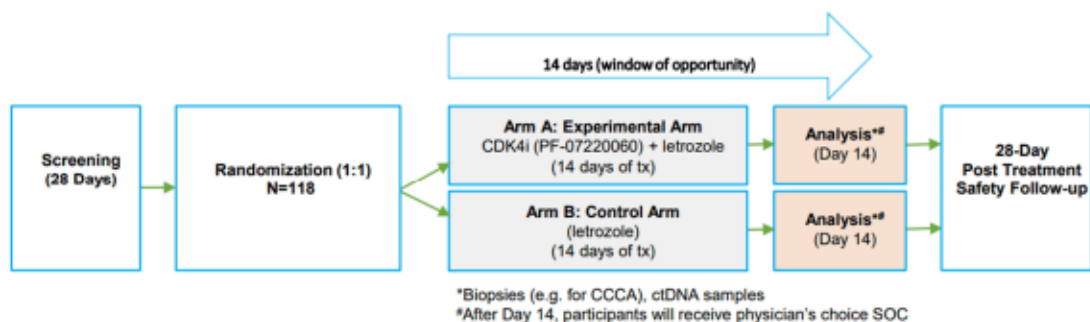
The study interventions are administered for 14 days.

| Study Arm(s)    |                                                                                                                                                                                                                                                                      |                                                                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Arm Title       | Arm A<br>PF-07220060 + letrozole                                                                                                                                                                                                                                     | Arm B<br>letrozole                                                                                                                                 |
| Arm Type        | Experimental                                                                                                                                                                                                                                                         | Control                                                                                                                                            |
| Arm Description | Participants will receive: <ul style="list-style-type: none"> <li>PF-07220060 as three 100 mg tablets (i.e., 300 mg), orally, BID with food continuously for 14 days, plus</li> <li>letrozole as one 2.5 mg tablet, orally, QD continuously for 14 days .</li> </ul> | Participants will receive: <ul style="list-style-type: none"> <li>letrozole as one 2.5 mg tablet, orally, QD, continuously for 14 days.</li> </ul> |

#### Ethical Considerations:

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. Based on preliminary data, PF-07220060 has demonstrated favorable safety and efficacy. Based on preliminary experience with PF-07220060 and the well-known safety profile of the approved CDK4/6 inhibitors the potential risks for PF-07220060 include neutropenia, interstitial lung disease (ILD)/pneumonitis, gastrointestinal (GI) disorders, e.g., diarrhea, nausea and vomiting, decreased appetite, and testicular and embryo-fetal toxicity. All known potential risks are considered as manageable and will be monitored and managed according to the protocol and institutional standard of care. Furthermore, if deemed an appropriate candidate for neoadjuvant endocrine therapy, treatment within a window of opportunity setting will not be a detriment to expected prognosis.

## 1.2. Schema



### 1.3. Schedule of Activities

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

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

**Table 1. Schedule of Activities**

| Visit Identifier<br>Abbreviations used in this table may be found in <a href="#">Appendix 10</a> .<br><br>Study Day | Screen (within 28 days of Day 1 unless otherwise noted) | Treatment Period (14 days) |             | Follow-Up Visit               | Notes                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------|-------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                     |                                                         | Day 1                      | Day 14/ EOT | 28 Days after Last Study Dose |                                                                                                                                                                                                                                                    |
| Visit Window (days)                                                                                                 |                                                         | NA                         | +3          | +7                            | <ul style="list-style-type: none"> <li>Day relative to start of study intervention (Day 1).</li> <li>Contact may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.</li> </ul> |
| Informed consent                                                                                                    | X                                                       |                            |             |                               | <ul style="list-style-type: none"> <li>All screening should be done <math>\leq 28</math> days before the first dose.</li> <li>See <a href="#">Section 8.4.3</a> for follow-up AE and SAE assessments.</li> </ul>                                   |
| Screen for inclusion/exclusion criteria                                                                             | X                                                       |                            |             |                               | <ul style="list-style-type: none"> <li>Informed consent should be obtained prior to performing testing for eligibility.</li> <li>See <a href="#">Section 10.1.3</a> for additional information.</li> </ul>                                         |
| Demographics, Oncological/Medical history                                                                           | X                                                       |                            |             |                               | <ul style="list-style-type: none"> <li>See <a href="#">Sections 5.1</a> and <a href="#">5.2</a> for additional information.</li> </ul>                                                                                                             |
| Complete PE                                                                                                         | X                                                       | X                          |             |                               | <ul style="list-style-type: none"> <li>Include disease process (e.g., staging) and concurrent illness, including prior treatments. See <a href="#">Section 8.1.1</a>.</li> </ul>                                                                   |
| Abbreviated (symptom-directed) PE                                                                                   |                                                         |                            | X           | X                             | <ul style="list-style-type: none"> <li>See <a href="#">Section 8.3.1</a> for additional information.</li> <li>Physical examinations to be completed before administration of study intervention.</li> </ul>                                        |
| ECOG PS                                                                                                             | X                                                       |                            |             |                               | <ul style="list-style-type: none"> <li>Abbreviated PE is symptom-based.</li> </ul>                                                                                                                                                                 |
|                                                                                                                     |                                                         |                            |             |                               | <ul style="list-style-type: none"> <li>ECOG PS should be 0 or 1 during screening.</li> </ul>                                                                                                                                                       |

**Table 1. Schedule of Activities**

| Visit Identifier<br>Abbreviations used in this table may be found in <a href="#">Appendix 10</a> . | Screen (within 28 days of Day 1 unless otherwise noted) | Treatment Period (14 days) |                 | Follow-Up Visit               | Notes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------|-----------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Day                                                                                          |                                                         | Day 1                      | Day 14/<br>EOT  | 28 Days after Last Study Dose | <ul style="list-style-type: none"> <li>Day relative to start of study intervention (Day 1).</li> <li>Contact may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                  |
| Visit Window (days)                                                                                |                                                         | NA                         | +3              | +7                            | <ul style="list-style-type: none"> <li>All screening should be done <math>\leq 28</math> days before the first dose.</li> <li>See <a href="#">Section 8.4.3</a> for follow-up AE and SAE assessments.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                    |
| Vital signs                                                                                        | X                                                       | X                          | X               |                               | <ul style="list-style-type: none"> <li>Includes height (at screening only), weight, temperature, BP, pulse rate, respiratory rate (record in sitting or semi-recumbent position [recommended] after 5 minutes rest).</li> <li>See <a href="#">Section 8.3.2</a> for additional information.</li> </ul>                                                                                                                                                                                                                                                                                                              |
| 12-Lead ECG                                                                                        | X                                                       | X<br>(pre-dose)            | X<br>(pre-dose) | X                             | <ul style="list-style-type: none"> <li>See <a href="#">Section 8.3.3</a> for additional information.</li> <li>Screening ECG will be a single 12-lead ECG, performed on site</li> <li>Day 14 ECG performed prior to pre-dose PK/Labs collection</li> <li>During follow-up, if clinically indicated</li> </ul>                                                                                                                                                                                                                                                                                                        |
| Prior/Concomitant treatment(s)                                                                     | X                                                       | X                          | X               | X                             | <ul style="list-style-type: none"> <li>All medications or medical treatments including over-the-counter medications and/or herbal supplements taken up to 28 days prior to enrollment, through treatment period, and during follow-up.</li> <li>See <a href="#">Section 6.9</a> for additional information</li> </ul>                                                                                                                                                                                                                                                                                               |
| Tumor biopsy (FFPE)                                                                                | X                                                       |                            | X               |                               | <ul style="list-style-type: none"> <li>At screening, core needle biopsies of the primary breast tumor must be collected during baseline. Fine needle aspirations are not allowed. It is possible to use the initial tumor biopsy from diagnosis provided no treatment occurred between collection and study treatment start and is within 3 months.</li> <li>Core biopsies at Day 14 visit must be obtained from the same site as the baseline/pre-dose biopsy, if possible, and must be collected post PK sample collection.</li> <li>Specimens must be processed and shipped per the Laboratory Manual</li> </ul> |

**Table 1. Schedule of Activities**

| Visit Identifier<br>Abbreviations used in this table may be found in <a href="#">Appendix 10</a> . | Screen (within 28 days of Day 1 unless otherwise noted) | Treatment Period (14 days) |                | Follow-Up Visit               | Notes                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------|----------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Day                                                                                          |                                                         | Day 1                      | Day 14/<br>EOT | 28 Days after Last Study Dose | <ul style="list-style-type: none"> <li>Day relative to start of study intervention (Day 1).</li> <li>Contact may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.</li> </ul>                                                                                                     |
| Visit Window (days)                                                                                |                                                         | NA                         | +3             | +7                            | <ul style="list-style-type: none"> <li>All screening should be done <math>\leq 28</math> days before the first dose.</li> <li>See <a href="#">Section 8.4.3</a> for follow-up AE and SAE assessments.</li> </ul>                                                                                                                                       |
| ctDNA sample                                                                                       |                                                         | X                          | X              |                               | <ul style="list-style-type: none"> <li>Plasma sample collection predose (Day 1, Day 14). Specimens must be processed and shipped per the Laboratory Manual.</li> <li>Samples collected from all participants in Arm A and Arm B</li> </ul>                                                                                                             |
| <b>Laboratory Assessments</b>                                                                      |                                                         |                            |                |                               | <ul style="list-style-type: none"> <li>See <a href="#">Section 8.3.4</a> for additional information.</li> <li>See <a href="#">Appendix 2</a> for a list of Clinical Laboratory tests to be done.</li> <li>For laboratory collection volumes, see the laboratory manual.</li> </ul>                                                                     |
| Hematology                                                                                         | X                                                       | X                          | X              | X                             | <ul style="list-style-type: none"> <li>Hematology includes hemoglobin, WBC, absolute neutrophils, platelets. Additional hematology may be performed as clinically indicated.</li> <li>Day 1: Not required if acceptable screening assessment is performed within 3 days of randomization</li> <li>During follow-up, if clinically indicated</li> </ul> |
| Blood chemistry                                                                                    | X                                                       | X                          | X              | X                             | <ul style="list-style-type: none"> <li>During follow-up, if clinically indicated</li> <li>Day 1: Not required if acceptable screening assessment is performed within 3 days of randomization</li> </ul>                                                                                                                                                |
| Urinalysis                                                                                         | X                                                       | X                          |                |                               | <ul style="list-style-type: none"> <li>Urine dipstick testing is acceptable.</li> <li>Day 1: Not required if acceptable screening assessment is performed within 3 days of randomization</li> </ul>                                                                                                                                                    |
| Coagulation                                                                                        | X                                                       | X                          | X              |                               | <ul style="list-style-type: none"> <li>Day 1: Not required if acceptable screening assessment is performed within 3 days of randomization</li> <li>Day 14, if clinically indicated.</li> </ul>                                                                                                                                                         |
| Viral disease screening                                                                            | X                                                       |                            |                |                               | <ul style="list-style-type: none"> <li>HIV testing if required by local regulations.</li> </ul>                                                                                                                                                                                                                                                        |

**Table 1. Schedule of Activities**

| Visit Identifier<br>Abbreviations used in this table may be found in <a href="#">Appendix 10</a> . | Screen (within 28 days of Day 1 unless otherwise noted) | Treatment Period (14 days)    |                | Follow-Up Visit               | Notes                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------|----------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Day                                                                                          |                                                         | Day 1                         | Day 14/<br>EOT | 28 Days after Last Study Dose | <ul style="list-style-type: none"> <li>Day relative to start of study intervention (Day 1).</li> <li>Contact may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.</li> </ul>                                                                |
| Visit Window (days)                                                                                |                                                         | NA                            | +3             | +7                            | <ul style="list-style-type: none"> <li>All screening should be done <math>\leq 28</math> days before the first dose.</li> <li>See <a href="#">Section 8.4.3</a> for follow-up AE and SAE assessments.</li> </ul>                                                                                                  |
| Documentation of clinical TNM stage                                                                | X                                                       |                               |                |                               | <ul style="list-style-type: none"> <li>Clinical TNM stage, along with the imaging modality utilized for staging, must be documented in the eCRF.</li> <li>Imaging from up to 3 months prior to initiation of study treatment is acceptable</li> </ul>                                                             |
| FSH (as applicable)                                                                                | X                                                       |                               |                |                               | <ul style="list-style-type: none"> <li>To confirm a postmenopausal status of female participants under 60 years of age, cessation of regular menses for 12 consecutive months and with no alternative medical cause. See <a href="#">Appendix 2</a>.</li> </ul>                                                   |
| <b>Randomization</b>                                                                               |                                                         |                               |                |                               |                                                                                                                                                                                                                                                                                                                   |
| Randomization                                                                                      |                                                         | Day 1 (pre-dose)              |                |                               | <ul style="list-style-type: none"> <li>Randomization must occur after having carefully reviewed all eligibility criteria and confirmed they are satisfied.</li> <li>At randomization, participant number and treatment arm are assigned.</li> <li>May occur up to -3 days prior to Day 1 if necessary.</li> </ul> |
| <b>Study intervention and other treatments</b>                                                     |                                                         |                               |                |                               | <ul style="list-style-type: none"> <li>See <a href="#">Section 6</a> for additional information.</li> </ul>                                                                                                                                                                                                       |
| Letrozole administration                                                                           |                                                         | QD continuously until biopsy  |                |                               | <ul style="list-style-type: none"> <li>Orally in the morning, with or without food.</li> <li>On Day 14 (or day of biopsy), the dose will be administered in the clinic</li> </ul>                                                                                                                                 |
| PF-07220060 administration                                                                         |                                                         | BID continuously until biopsy |                |                               | <ul style="list-style-type: none"> <li>Orally with food.</li> <li>On Day 14 (or day of biopsy), only the morning dose is required and will be administered in the clinic</li> </ul>                                                                                                                               |
| Compliance / patient diary                                                                         |                                                         | X                             | X              |                               | <ul style="list-style-type: none"> <li>Confirm and reconcile return of the bottle and remaining tablets of study interventions, as well as the completed patient diary.</li> </ul>                                                                                                                                |

**Table 1. Schedule of Activities**

| Visit Identifier<br>Abbreviations used in this table may be found in <a href="#">Appendix 10</a> . | Screen (within 28 days of Day 1 unless otherwise noted) | Treatment Period (14 days) |                | Follow-Up Visit               | Notes                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------|----------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Day                                                                                          |                                                         | Day 1                      | Day 14/<br>EOT | 28 Days after Last Study Dose | <ul style="list-style-type: none"> <li>Day relative to start of study intervention (Day 1).</li> <li>Contact may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.</li> </ul>                                                                                                                                             |
| Visit Window (days)                                                                                |                                                         | NA                         | +3             | +7                            | <ul style="list-style-type: none"> <li>All screening should be done <math>\leq 28</math> days before the first dose.</li> <li>See <a href="#">Section 8.4.3</a> for follow-up AE and SAE assessments.</li> </ul>                                                                                                                                                                               |
| Serious and nonserious AE monitoring                                                               | X                                                       | X                          | X              | X                             | <ul style="list-style-type: none"> <li>See <a href="#">Section 8.4</a> for additional information.</li> </ul>                                                                                                                                                                                                                                                                                  |
| <b>Pharmacokinetic Assessments</b>                                                                 |                                                         |                            |                |                               |                                                                                                                                                                                                                                                                                                                                                                                                |
| Blood Sample for PF-07220060 PK (pre-dose)                                                         |                                                         |                            | X              |                               | <ul style="list-style-type: none"> <li>Pre-dose PF-07220060 PK sample should be collected within 30 minutes prior to dosing in participants randomized to Arm A (Experimental) only.</li> <li>See <a href="#">Section 8.5</a> and Laboratory Manual.</li> </ul>                                                                                                                                |
| Blood Sample for PF-07220060 PK (post-dose)                                                        |                                                         |                            | X              |                               | <ul style="list-style-type: none"> <li>Post-dose PF-07220060 PK sample should be collected 1 hour before or 1 hour after biopsy, in participants randomized to Arm A (Experimental) only.</li> <li>See <a href="#">Section 8.5</a> and Laboratory Manual.</li> </ul>                                                                                                                           |
| Blood Sample for Pharmacogenomics (Arm A only)                                                     |                                                         | X                          |                |                               | <ul style="list-style-type: none"> <li>Post-randomization, pre-dose in participants randomized to Arm A (Experimental) only</li> <li>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.</li> <li>See <a href="#">Section 8.6.1.1</a> and Laboratory Manual.</li> </ul> |

Note: Assessments should be performed prior to dosing on the visit day. On mornings where participants are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite.

For screening activities, additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

## 2. INTRODUCTION

PF-07220060 is a selective CDK4 inhibitor that is being investigated in this study for participants with HR-positive, HER2-negative breast cancer in the neoadjuvant setting.

### 2.1. Study Rationale

The purpose of the study is to evaluate the effects of PF-07220060 plus letrozole and letrozole alone, respectively, on Ki-67 expression in tumors after 2 weeks of treatment in participants with postmenopausal, HR-positive, HER2-negative early BC in the neoadjuvant setting, who have not been previously treated. Ki-67 is extensively used as a prognostic and predictive marker for cancer diagnosis and treatment, which may be an effective target in cancer therapy. The endpoint will further demonstrate activity of CDK4 in CCCA and, in addition to current ongoing Phase 1/2 studies and translational work that has been done, will inform further investigation in the early breast cancer setting.

PF-07220060 is a small molecule highly potent inhibitor of CDK4, which differs from currently approved dual CDK4/6i (e.g., 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 allows PF-07220060 to attain higher tolerated plasma concentrations and better target coverage, potentially allowing greater inhibition of the CDK4 in tumors. In the first-in-human study, PF-07220060 has shown early evidence of efficacy when combined with endocrine therapy (letrozole or fulvestrant) in advanced breast cancer after multiple prior lines of systemic therapies.

### 2.2. Background

#### **Breast Cancer**

BC is estimated to be the most diagnosed among all cancer types, having surpassed lung cancer, and is the leading cause of cancer death among women in 2020 ([Sung et al, 2021](#)). Approximately, 0.5%-1% of BCs occur in men. BC occurs in every country of the world in women at any age after puberty but with rates increasing in later life. GLOBOCAN estimated 2.3 million new cases of BC in 2020 (representing 11.7% of all cancer cases) and 685,000 deaths making it the fifth leading cause of cancer mortality worldwide ([Sung et al, 2021](#)). As of the end of 2020, the WHO estimated that there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer ([WHO, 2023](#)).

In Europe, there were an estimated 531,086 new cases of BC in 2020 and an estimated 141,765 deaths from the disease. The 2020 incidence estimate trends across EU-27 countries were mainly increasing, likely related to reproductive factors, increasing obesity and physical inactivity as well as increased screening intensity. Mortality trends in the EU-27, on the other hand, tend to be in decline likely due to effective treatment and tools for detecting the disease at early stages. Estimated age-adjusted breast cancer incidence rates range from 100 through 194 per 100,000. Age-adjusted death rates ranged from 23.8 to 49.3 ([ECIS, 2020](#)).

In the US, a total of 300,590 incident cases of BC were estimated for 2023. 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. From 2016 to 2020, in the US, the estimated age-adjusted rate of new cases of breast cancer was 126.9 per 100,000 women per year and has remained stable from the estimate of 127.5 for the prior period 2012-2016. The US estimated age-adjusted mortality rate from breast cancer was just slightly lower in 2016-2020 than the prior period of 2012 to 2016 with a rate of death of 19.5 vs 20.6 per 100,000 women per year respectively. In 2020, there were 3,886,830 women alive who were diagnosed with breast cancer in the US (Siegel et al, 2023).

The estimated BC incidence and mortality rates vary widely geographically. National differences can in part be explained by varying levels of healthcare expenditure and resulting quality of diagnosis and treatment, with countries with a low HDI carrying a disproportionate share of breast cancer deaths. Age adjusted mortality rate due to BC are estimated to be 20.1 compared to the worldwide risk of 13.6. By 2040, about 3 million new breast cancer cases are expected, an increase of about 40%, with deaths attributed to BC almost doubling to be about 1 million, worldwide (Arnold et al, 2022).

### **Neoadjuvant Endocrine Therapy for HR+/HER2- eBC**

Pre-operative therapy (i.e., neoadjuvant therapy) can be potentially down staged and improve suitability of breast conservation for EBC. Neoadjuvant chemotherapy (NCT) has been the mainstay in this indication and no endocrine therapy has been approved for treatment in the neoadjuvant setting. However, neoadjuvant ET (NET) has been given to select patients considered to be appropriate recipients in clinical practice.

In addition, clinical trials evaluating pre-operative endocrine therapy in ER+, HER2- BC have been conducted as they allow for rapid assessment of novel therapeutic approaches (Guerrero-Zotano & Arteaga, 2017; Denduluri et al, 2018). Some of the trials were designed as window-of-opportunity studies in which the study drugs were given for a short period (e.g., 2-4 weeks) prior to surgery and/or additional pre-operative treatments; the efficacy evaluation focused on biomarkers (e.g., Ki-67). The other trials were designed as treatment studies in which the study drugs were given with a longer period of 3-6 months, and the efficacy evaluation included both biomarkers and clinical measures, such as the rates of OR, tumor downstaging, and BCS.

Several trials evaluating pre-operative endocrine therapy have focused on biologic activity endpoints in tumor samples (Ellis et al, 2011). Ki-67 has been used as biomarker to assess the activity of agents targeting the ER pathway. Several trials have assessed the reduction of Ki-67  $\leq 2.7\%$  (CCCA) in tumor biopsies and demonstrated that reduction in Ki-67 in the neoadjuvant setting correlates with relapse free survival after definitive surgical resection (Ellis et al, 2008; Smith et al, 2020) and with beneficial outcomes in the adjuvant or metastatic setting (Guerrero-Zotano & Arteaga, 2017). For example, the improved Ki-67 suppression with AIs compared with tamoxifen in the neoadjuvant setting in the IMPACT and P024 trial (Smith et al, 2005; Ellis et al, 2008) parallels the improved disease-free survival seen with AIs in the adjuvant setting (Ellis et al, 2008). Furthermore, the similarity in Ki-67 suppression between nsAIs and sAIs in the neoadjuvant setting (Ellis et al, 2011) parallels the similar disease-free survival with these agents in the adjuvant setting (Breast International Group 1-98 Collaborative et al, 2005; Howell et al, 2005).

CDK4/6 inhibition was identified as a mechanism to circumvent deregulated cell-cycle progression, halting transition through the G1 phase of the cell cycle; importantly, this strategy was found to be synergistic when combined with ET for HR-positive BC cells and disease models (Spring et al, 2020). The CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, and ribociclib) in combination with ET have consistently demonstrated superior efficacy on PFS and/or OS over ET for HR+/HER2- aBC and have been approved and recommended by clinical guidelines as the first-line therapy (NCCN, 2023).

A number of clinical studies have been conducted to evaluate the CDK4/6i plus ET in the neoadjuvant setting, which have consistently shown enhanced anti-proliferative activity as measured by Ki-67 (Johnston et al, 2019; Hurvitz et al, 2020; Prat et al, 2020; Gil-Gil et al, 2021). The neoMonarch study positively predicted the success of abemaciclib plus letrozole in the adjuvant setting.

## 2.2.1. Clinical Overview

### 2.2.1.1. PF-07220060

PF-07220060 is a selective CDK4 inhibitor that is currently being investigated in participants with metastatic or advanced solid tumors.

CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, ribociclib), when dosed in combination with ET, have significantly improved PFS and/or OS and the toxicity profile is generally manageable in HR-positive, HER2-negative mBC (Spring et al, 2020). Cytopenias, and specifically neutropenia, are very commonly observed, on target AEs for all CDK4/6 inhibitors. Neutropenia is believed to be mediated mainly by inhibition of CDK6 rather than CDK4 in the neutrophil and its progenitors (Maurer et al, 2021). Higher doses and/or continuous daily dosing of palbociclib are not tolerated due to the dose limiting toxicities from cytopenias. Therefore, an intermittent dosing schedule of 3-weeks on and 1-week off has been the approved regimen.

PF-07220060 is a highly potent and selective inhibitor of CDK4 in complex with cyclin D1, D2, and D3. In preclinical BC cell lines, PF-07220060 induced G1 cell cycle arrest and cellular senescence, consistent with CDK4 inhibition. A survey of human cancer lines derived from a broad variety of human tumor types revealed that HR-positive, HER2-negative BC cell lines display the greatest degree of CDK4 dependency. Consistent with this, in-vivo, single agent PF-07220060 showed significant tumor growth inhibition in xenograft and PDx models of HR-positive, HER2-negative BC. In dog studies, palbociclib induced Grade 2 equivalent neutropenia at 100 nM in plasma whereas PF-07220060 induced the same level of neutropenia at 1500 nM, suggesting PF-07220060 has a wider safety margin for neutropenia. Taken together, these features of PF-07220060 may allow participants to receive doses which lead to higher exposure to block the CDK4/6-Rb-axis continuously while maintaining neutrophil counts. Thus, it is postulated as an overarching hypothesis that sparing CDK6 activity allows for increased exposure of a CDK4 selective inhibitor. This would then translate to increased CDK4 target coverage (vs palbociclib and other dual CDK4/6 inhibitors), thus permitting maximal and continuous inhibition of the CDK4 oncogene (CDK4 selective inhibitor thereafter). As a result, superior clinical responses, with tumor regression as well as increased response durability, may be achievable in mBC and in

other tumor types relying on CDK4 kinase activity. Consistent with this hypothesis, we further postulate that insufficient CDK4 target coverage by dual CDK4/6 inhibitors would leave CDK4 kinase activity in some HR-positive, HER2-negative tumors in a partially active state; such CDK4-dependent tumors may thus continue to grow during treatment with these agents. Hence, we postulate that PF-07220060, through increased CDK4 target coverage, may inhibit the growth of some tumors that progressed in the presence of dual CDK4/6 inhibitors.

#### 2.2.1.1.1. Preliminary Safety and Efficacy Data in Humans

##### PF-07220060

A Phase 1/2a multi-part, dose escalation, finding and expansion study (C4391001) is ongoing. The study evaluates 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.

As of August 2023, a total of 205 participants with advanced breast cancer, prostate cancer, and other solid tumors have received PF-07220060 in Study C4391001, including 129 participants in Part 1, 64 participants in Part 2, 9 participants in China monotherapy cohort and 3 participants in Japan monotherapy cohort.

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. 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 1B, participants with advanced or mBC received letrozole together with PF-07220060. In Part 1C, participants with advanced or mBC received fulvestrant with PF-07220060. Part 1D is to assess the effect of food on the PK of PF-07220060. Part 1E is to assess the potential DDI between midazolam and PF-07220060 given at the MTD or RDE established in Part 1A. In Part 1F, participants with metastatic prostate cancer will receive PF-07220060 in combination with enzalutamide.

Part 2A is an expansion cohort for combination therapy of PF-07220060 with fulvestrant in participants with HR-positive/HER2-negative advanced or mBC who have disease progression following prior CDK4/6i treatment. Part 2B is an expansion cohort of PF-07220060 in combination with letrozole in participants with HR-positive, HER2-negative advanced or mBC who have not received any prior systemic anti-cancer therapies for the advanced disease. Part 2C is an expansion cohort of PF-07220060 in combination with fulvestrant in participants with HR-positive, HER2-negative advanced or mBC whose disease has progressed on prior endocrine therapy. Part 2D is an expansion cohort of PF-07220060 in combination with enzalutamide at the dose identified in Part 1F in participants with mCRPC.

In Part 1, of the 101 participants evaluable for DLTs, 3 (3.0%) participants experienced DLTs; 2 (50.0%) participants from Part 1A PF-07220060 500 mg BID group experienced

DLTs of Grade 3 thrombocytopenia, and 1 (14.3%) participant from Part 1C PF-07220060 400 mg BID plus fulvestrant group experienced DLT of Grade 3 neutropenia and Grade 3 leukopenia. No DLTs were reported at the PF-07220060 RDE 300 mg BID in monotherapy or in combination.

Overall, in Part 1, 120 (93.0%) participants reported 766 all-causality TEAEs. Forty-one (31.8%) participants reported Grade 3 and 2 (1.6%) reported Grade 4 TEAEs and 2 (1.6%) participants experienced Grade 5 TEAEs.

In Part 1A, all (N=34) participants reported 238 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were neutrophil count decreased (47.1%), anaemia (38.2%), diarrhea, white blood cell count decreased, nausea (35.3% each), aspartate aminotransferase increased, platelet count decreased (23.5% each), and fatigue and vomiting (20.6% each). Fifteen (44.1%) participants reported Grade 3 TEAEs. There were no Grade 4 TEAEs reported. One (2.9%) participant experienced Grade 5 TEAE of respiratory failure, which was not considered study treatment related.

In Part 1B, 27 (90.0%) of the 30 participants reported 134 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were diarrhea and nausea (36.7% each), neutrophil count decreased (33.3%), and anaemia and fatigue (23.3% each). Nine (30.0%) participants reported Grade 3 TEAEs. One (3.3%) participant reported Grade 4 TEAE of hypokalaemia. There were no Grade 5 TEAEs reported.

In Part 1C, 33 (86.8%) of the 38 participants reported 283 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were neutrophil count decreased (39.5%), white blood cell count decreased (31.6%), diarrhea and hyperglycaemia (28.9% each), nausea (26.3%), and arthralgia, fatigue (23.7% each), platelet count decreased (21.1%). Nine (23.7%) participants reported Grade 3 TEAEs. There were no Grade 4 TEAEs reported. One (2.6%) participant experienced Grade 5 TEAE of disease progression.

In Part 1D, all (N=6) participants reported 43 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were neutrophil count decreased (66.7%), diarrhea, rash, white blood cell count decreased (50.0%), blood creatinine increased, dry skin, fatigue (33.3%). Two (33.3%) participants reported Grade 3 TEAEs. One (16.7%) participant reported Grade 4 TEAE of respiratory failure. There were no Grade 5 TEAEs reported.

In Part 1E, all (N=4) participants reported 16 all-causality TEAEs. The most frequently reported ( $\geq 50\%$ ) all-causality TEAE was neutrophil count decreased (75.0%). Two (50.0%) participants reported Grade 3 TEAEs. There were no Grade 4 or 5 TEAEs reported.

In Part 1F, 16 (94.1%) participants reported 52 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were fatigue (35.3%), and neutrophil count decreased and platelet count decreased (23.5% each). Four (23.5%) participants reported Grade 3 TEAEs. There were no Grade 4 or 5 TEAEs reported.

In Part 2, 56 (87.5%) of the 64 participants reported 314 all-causality TEAEs. Twenty (31.3%) participants reported Grade 3 TEAEs. There were no Grade 4 TEAEs reported. Two (3.1%) participants experienced Grade 5 TEAEs not considered study treatment related.

In Part 2A, 2 (66.6%) of the 3 participants reported 9 all-causality TEAEs that were Grade 1 or 2. There were no Grade 3 or higher TEAEs reported.

In Part 2B, 33 (97.1%) of the 34 participants reported 150 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were neutropenia (41.2%), neutrophil count decreased (20.6%), and hyperglycaemia, white blood cell count decreased (23.5%). Thirteen (38.2%) participants reported Grade 3 TEAEs. There were no Grade 4 TEAEs reported. One (2.9%) participant reported Grade 5 TEAE of respiratory distress.

In Part 2C, 21 (77.8%) of the 27 participants reported 155 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were white blood cell count decreased (29.6%), anaemia (25.9%), diarrhea, nausea, neutropenia (22.2% each). Seven (25.9%) participants reported Grade 3 TEAEs. There were no Grade 4 TEAEs reported. One (3.7%) participant reported Grade 5 TEAE of disease progression.

In China monotherapy cohort, all (N=9) participants reported 55 all-causality TEAEs. The most frequently reported ( $\geq 20\%$ ) all-causality TEAEs were neutrophil count decreased, white blood cell count decreased (77.8% each), anaemia, aspartate aminotransferase increased, cough and hyperglycaemia (33.3% each), hypertriglyceridaemia, hyperuricaemia, blood alkaline phosphatase increased, gamma-glutamyl transferase increased (22.2%). Six (66.7%) participants reported Grade 3 TEAEs. There were no Grade 4 or 5 TEAEs reported.

There were no TEAEs reported in Japan monotherapy cohort (N=3).

As of 11 July 2024, PF-07220060 has demonstrated signs of anti-tumor activity in combination with endocrine therapy in HR-positive, HER2-negative mBC participant population in Parts 1B and 1C of Study C4391001. Confirmed objective responses per RECIST v1.1 were observed in 8/25 (32% [95% CI: 14.9, 53.5]) participants (1 complete response, 7 partial responses) with HR-positive, HER2-negative mBC with measurable disease who progressed on prior CDK4/6i plus ET and were treated with PF-07220060 (300/400 mg BID) plus ET. Clinical benefit response was observed for 20/33 (60.6%) participants. Median PFS was 8.1 months (95% CI: 5.3, 10.9) (Yap et al, 2024).

#### 2.2.1.2. Letrozole

Letrozole has been approved worldwide and used as standard of care for the first-line hormonal treatment of postmenopausal women with ER-positive advanced breast cancer, and has demonstrated efficacy in combination with CDK4/6 inhibitors like palbociclib.

Letrozole has also been studied in the neoadjuvant setting as monotherapy and/or in combination with CDK4/6i. In the PALLET study, clinical response at week 14 was not significantly different between palbociclib plus letrozole and letrozole groups ( $p=0.20$ ; CR + PR, 54.4% versus 49.5%), and progressive disease was 3.2% versus 5.4%, respectively (Johnston et al, 2019). Median log-fold change in Ki-67 was greater with palbociclib plus letrozole compared with letrozole (-4.1 versus -2.2;  $p < 0.001$ ) in the 190 evaluable patients (61.9%), corresponding to a geometric mean change of -97.4% versus -88.5%. More patients on palbociclib plus letrozole achieved complete cell-cycle arrest (90% versus 59%;  $p < 0.001$ ). Median log-fold change (suppression) of cleaved poly (ADP-ribose) polymerase

was greater with palbociclib plus letrozole versus letrozole (-0.80 versus -0.42;  $p < 0.001$ ). Adding palbociclib to letrozole significantly enhanced the suppression of malignant cell proliferation (Ki-67) in primary ER-positive BC.

### 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07220060 may be found in the most current version of the IB, and in the UK SmPC for letrozole, which are the SRSDs 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                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PF-07220060</b>                                                                                                         |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                             |
| Potential risks associated with PF-07220060 include:                                                                       | <p>PF-07220060 IB</p> <p>The primary target organs identified in exploratory and 1-month pivotal GLP toxicity studies were the gastrointestinal tract, hematolymphopoietic system, and the testes.</p> | <p>Eligibility criteria have been selected to ensure that only appropriate participants, who are not at apparent increased risk, are included in the study (Section 5).</p> <p>Dose modification guidelines for study intervention toxicity are provided (Section 6.6).</p> |
| <p>Hematologic</p> <ul style="list-style-type: none"> <li>neutropenia</li> <li>thrombocytopenia</li> <li>anemia</li> </ul> |                                                                                                                                                                                                        | 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 (Section 6.6).                   |
| <ul style="list-style-type: none"> <li>ILD/pneumonitis</li> </ul>                                                          |                                                                                                                                                                                                        | Monitor participant for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). Investigator will instruct participants to promptly contact sites for any new or worsening respiratory symptoms associated with ILD/pneumonitis.                  |
| <ul style="list-style-type: none"> <li>gastrointestinal disorders (stomatitis, diarrhea, nausea, vomiting)</li> </ul>      |                                                                                                                                                                                                        | Careful monitoring for GI disorders (e.g., stomatitis, diarrhea, nausea, vomiting) will be conducted. Investigator will instruct participants to promptly contact sites for any new or worsening GI symptoms.                                                               |
| <ul style="list-style-type: none"> <li>metabolism and nutrition disorders (decreased appetite)</li> </ul>                  |                                                                                                                                                                                                        | Careful monitoring of appetite and body weight will be conducted.                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>testicular and embryo-fetal toxicity</li> </ul>                                     |                                                                                                                                                                                                        | Per inclusion criterion 1, only postmenopausal women are included.                                                                                                                                                                                                          |
| <b>Letrozole</b>                                                                                                           |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                             |
| Potential risks associated with letrozole include:                                                                         |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>Bone effects</li> </ul>                                                             | Use of letrozole may cause decreases in bone mineral density.                                                                                                                                          | Consideration should be given to monitoring BMD.                                                                                                                                                                                                                            |
| <ul style="list-style-type: none"> <li>Hypercholesterolemia</li> </ul>                                                     |                                                                                                                                                                                                        | Consideration should be given to monitoring serum cholesterol.                                                                                                                                                                                                              |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk                         | Mitigation Strategy                                                                                                       |
|-----------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| • Hepatic Impairment                    |                                                            | Careful monitoring of liver function test results will be conducted                                                       |
| • Fatigue and Dizziness                 | Fatigue, dizziness, and somnolence have been reported      | Caution should be advised when driving or using heavy machinery until it is known how the patient reacts to letrozole use |
| • Laboratory Test Abnormalities         | Moderate decreases in lymphocyte counts have been observed | Careful monitoring of laboratory tests as clinically indicated                                                            |

| STUDY PROCEDURES                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Potential Risk of Clinical Significance                                                                                                                                                                                                                                                                                                                                                                                                                                     | Summary of Data/Rationale for Risk                                                                                                                                                                                                                                                                                                    | Mitigation Strategy                                                                                                                                                                                                                                  |
| <p>Potential risks associated with de novo (fresh) tumor biopsy include:</p> <ul style="list-style-type: none"> <li>stinging pain from injection of local anesthetic;</li> <li>pain or discomfort from the biopsy procedure;</li> <li>discomfort from lying still for an extended time;</li> <li>bleeding, swelling, scarring, soreness, or bruising at the biopsy site;</li> <li>contamination of cancer cells to unaffected tissue when removing biopsy needle</li> </ul> | <p>These potential risks are based on standard medical practice.</p> <p>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.</p> | <p>Local anesthetic will be administered.</p> <p>Sterile techniques will be used.</p> <p>Procedures will be performed by qualified medical practitioners.</p>                                                                                        |
| Blood sample collections for safety assessments, pharmacokinetics, and biomarkers                                                                                                                                                                                                                                                                                                                                                                                           | <p>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.</p>                                                                      | <p>All blood draws will be completed by qualified and trained medical personnel.</p> <p>Sterile technique will be used.</p> <p>Blood sample collections will be conducted at facilities prepared for adverse reactions related to the collection</p> |

| STUDY PROCEDURES                                                                      |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Potential Risk of Clinical Significance                                               | Summary of Data/Rationale for Risk                                                                                                                                                                                  | Mitigation Strategy                                                                                                                                                                                                                                                                                                                                                                                                     |
| Delay in standard of care treatment/risk of disease progression within 1 month period | Participants diagnosed with this disease typically receive standard of care therapy at initial diagnosis. Participating in this signal finding study will delay the start of such therapy by approximately 1 month. | <p>Inclusion/Exclusion criteria including TNM staging are set to ensure the correct population are included and appropriate with regards to delayed treatment. Criterion adapted from learnings from other window of opportunity studies.</p> <p>Communication of risk outlined in ICD.</p> <p>Participants will be monitored throughout for safety considerations and will be removed from treatment if necessary.</p> |

### 2.3.2. Benefit Assessment

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-positive, HER2-negative mBC who progressed on prior CDK4/6i + ET (Study C4391001).

NET provides a less toxic alternative to chemotherapy that can lead to clinical responses that are comparable to neoadjuvant chemotherapy (Sella et al, 2021). An optimal NET regimen has yet to be determined. In the neoadjuvant setting, select ER down-regulators and degraders and nsAIs demonstrate similar safety profiles, clinical response rates, breast conservation rates, and Ki-67 reduction (Hernando et al, 2021).

This 2 week (+3 days) window of opportunity study may provide initial clinical benefit as well as early information of biomarker response which may help investigator's decision on the subsequent treatments.

### 2.3.3. Overall Benefit/Risk Conclusion

All known potential risks are considered as manageable and will be monitored and managed according to the protocol and institutional standard of care.

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07220060 are justified by the anticipated benefits that may be afforded to participants with HR-positive, HER2-negative breast cancer.

## 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives                                                                                                                                                                                        | Endpoints                                                                                                                           | Estimands                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Primary:</b>                                                                                                                                                                                   | <b>Primary:</b>                                                                                                                     | <b>Primary:</b>                                                   |
| <ul style="list-style-type: none"> <li>Evaluate the effects of PF-07220060 plus letrozole and letrozole alone, respectively, on Ki-67 expression in tumors after 2 weeks of treatment.</li> </ul> | <ul style="list-style-type: none"> <li>CCCA (Ki-67 <math>\leq 2.7\%</math>) rates at Day 14 (centrally assessed biopsy).</li> </ul> | <ul style="list-style-type: none"> <li>See below.</li> </ul>      |
| <b>Secondary:</b>                                                                                                                                                                                 | <b>Secondary:</b>                                                                                                                   | <b>Secondary:</b>                                                 |
| <ul style="list-style-type: none"> <li>Evaluate the safety and tolerability of PF-07220060 plus letrozole and letrozole alone after 2 weeks of treatment.</li> </ul>                              | <ul style="list-style-type: none"> <li>Incidence of all AEs, SAEs, and AEs leading to study drug discontinuation.</li> </ul>        | <ul style="list-style-type: none"> <li>Not applicable.</li> </ul> |
| <ul style="list-style-type: none"> <li>Evaluate ctDNA response on treatment after 2 weeks of treatment.</li> </ul>                                                                                | <ul style="list-style-type: none"> <li>ctDNA measurements at baseline and Day 14.</li> </ul>                                        | <ul style="list-style-type: none"> <li>Not applicable.</li> </ul> |

| Objectives                                                                                                                                                               | Endpoints                                                                                                                                                                                                  | Estimands                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>To determine steady-state plasma concentrations of PF-07220060 in combination with letrozole.</li> </ul>                          | <ul style="list-style-type: none"> <li>C<sub>trough</sub> and peri-biopsy plasma concentrations of PF-07220060.</li> </ul>                                                                                 | <ul style="list-style-type: none"> <li>Not applicable.</li> </ul> |
| <ul style="list-style-type: none"> <li>Determine changes in Ki-67 expression.</li> </ul>                                                                                 | <ul style="list-style-type: none"> <li>Ki-67 staining.</li> </ul>                                                                                                                                          | <ul style="list-style-type: none"> <li>Not applicable</li> </ul>  |
| Exploratory:                                                                                                                                                             | Exploratory:                                                                                                                                                                                               | Exploratory:                                                      |
| <ul style="list-style-type: none"> <li>Evaluate the TME response to PF-07220060 plus letrozole and letrozole alone.</li> </ul>                                           | <ul style="list-style-type: none"> <li>Spatial stromal, immune tumor cell omics.</li> </ul>                                                                                                                | <ul style="list-style-type: none"> <li>Not applicable.</li> </ul> |
| <ul style="list-style-type: none"> <li>To explore the impact of allelic variants of drug metabolizing enzymes and transporters on PK exposure of PF-07220060.</li> </ul> | <ul style="list-style-type: none"> <li>Allelic variants of drug metabolizing enzymes and transporters.</li> </ul>                                                                                          |                                                                   |
| <ul style="list-style-type: none"> <li>Evaluate associations of tumor gene mutations with treatment outcome by ctDNA analyses.</li> </ul>                                | <ul style="list-style-type: none"> <li>Tumor gene alterations in ctDNA include, but limited to, in cell cycle, signaling transduction, cell proliferations.</li> </ul>                                     |                                                                   |
| <ul style="list-style-type: none"> <li>Evaluate associations of gene expression profiles with treatment outcome by using tumor tissues.</li> </ul>                       | <ul style="list-style-type: none"> <li>Tumor gene expression profiles include, but not limited to, in cell cycle, signaling transduction, cell proliferation, and intrinsic molecular subtypes.</li> </ul> |                                                                   |

#### Primary Estimand

The primary estimand of this study estimates the treatment effect on CCCA rates (Ki-67  $\leq 2.7\%$ ) at Day 14 if all participants maintain their randomized treatment and adhere to the protocol, respectively. The estimand is defined according to the primary objective for CCCA and is in alignment with the primary endpoint CCCA. It includes the following 5 attributes:

- Treatments:** PF-07220060 plus letrozole versus letrozole alone.
- Population:** Postmenopausal women with newly diagnosed and treatment naive HR-positive, HER2-negative BC that is amenable to definitive surgical resection.
- Variable:** Rate of CCCA by centrally assessed biopsy at Day 14 reaching Ki-67  $\leq 2.7\%$ .
- Intercurrent events:** only participants with evaluable Ki-67 results from baseline (locally or centrally assessed) and Day 14 (centrally assessed) visits will be included in the primary analysis. No participants will be censored or excluded due to any reasons other than missing Ki-67 data. The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention (dose and product)” are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.
- Population-level summary:** Analysis of Ki-67 reduction will be based on a Ki-67 evaluable population. The rates of CCCA will be provided along with the corresponding 2-sided 95% CIs using an exact method for each treatment arm.

#### Secondary Estimands

No estimands are defined for any of the secondary or exploratory endpoints.

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a Phase 2 open-label, randomized, multicenter study of PF-07220060 plus letrozole compared to letrozole alone in participants with HR-positive, HER2-negative BC in the

neoadjuvant setting to evaluate the biological activity of PF-07220060 plus letrozole and letrozole alone.

The study will target enrolling approximately 50 Ki-67 evaluable participants in each arm. The estimated total number of enrolled participants is 118 under the assumption that about 85% of the enrolled participants will have Ki-67 evaluable data. Participants will be randomized in a 1:1 manner to:

- Arm A (Experimental Arm; n = approximately 59): Participants will receive:
  - PF-07220060 300 mg, orally, twice daily, continuously for 14 days, plus letrozole 2.5 mg, orally, once daily, continuously for 14 days
- Arm B (Control Arm; n = approximately 59): Participants will receive:
  - letrozole 2.5 mg, orally, once daily, continuously for 14 days (window of opportunity)

It is estimated that this sample size will provide approximately 50 evaluable participants with paired biopsies in the experimental arm and 50 evaluable participants with paired biopsies in the control arm (baseline, Day 14).

Participants will have both a baseline biopsy and an on-treatment biopsy (Day 14). The baseline biopsy must be de novo (newly collected fixed biopsy sample; sample collected for diagnosis could be used as long as it was collected within 3 months of study treatment initiation, and no other treatment has occurred between biopsy and initiation of study treatment, and fulfills the sample collection requirements). After the 14-day treatment cycle, participants will come off study and continue on SOC therapy (e.g., surgery, radiotherapy, chemotherapy) as per physician's choice.

## **4.2. Scientific Rationale for Study Design**

### **4.2.1. Diversity of Study Population**

The diversity strategy will include high performing sites with the potential to support the recruitment of diverse and under-represented populations. The strategy to ensure diversity includes recognition that the presentation of advanced breast cancer varies by gender, age, race, and geographic location; inclusion of diverse principal investigators; site-level training on clinical study diversity; support sites in recruitment plans in order to randomize a more diverse patient population; customized diverse recruitment materials, advertising, and referrals to support their efforts; accelerating an education campaign to community oncologists, patient advocacy groups, and breast cancer social media sites to increase awareness about this clinical trial option.

### **4.2.2. Rationale for Comparator**

Letrozole is used as both an active comparator and an experimental treatment when in combination with PF-07220060 .

Further development of PF-07220060 is expected in the adjuvant setting. Letrozole is indicated in the adjuvant treatment of postmenopausal women with HR-positive early breast cancer and therefore has been selected as the comparator agent.

The PALLET study with letrozole showed significantly enhanced suppression of malignant cell proliferation (Ki-67) in primary ER-positive breast cancer ([Johnston et al, 2019](#)).

#### 4.2.3. Rationale for Primary Endpoint

This trial will enroll postmenopausal women with treatment naïve HR+/HER2- breast cancer that is amenable to definitive surgical resection. Participants must also have tumor that is at least 1.5 cm as confirmed by imaging due to biopsy requirements for this study ([Section 8.2.1](#)).

The selection of the endpoint of CCCA (Ki-67  $\leq 2.7\%$ ) rates at Day 14 was based on several trials that have assessed the reduction of CCCA in tumor biopsies and demonstrated that reduction in Ki-67 in the neoadjuvant setting may correlate with relapse free survival after definitive surgical resection and with beneficial outcomes in the adjuvant or metastatic setting ([Guerrero-Zotano & Arteaga, 2017](#)).

Given the variability within the assessment of Ki-67 by IHC, the study requires a value of  $\geq 10\%$  (assessed locally), to ensure an evaluable centrally assessed value to measure CCCA rate and detect changes from the baseline Ki-67 value.

This is a window of opportunity, signal finding trial whose data may enable further development of the study treatment in the adjuvant setting.

#### 4.3. Justification for Dose

##### 4.3.1. PF-07220060

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 400 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 300 mg or 400 mg BID in combination with letrozole or fulvestrant (see [Section 2.2.1.1.1](#)).

As detailed in the IB Section 6.1, preliminary PK showed that PF-07220060 exposure increased with increasing dose from 100 to 300 mg BID. No substantial increase in exposure was observed at doses higher than 300 mg BID. The Cycle 1 Day 15 mean exposure at 500 mg BID appears to be slightly higher; however, the sample size is limited to have a definite comparison. Exposure of PF-07220060 at 300 mg and 400 mg BID were comparable across monotherapy, in combination with letrozole, and in combination with fulvestrant, suggesting a lack of effect of letrozole or fulvestrant on PK of PF-07220060. The totality of the data including safety, efficacy, and PK supports 300 mg BID as the dose to be used in this study.

#### 4.3.2. Letrozole

The recommended dose of letrozole is 2.5 mg QD. Refer to the SmPC for detailed information.

Please refer to the current letrozole approved local product prescribing information for a summary of the expected safety profile in participants with HR+/HER2- BC, including a full list of all Warnings and Precautions.

#### 4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in the [SoA](#), or have met any of the discontinuation criteria per [Section 7.2](#).

### 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. Female participants  $\geq 18$  years (or the minimum age of consent in accordance with local regulations) with natural or surgical post menopause at screening
  - Refer to [Appendix 4](#) for reproductive criteria.
  - Post-menopausal status will be defined by at least one of the following: prior bilateral oophorectomy, age  $\geq 60$  years and amenorrheic for at least 12 months, or age  $< 60$  years and amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, ovarian suppression, or any additional medical intervention that may have induced amenorrhea) and FSH in the postmenopausal range.

**Disease Characteristics:**

2. Histologically confirmed HR-positive and HER2-negative BC (per local assessment).

HR and HER2 status must be documented:

- a. Documented ER and/or PR positive disease, with ER or PR staining of  $\geq 1\%$  of tumor cell nuclei by immunohistochemistry (IHC) per ASCO/CAP Guidelines (Allison et al, 2020) (assessed locally).
- b. Documented HER2 negative disease by either IHC or ISH per ASCO/CAP guidelines (Wolff et al, 2018) (assessed locally).

**Other Inclusion criteria:**

3. Must have Ki-67 score  $\geq 10\%$  (analyzed locally).
4. Must have unilateral, invasive T1c-T4c, N0-N2, M0 BC (AJCC; Version 8)
  - a. The primary tumor must be at least 1.5 cm
5. ECOG PS 0 or 1.
6. Willingness to undergo a baseline biopsy (if not done previously, which meets the sample collection requirement outlined in Section 8.2.1), and an on-treatment biopsy (per Section 8.7.1)

**5.2. Exclusion Criteria**

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

**Medical Conditions:**

1. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or cervical carcinoma in situ.
2. 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
  - Symptomatic pulmonary embolism or other clinically significant episode of thromboembolism
3. Active inflammatory GI disease, chronic diarrhea, known uncontrolled diverticular disease or previous gastric resection or lap band surgery.
  4. History of allergy or reaction to any of the drug components for PF-07220060, letrozole (or other study medications), including participants with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
  5. Inability to take oral medication without crushing, dissolving, or chewing tablets.
  6. Participants with known active, bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness.
  7. Major surgery (as defined by the investigator) within 2 weeks of first dose of study intervention or has not recovered from major side effects.
  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.
    - a. Participants who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

**Diagnostic Assessments:**

9. Inadequate bone marrow, renal, and/or liver function:
  - a. Inadequate bone marrow function, defined as (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):
    - $ANC < 1,500/mm^3$  or  $1.5 \times 10^9/L$ ;
    - Platelets  $< 100,000/mm^3$  or  $100 \times 10^9/L$ ;
    - Hemoglobin  $< 9$  g/dL.
    - $aPTT > 1.25 \times ULN$  and/or  $INR > 1.25$ .

**Note:** Unless the participant is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.

- b. Inadequate renal function defined as serum creatinine of  $>1.5 \times \text{ULN}$  or an  $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$  calculated by CKD-EPI equation
- c. Inadequate liver function, defined as:
  - Total bilirubin  $>1.5 \times \text{ULN}$  (except for Gilbert's syndrome, in which direct bilirubin  $>\text{ULN}$  is exclusionary)
  - AST and/or ALT  $>2.5 \times \text{ULN}$ .

**Prior/Concomitant Therapy:**

10. Prior and/or current prohibited treatment including:

- a. Systemic therapy (e.g., chemotherapy, hormonal therapy), radiation, surgery, or any investigational agents for the treatment of BC.
- b. Use of HRT or any other estrogen-containing medication (including vaginal estrogen) within 2 weeks prior to diagnostic tissue sample taken
- c. Any live vaccines within 14 days of planned start of first dose of study intervention.
- d. Current use or anticipated need for use of any prohibited food, supplements or concomitant medication(s) or participants unwilling or unable to use a required concomitant medication(s). Refer to [Appendix 9](#).

**Prior/Concurrent Clinical Study Experience:**

- 11. Previous administration with an investigational product within 2 weeks (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 at any time during their participation in this study.

**Other Exclusion Criteria:**

- 12. Participants who are involuntarily incarcerated. (Note: Under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Sponsor approval is required).
- 13. 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.

### 5.3. Lifestyle Considerations

#### 5.3.1. Meals and Dietary Restrictions

Participants should take PF-07220060 as outlined in [Section 6.1.1.1](#).

Participants should refrain from consuming grapefruit juice or grapefruit/grapefruit related citrus fruits (e.g., Seville oranges, pomelos) during treatment with PF-07220060 as listed in [Appendix 9](#).

Participants taking letrozole should be provided with corresponding meal and dietary restrictions consistent with locally approved prescribing information.

#### 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 only once.

### 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (e.g., 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 PF-07220060 and letrozole.

#### 6.1. Study Intervention(s) Administered

The study interventions are administered for 14 days.

| Study Intervention(s) |              |                                    |
|-----------------------|--------------|------------------------------------|
| Intervention Name     | PF-07220060  | Letrozole                          |
| Type                  | Drug         | Drug                               |
| Use                   | Experimental | Experimental and Active comparator |
| IMP or NIMP/AxMP      | IMP          | IMP                                |
| Dose Formulation      | Tablet       | Tablet                             |
| Unit Dose Strength(s) | 100 mg       | 2.5 mg                             |

| Study Intervention(s)   |                                                                                                                  |                                                                                                                                                              |
|-------------------------|------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dosage Level(s)         | 300 mg BID<br>Refer to <a href="#">Section 6.1.1.1.</a>                                                          | 2.5 mg QD<br>Refer to <a href="#">Section 6.1.1.2.</a>                                                                                                       |
| Route of Administration | Oral                                                                                                             | Oral                                                                                                                                                         |
| Sourcing                | Provided centrally by the sponsor<br><br>Please refer to the IPM                                                 | Provided centrally by the sponsor<br><br>Please refer to the IPM                                                                                             |
| Packaging and Labeling  | Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. | Study intervention will be provided in commercial bottles or blister packs. Each bottle or blister pack will be labeled as required per country requirement. |
| SRSD                    | IB                                                                                                               | UK SmPC                                                                                                                                                      |

| Study Arm(s)    |                                                                                                                                                                                                                                                                                      |                                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Arm Title       | Arm A<br>PF-07220060 + letrozole                                                                                                                                                                                                                                                     | Arm B<br>letrozole                                                                                                                                         |
| Arm Type        | Experimental                                                                                                                                                                                                                                                                         | Control                                                                                                                                                    |
| Arm Description | Participants will receive: <ul style="list-style-type: none"> <li>PF-07220060 as three 100 mg tablets (i.e., 300 mg), orally, twice daily with food continuously for 14 days, plus</li> <li>letrozole as one 2.5 mg tablet, orally, once daily continuously for 14 days .</li> </ul> | Participants will receive: <ul style="list-style-type: none"> <li>letrozole as one 2.5 mg tablet, orally, once daily, continuously for 14 days.</li> </ul> |

### 6.1.1. Administration

Participants in Arm A (Experimental) will receive PF-07220060 plus letrozole while participants in Arm B (Control) will receive letrozole. Study interventions will be provided open-label. All study interventions will be provided in tablet form and will be self-administered for 14 (+3) consecutive days until biopsy, except when administered at the clinic.

Participants should be scheduled to visit the investigational site in morning on the Day 14 visit. Participants must be instructed to bring their study intervention to the investigational site, and to withhold their last dose until pre-dose assessments per [SoA](#) have been completed.

On the Day 14 visit, only the morning dose will be taken and will be administered at the clinic/site.

Administration of study intervention(s) will be performed at the clinic/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), participants will be observed for the duration of the clinic/site visit 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.

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

#### **6.1.1.1. PF-07220060 Administration**

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to those outlined in [Section 6.9.4](#).

PF-07220060 will be administered as open-label tablets. Participants will be instructed to swallow oral study interventions whole and to not manipulate or chew the study interventions prior to swallowing.

PF-07220060 will be administered with food, orally BID approximately 12 hours apart.

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. In addition, if a participant vomits any time after taking a dose, they must be instructed not to "make it up" but to resume subsequent doses at the next scheduled dose as prescribed. If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of PF-07220060.

Dose modifications for toxicity related to study intervention are presented in [Section 6.6](#).

#### **6.1.1.2. Letrozole Administration**

Letrozole will be administered continuously once a day in the morning with or without food.

Participants should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time.

If a participant misses a day of treatment, he/she must be instructed not to "make it up" but to resume subsequent doses as prescribed and instructed by the investigator.

If a participant vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of letrozole.

## 6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm that appropriate conditions (e.g., 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 or other specified location.
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 (i.e., 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 intervention that is 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**

A qualified staff member will dispense the study intervention via an IRT system using unique container numbers on the study intervention provided, in quantities appropriate according to the [SoA](#). A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the containers provided throughout the course of dosing and return the containers to the site at the next study visit, whether they are used or unused. Returned study intervention must not be redispensed to the participants.

Site personnel must ensure that participants clearly understand the directions for self-medication of PF-07220060 and letrozole. 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 for detailed administration instructions for all the study interventions administered in this study.

#### **6.3. Assignment to Study Intervention**

Participants will be randomized according to details outlined in [Section 4.1](#). Randomization must occur after having carefully reviewed all eligibility criteria and confirmed they are satisfied. At randomization, participant number and treatment arm are assigned and may occur up to -3 days prior to Day 1 if necessary. The study intervention to be dispensed to the participant will be assigned using an IRT system. The site will utilize the IRT system to assign the DU or container number(s) prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. This is an open-label study. The investigator's knowledge of the treatment assignment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

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

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

#### **6.4. Blinding**

This is an open-label study.

## **6.5. Study Intervention Compliance**

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, and review of participant-completed dose administration diary during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of each study treatment, including premedication, dispensed to, and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

## **6.6. Dose Modification**

Every effort should be made to administer study interventions on the planned dose and schedule. However, in the event of significant treatment related toxicity, administration of study intervention may need to be interrupted based on the toxicity observed. In the event of multiple toxicities, dose interruption 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 interruptions, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Depending on the nature of the toxicity observed, dosing interruptions 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 interruptions may occur within the treatment period until adequate recovery, if required.

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

All dose interruptions and/or discontinuations must be clearly documented in the participant's source notes and IP administration CRF.

### **6.6.1. PF-07220060**

#### **6.6.1.1. PF-07220060 Dose Modification Levels**

PF-07220060 dose reductions are not permitted.

#### **6.6.1.2. PF-07220060 Dose Modifications**

Dose reductions are not permitted, however can be interrupted due to toxicity.

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

PF-07220060 doses may be held until toxicity resolution. In order to fulfill the requirements for the study endpoints, the PF-07220060 doses must be taken consistently during the last 7 days of the study treatment period prior to the Day 14 biopsy. If a dose interruption occurs and/or lasts such that the participant is unable to be administered the study treatment during the last 7 days prior to the Day 14 biopsy, PF-07220060 should be permanently discontinued and the Day 14 biopsy will not be collected.

When PF-07220060 is interrupted, letrozole may continue as scheduled at the investigator's discretion. When PF-07220060 is discontinued, letrozole must also be discontinued.

#### **6.6.2. Letrozole**

Dose reduction of letrozole is not allowed.

Management of AEs related to letrozole should follow the respective SRSD.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

#### **6.8. Treatment of Overdose**

For this study, any dose of PF-07220060 greater than the intended dose within a 24-hour time period ( $\pm$  5 hours) will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator 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](#)).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis if requested by the study medical monitor (determined on a case-by-case basis).

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

Please refer to the current local prescribing information for letrozole for management of overdose.

## 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.

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

All prior and concomitant medications and treatments (e.g., over-the counter medications, prescription medications, vitamins, vaccines, herbal supplements) and non-drug interventions (e.g., transfusions, medical procedures) must be recorded in the CRF. Prior and concomitant medications and treatments, and non-drug interventions are to be recorded from 28 days before the first dose of study intervention until 35 days after the last dose of study intervention or until the participant begins a new anti-cancer therapy, whichever occurs first.

### 6.9.1. Prior and Concomitant Therapy Specific for PF-07220060

#### 6.9.1.1. Prohibited and Cautioned Concomitant Medications Due to Potential Pharmacokinetic Driven DDI With PF-07220060

##### 6.9.1.1.1. PF-07220060 as a Substrate of CYP3A4/5 and UGT2B7

Prohibited and cautioned medications due to the potential increase or decrease of PF-07220060 exposure are listed in [Appendix 9](#).

- Inhibition of CYP3A4/5 isoenzymes may increase PF-07220060 exposure leading to potential increases in toxicities, therefore the use of known strong inhibitors is not permitted within 5 half-lives of the CYP3A4/5 inhibitors prior to the first dose of PF-07220060 and throughout the conduct of the study.
- Use of moderate CYP3A4/5 inhibitors should be avoided if possible or used with caution if it is deemed medically necessary by the investigator.
- Induction of CYP3A4/5 isoenzymes may decrease PF-07220060 exposure leading to potential decrease in efficacy, therefore the use of strong CYP3A4/5 inducers is not permitted within 10 days or 5 half-lives of the CYP3A4/5 inducers, whichever is longer prior to the first dose of PF-07220060 and throughout the conduct of the study.
- Use of moderate CYP3A4/5 inducers should be avoided if possible or used with caution if it is deemed medically necessary by the investigator.
- Inhibition of UGT2B7 isoenzymes may increase PF-07220060 exposure leading to potential increases in toxicities, therefore the use of known strong UGT2B7 inhibitors is not permitted within 5 half-lives of the UGT2B7 inhibitors prior to the first dose of PF-07220060 and throughout the conduct of the study.

- Induction of UGT2B7 isoenzymes may decrease PF-07220060 exposure leading to potential decrease in efficacy, therefore the use of strong UGT2B7 inducers is not permitted within 10 days or 5 half-lives of the UGT2B7 inducers, whichever is longer, prior to the first dose of PF-07220060 and throughout the conduct of the study.
- Use of other known UGT2B7 inhibitors or inducers should be avoided if possible or used with caution if it is deemed medically necessary by the investigator.

#### 6.9.1.1.2. PF-07220060 as a Perpetrator of Drug Interactions

Concomitant use of PF-07220060 and substrates of CCI may CCI the exposure of the substrate, based on in vitro findings that PF-07220060 may CCI these pathways, but the exact risk in vivo is uncertain at this time. Caution is warranted for the coadministration of PF-07220060 with CCI, P-gp, BCRP substrates with narrow therapeutic indices as listed in [Appendix 9](#). See below regarding specific guidance for CCI and CCI.

CCI

Due to the potential CCI by PF-07220060 based on in vitro data, CCI are CCI as listed in [Appendix 9](#). CCI is permitted with caution and with additional CCI. Stable dose of CCI for at least 2 weeks before the first dose of PF-07220060 is required for participants who have been on CCI before enrollment.

CCI

PF-07220060 is a potential CCI and potential CCI, therefore, recommendations of avoiding the use of certain CCI or limiting the daily dose of certain CCI are provided in [Appendix 9](#).

#### 6.9.1.1.3. Acid Reducing Agents

ARAs may CCI PF-07220060 absorption and systemic exposure. The potential impact to absorption and exposure may be the greatest with CCI. Use of CCI are prohibited within 7 days prior to the first dose of study intervention. Please refer to [Appendix 9](#) for the list of CCI.

Participants who are currently taking CCI should be switched to antacids or H2-receptor antagonists at least 7 days prior to the first dose of study intervention, assuming there is no known or expected DDI and the drug is not included as a prohibited medication in [Appendix 9](#). If needed, administer H2-receptor antagonists with a staggered dosing regimen (BID). Administration of PF-07220060 is recommended to occur at least 8 hours after and 2 hours before the H2-receptor antagonist doses.

If needed, local antacids should be given at least 2 hours before or at least 2 hours after PF-07220060 administration.

### **6.9.2. Other Prohibited and/or Limited use of Antitumor/Anticancer or Experimental Drugs, or Procedures**

Any concomitant therapy intended for the treatment of cancer (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or radiotherapy) is prohibited until the completion or discontinuation of study treatment.

Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate, oral contraception, hormone-eluting intrauterine devices, LHRH agonists, and selective ER modulators (e.g., raloxifene) are prohibited until the completion or discontinuation of study treatment.

Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.

#### **6.9.2.1. Prior and Concomitant Therapy Specific for Letrozole**

For additional considerations of prior and concomitant medications related to letrozole, including potential DDI, please follow the local prescribing information and/or institutional standard of care.

#### **6.9.3. Supportive Care**

Supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

#### **6.9.4. Antidiarrheal, Antiemetic Therapy**

The choice of the prophylactic and/or treatment drugs as well as the duration of treatment is up to the investigator assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section ([Section 6.9](#)).

**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 continue to be administered as needed.

**Antiemetic Therapy:** Nausea and vomiting should be treated aggressively. Consideration should be given prior to subsequent doses for the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

#### **6.9.5. Corticosteroids**

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

#### **6.9.6. Anti-Inflammatory or Narcotic Analgesics**

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 in the Concomitant Therapy section ([Section 6.9](#)).

#### **6.9.7. Surgery**

Surgical procedures for disease are prohibited during the study treatment period. Caution is advised for any non-disease related surgical procedures during the study. The appropriate interval of time between surgery and PF-07220060 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07220060 is recommended at least 3 days prior to surgery. Postoperatively, the decision to reinstate PF-07220060 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

### **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 28 days. 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, and no more than 35 calendar days after discontinuation of study intervention, participants will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related AEs. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

#### **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) OR (iii) urine volume <0.5 mL/kg/h for 6 consecutive hours. In the absence of increase in Screat and decrease in Screat-based eGFR or eCrCl, DIKI and other causes of AKI should be suspected if either there is new-onset or worsening proteinuria are detected or if urine volume (if measured) is less than 0.5 mL/kg/h for 6 consecutive hours.

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.

#### **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:

- Lost to follow-up;
- Death;
- Study terminated by sponsor;

- Withdrawal by participant.

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

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

### 8.1. Administrative and Baseline Procedures

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

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

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.

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 study team must be informed of these incidents in a timely manner.

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

#### 8.1.1. Baseline Procedures

Per the [SoA](#), baseline/screening procedures will be conducted.

**Demographics** will be recorded at screening for each participant.

**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 signature.

**Oncological history** will be recorded at screening for each participant and includes details regarding the disease process (e.g., staging) under study and concurrent illness, including prior treatments, tumor histologic grade, HR, HER2 status per local standards, relevant disease characteristics, and TNM staging per the AJCC; (8<sup>th</sup> edition) cancer staging manual

(Giuliano et al, 2018). Clinical TNM stage, along with the imaging modality utilized for staging, must be documented in the eCRF.

## 8.2. Efficacy Assessments

### 8.2.1. Tumor Biopsy (FFPE)

To meet the primary endpoint of the study, participants will have a screening biopsy and an on-treatment biopsy on Day 14 (+3 days).

During screening, core needle biopsies of the primary breast tumor must be collected during baseline. Fine needle aspirations are not allowed. For multi-focal tumors, it is only necessary to collect a biopsy sample from one mass. It is possible to use the initial tumor biopsy from diagnosis provided no treatment occurred between collection and study treatment start and is within 3 months, and it meets the requirement detailed in [Section 8.7.1](#).

Core biopsies at Day 14 visit must be obtained from the same site as the baseline/pre-dose biopsy, if possible, and for those participants randomized to Arm A (Experimental), must be collected post PK sample collection. Specimens must be processed and shipped to a central laboratory for assessment per the Laboratory Manual.

To confirm adequate material will be obtained from each tumor biopsy, the primary tumor must be at least 1.5 cm, assessed per local imaging standards. Imaging from up to 3 months prior to initiation of study treatment may be utilized to confirm this requirement.

### 8.2.2. Tumor Assessment

Not applicable.

## 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 will include assessments of all the major body systems. A complete PE will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height (screening only) and weight will also be measured and recorded.

Symptom-directed PEs will be performed at subsequent visits as per the [SoA](#). Additional PEs may be performed if clinically indicated. On dosing days physical examinations must be performed prior to study intervention administration.

PEs may be conducted by an appropriately qualified and trained healthcare provider as allowed by local, state, and institutional guidance.

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

Physical examination should precede blood draw for clinical laboratory tests.

### 8.3.2. Vital Signs

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

All vital sign measurements will be taken per the [SoA](#) and should be performed prior to study intervention administration.

Vital signs will be assessed while the participant is in a sitting position or semi-recumbent position (recommended). It is recommended that the same position be used consistently throughout the duration of the study unless circumstances, e.g., hospitalization, dictate otherwise.

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

Abnormal readings should be repeated and confirmed.

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](#).

#### 8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a sitting or semi-recumbent position, in a quiet setting without distractions.

BP and PR will be taken before blood collection for laboratory tests and consist of a single measurement of PR and single BP measurement.

#### 8.3.2.2. Temperature and Respiratory Rate

Oral or Temporal artery temperature, and respiratory rate, will be assessed.

#### 8.3.2.3. Performance Status

The participant's performance status will be assessed using the ECOG PS. Performance status will be completed at screening using the ECOG Performance Status Scale and recorded on the eCRF.

### 8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the [SoA](#) section of this protocol using an ECG system that automatically calculates the heart rate and measures PR interval, QT interval, QTcF, 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. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

If a) a postdose QTcF interval remains  $\geq 60$  ms from the baseline and is  $>450$  ms; or b) an absolute QT value is  $\geq 500$  ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring.

Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs ([Appendix 8](#)) and should be evaluated further, as clinically warranted.

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](#).

ECG assessments should precede any blood collections scheduled at the same time point (e.g. safety laboratory assessments, PK samples, biomarker samples).

### 8.3.4. Clinical Safety Laboratory Assessments

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

At screening, safety laboratory results from the central laboratory (unless otherwise specified) should be used by the investigator to determine the participant's eligibility for the study. If results from the central laboratory are unavailable, local laboratory results may be utilized for confirmation of eligibility at the Investigator's discretion.

Laboratory assessments for hematology, chemistry, coagulation, and urinalysis are not required on Day 1 if acceptable screening assessment is performed within 3 days prior to randomization.

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.

In cases where there are discrepant values between the central laboratory and local laboratory, treatment decisions and management will be at the investigator's discretion.

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.

#### **8.4. 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 the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

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

During the active collection period as described in [Section 8.4.1](#), 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 PSSA.

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

#### **8.4.1.1. Reporting 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 on the PSSA 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 its 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 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.

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

#### **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](#)).

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

Further information on follow-up procedures is 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 (e.g., 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 female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female 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 female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention ingestion, inhalation, or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, 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).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the PSSA and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 30 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the PSSA and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the

information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP. 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 (i.e., 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 (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

#### **8.4.5.2. Exposure During Breastfeeding**

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (i.e., environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, 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. The information must be reported using the PSSA. 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 PSSA is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., 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 using the PSSA 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 PSSA must be maintained in the investigator site file.

#### **8.4.6. Cardiovascular and Death Events**

Not applicable.

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

Not applicable.

#### **8.4.8. Adverse Events of Special Interest**

Hematologic toxicities such as anemia, neutropenia and thrombocytopenia are considered AESI. Additional laboratory tests for CBC with differentials maybe be required to be performed and recorded as an unscheduled visit. Hematologic toxicities should be monitored on a more frequent basis (e.g., 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.

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, e.g., 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 AESIs must be reported as an AE or SAE following the procedures described in [Sections 8.4.1 through 8.4.4](#). An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the PSSA.

#### 8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

#### 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 on the PSSA 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.

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 AE(s), serious (all) and nonserious (only, if leading to permanent discontinuation of the study treatment), 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 on a PSSA **only when associated with an SAE**.

#### 8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of PF-07220060 as specified in the [SoA](#). Post-dose biopsy PK sample should be collected within  $\pm 1$  hour to biopsy. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples 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.

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 (e.g., 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**

#### **8.6.1.1. Pharmacogenomics**

A 4-mL blood pharmacogenomic sample for DNA isolation will be collected. DNA samples will be analyzed for the purpose of exploring the impact of allelic variants of drug metabolizing enzymes and transporters on PK exposure or AEs of PF-07220060.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

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

#### **8.6.1.2. ctDNA Analysis**

Peripheral blood will be collected at baseline, prior to dosing, and on or after treatment and will be used to characterize and analyze ctDNA in relation to efficacy of treatment therapy, as well as in relation to known relevant biological pathways. Blood sample collections from all participants will adhere to the timepoints specified in the [SoA](#). Details for handling of these specimens including processing, storage and shipment will be provided in the Laboratory Manual.

### 8.6.1.3. Retained Research Samples for Genetics

Retained Research Samples for Genetics are not collected in this study.

## 8.7. Biomarkers

Local assessment of Ki-67 will be used for eligibility and enrollment.

On study Ki-67 testing will be conducted in certified Clinical Laboratory Improvement Amendments central testing laboratories. Ki-67 expression will be measured by IHC. All analyses will be conducted in a blinded manner at the central laboratory

Analysis of additional PD and other biomarkers thought to play a role in breast cancer or drug response may also be performed including, but not limited to, PgR expression, luminal A/B subtype analysis, RNA profiling, DNA sequencing of specific candidate genes/genome-wide sequencing, or other tissue biomarkers to evaluate their association with responses to the study drugs.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to the study drugs.

### 8.7.1. Mandatory Tumor Biopsies

Tumor biospecimens from de novo biopsies will be used to analyze candidate nucleic acid and protein biomarkers for their ability to identify those participants who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the TME.

Tumor sample must be 1 block or a minimum of 15 unstained slides of analyzable tissue.

Tumor biopsies will be collected at baseline and Day 14.

- **Baseline:** At baseline/screening, 3-5 core needle biopsies of the primary breast tumor must be collected. Fine needle aspirations are not allowed. For multi-focal tumors, it is only necessary to collect a biopsy sample from one mass.
- **Day 14:** On Day 14, 3-5 core needle biopsies of the primary breast tumor (from the same site as the baseline biopsy, if possible) must be collected. The Day 14 biopsy must be obtained post morning dose. For participants in Arm A (Experimental), the biopsy must be obtained within 1 hour before or after the post-dose PK sample.

Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

## 8.8. Immunogenicity Assessments

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 will be no formal hypothesis testing for this study.

#### 9.1.1. Estimands

##### 9.1.1.1. Primary Estimand

The primary estimand of this study estimates the treatment effect on CCCA rates (Ki-67  $\leq 2.7\%$ ) at Day 14 if all participants maintain their randomized treatment and adhere to the protocol from each substudy, respectively. The estimand is defined according to the primary objective for CCCA and is in alignment with the primary endpoint CCCA. The estimand is defined by the following attributes:

- **Population:** Post-menopausal women with newly diagnosed and treatment naive HR positive, HER2 negative breast cancer that is amenable to definitive surgical resection.
- **Endpoint:** Rate of CCCA by centrally assessed biopsy at Day 14 visit reaching Ki-67  $\leq 2.7\%$ .
- **Treatment condition:** the randomized treatment of either PF-07220060 plus letrozole (experimental arm) or letrozole alone (control arm).
- **Intercurrent events:** Only participants with evaluable Ki-67 results from baseline (locally or centrally assessed) and Day 14 (centrally assessed) visits will be included in the primary analysis. No participants will be censored or excluded due to any reasons other than missing Ki-67 data.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention (dose and product)” are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

- **Population-level summary:** Analysis of Ki-67 reduction will be based on a Ki-67 evaluable population. The rates of CCCA will be provided along with the corresponding 2-sided 95% CIs using an exact method for each treatment arm.

### 9.1.1.2. Secondary Estimands

No key secondary endpoints in this study and therefore estimands are not defined for any of the secondary endpoints.

## 9.2. Analysis Sets

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

Note: "Enrolled" means a participant's agreement (which may include support from their legally authorized representative, as permitted by local regulations) to participate in a clinical study following completion of the informed consent process and assignment to study intervention (PF-07220060 plus letrozole or letrozole alone). Legally authorized representatives are those who can assist a participant with the ICD process. It is not the intent of this study to include participants who are otherwise incapacitated and unable to consent for themselves. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity, including assignment to study intervention. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

| Participant Analysis Set                      | Description                                                                                                                                                                                                                                                |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Full analysis set                             | All participants randomly randomized/assigned to study intervention and who take at least 1 dose of study intervention.                                                                                                                                    |
| Safety analysis set (SAS)                     | All enrolled participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.                                                     |
| Ki-67 evaluable analysis Set                  | All participants randomized/assigned to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (assessed locally or centrally) and Day 14 (assessed centrally) visits per central lab. |
| PK concentration set                          | All enrolled participants who are treated and have at least 1 analyte concentration.                                                                                                                                                                       |
| Pharmacodynamic/<br>Biomarker analysis set(s) | The Pharmacodynamic/Biomarker analysis population is defined as all enrolled participants with at least 1 of the Pharmacodynamic/Biomarkers evaluated at pre and/or postdose.                                                                              |

## 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 primary and secondary Ki-67 endpoints will be analyzed using the Ki-67 evaluable analysis set. Any other antitumor activity analyses will be performed using Ki-67 evaluable analysis set. 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. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% CIs using an exact method.

### 9.3.2. Primary Endpoint(s)/Estimand(s)/Analysis

#### 9.3.2.1. Definition of Endpoint

CCCA (Ki 67  $\leq 2.7\%$ ) rates at Day 14 (centrally assessed biopsy).

#### 9.3.2.2. Main Analytical Approach

Analysis of the primary endpoint will be based on the Ki-67 evaluable analysis set. The Ki-67 evaluable participants are participants randomized/assigned to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (assessed locally or centrally) and Day 14 (assessed centrally) visits per central lab. The rate of patients with CCCA in each group will be calculated along with the 2-sided 95% CI using the exact method.

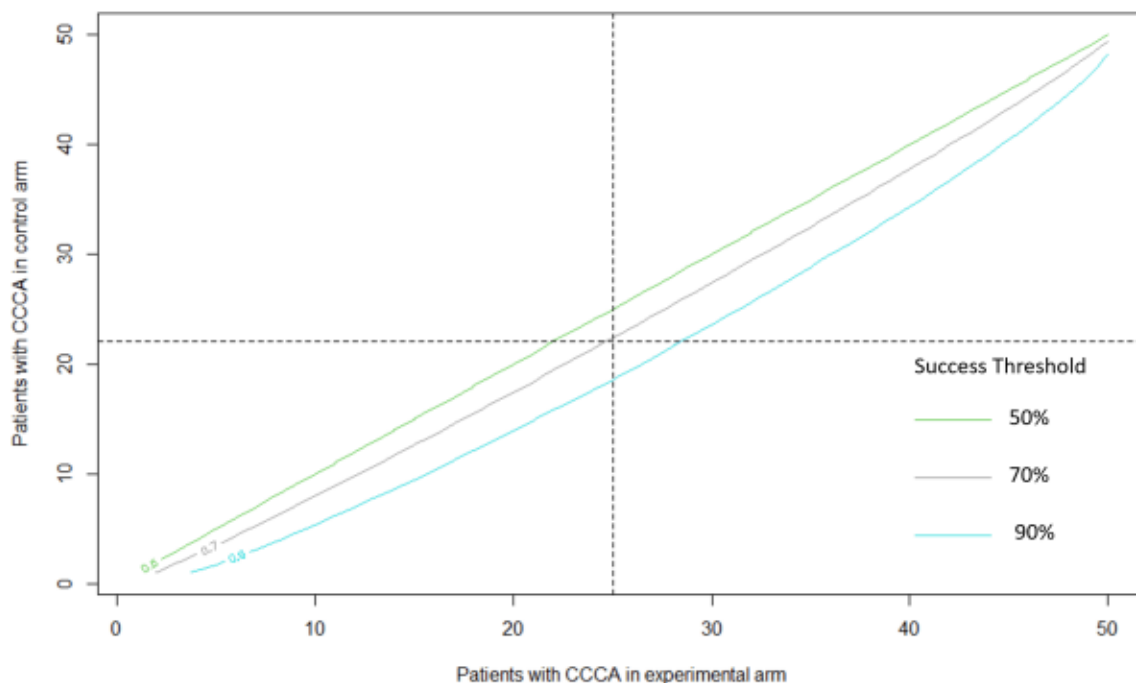
Analysis of the CCCA rates using Bayesian analysis will be performed. A Beta-Binomial model, using a non-informative prior (i.e., Jefferey's prior) will be used to estimate the posterior probability that the CCCA rate in the experimental arm is same as or better than the control arm given the observed CCCA rate in each arm. Assuming a total of 118 participants are enrolled, it is estimated that Ki-67 evaluable data from about 50 participants will be available from the experimental arm and control arm each. The criteria of success may be defined as follows:

$$\text{Posterior probability}(\text{CCCA}_{\text{experimental arm}} > \text{CCCA}_{\text{control arm}}) > P\%$$

The prior for the above calculation can be assumed to be a Beta (0.5, 0.5).

Figure 1 shows the number of responders needed in the experimental arm (x-axis) that would satisfy the criteria above for every possible number of responders in the control arm (y-axis) for different  $P\%$  of 50%, 70% and 90%. For example, if the control arm has 43% or approximately 22 responders (horizontal dotted line), the experimental arm should have 25 (vertical dotted line) or more responders to have the posterior probability of the CCCA in the experimental arm being same as or greater than the CCCA in control arm being 70% or greater.

**Figure 1. Number of CCCA Responders Required in Experimental Arm for Given Response Rate in Control Arm to Meet Success Criteria**



A Beta-Binomial model, using a non-informative prior, can also be used to estimate the posterior probability, based on observed CCCA rates. Table 2 shows some examples of the median and 95% credible interval, and the estimated posterior probability that the true CCCA rate is >45%, >60%, >70%, >80% for different observed CCCA rates out of 50 evaluable participants. For example, of 50 Ki-67 evaluable participants in the experimental arm, if 32 responders are seen, there is a median posterior CCCA rate of 64% and the posterior probability of the true CCCA rate being greater than 60% is 71%.

**Table 2. Posterior Probability Calculations for the True CCCA Rate for Given Number of Responders in 50 Participants**

| Number of CCCA in 50 Participants | Median Posterior CCCA Rate (95% Credible Interval) | P(CCCA rate>45%  data) | P(CCCA rate>60%  data) | P(CCCA rate>70%  data) | P(CCCA rate>80%  data) |
|-----------------------------------|----------------------------------------------------|------------------------|------------------------|------------------------|------------------------|
| 25                                | 0.5(0.37,0.64)                                     | 0.762                  | 0.076                  | 0.002                  | 0                      |
| 32                                | 0.64(0.5,0.76)                                     | 0.997                  | 0.716                  | 0.176                  | 0.004                  |
| 37                                | 0.74(0.61,0.85)                                    | 1                      | 0.981                  | 0.727                  | 0.145                  |
| 42                                | 0.84(0.72,0.92)                                    | 1                      | 1                      | 0.988                  | 0.754                  |
| 45                                | 0.9(0.8,0.96)                                      | 1                      | 1                      | 1                      | 0.969                  |
| 50                                | 1(0.95,1)                                          | 1                      | 1                      | 1                      | 1                      |

### 9.3.3. Secondary Endpoint(s)/Estimands Analysis

The secondary endpoints are as follows:

- Evaluate the safety and tolerability of PF-07220060 plus letrozole and letrozole alone after 2 weeks of treatment.
- Evaluate ctDNA response on treatment after 2 weeks of treatment.
- To determine steady-state plasma concentrations of PF-07220060 in combination with letrozole.
- Determine changes in Ki-67 expression.

All safety analyses will be performed on the safety population.

Analysis will be performed to study the change from baseline in Ki-67 levels. The log-transformed Ki-67 after approximately 2 weeks of treatment as a percentage of the baseline value, i.e., the ratio between the Ki-67 measurements obtained from Day 14 visit and baseline, will be modelled using a GLM, with both stratification factors (i.e., baseline Ki-67 score and the tumor size) and treatment as covariates. Treatment effects will be summarized using the LSM and their two-sided CIs on the log scale. In addition, for easier interpretation of the data, the treatment effects will be back transformed and expressed as the geometric means and their CIs on the original percentage scale by treatment arm. The percent change, in other words, relative reduction, of Ki-67 after 2 weeks of treatment will also be reported as the complement of the ratio between the Ki-67 measurement from Day 14 and

baseline (i.e.  $100\% \times [1 - \text{Ki-67 from Day 14} / \text{Ki-67 from baseline}]$ ). Exploratory stratified analysis may be performed subject to data availability.

#### 9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

The tertiary endpoints are:

- Evaluate the TME: Exploratory analysis will be performed to study the changes in the TME (stroma, immune and tumor cells) from baseline and on treatment, utilizing spatial omics platforms.
- Exploratory analysis will be performed to study the impact of allelic variants of drug metabolizing enzymes and transporters on PK exposure of PF-07220060.
- Exploratory evaluations will be done on the associations of tumor gene mutations with treatment outcome by ctDNA analyses.
- Exploratory evaluations will be performed on the associations of gene expression profiles with treatment outcome by using tumor tissues.

#### 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, 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, QTc, 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 QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

#### Safety QTcF Assessment

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

If more than 1 ECG is collected at a nominal time (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 QTc 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 on treatment QTc value and the average of the time-matched baseline values, or the average of the predose triplicate values on Day 1.

Any QT value >500 ms should be manually read and confirmed by the Investigator.

The analysis of ECG results will be based on participants in the safety analysis set with baseline (Day 1 predose) and on-treatment (Day 14 predose) 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.

Data will be summarized and listed for, HR, PR interval, QRS complex, QT interval, QTcF, and if appropriate Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute value of QTcF and changes from baseline in QTcF after treatment by study arm, 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 AEs on 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 treatment period. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

### **9.4. Interim Analyses**

No interim analysis will be conducted for this study.

### **9.5. Sample Size Determination**

The study is not designed to perform a formal hypothesis test but rather to evaluate the effects of PF-07220060 plus letrozole and letrozole alone, respectively on Ki-67 expression in tumors after 2 weeks of treatment to inform future studies.

The sample size for this study is determined to allow for sufficient assessment of cell cycle arrest activity, safety, and tolerability for PF-07220060 in combination with letrozole and letrozole alone. A sufficient number of participants will be screened to achieve 118 participants enrolled to study intervention in a 1:1 ratio to either the experimental arm (PF-07220060 plus letrozole) or control arm (letrozole). Since there are no formal hypothesis testing proposed for the study, no power calculation is performed. For the proposed number of participants enrolled, it is estimated about 85% of the participants (50 in experimental arm and 50 in control arm) would have evaluable Ki-67 data. [Figure 1](#) and [Table 2](#) above show some probable analysis, scenario and relevant credible intervals in this setting.

## **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 (e.g., 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 Medical Device Regulation 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 (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

#### **10.1.2. Financial Disclosure**

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

#### **10.1.3. Informed Consent Process**

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

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

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

The participant must be informed that 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.

#### **10.1.6. 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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the EudraCT/CTIS, and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial results on [www.clinicaltrials.gov](http://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.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts CSR synopses and plain-language study results summaries on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to [www.clinicaltrials.gov](http://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 “bona-fide 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. Participant-level 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 (e.g., 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 (e.g., 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 in 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 evaluation of AEs and SAEs as described in [Section 10.3.3](#) 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 re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee, in order to mitigate the risk of reidentification:

- 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 (e.g., birth date, date of hospital admission/discharge, date of death), participant identification numbers (e.g., Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (e.g., street address, city, country, postal code, IP address), participant contact information (e.g., 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 (e.g., Florence is the preferred system if available).
- There may be unplanned situations where the sponsor may request medical records (e.g., 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.

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. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

#### **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.

## 10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [SoA](#) section of this protocol.

**Table 3. Lab Tests**

| Core Lab Tests       |                              |                     |
|----------------------|------------------------------|---------------------|
| Hematology           | Chemistry                    | Other               |
| Hemoglobin           | ALT                          | PT/INR <sup>c</sup> |
| Platelets            | AST                          | aPTT <sup>c</sup>   |
| WBC                  | Alkaline Phosphatase         | FSH <sup>d</sup>    |
| Absolute Neutrophils | Total Bilirubin <sup>a</sup> |                     |
|                      | Albumin                      | Urinalysis          |
|                      | Sodium                       | Urine dipstick      |
|                      | Potassium                    |                     |
|                      | Calcium                      |                     |
|                      | BUN/Urea                     |                     |
|                      | Creatinine                   |                     |
|                      | Cystatin-C <sup>b</sup>      |                     |

a For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include eosinophils, total bile acids, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase.

b Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (See [Section 10.7.1](#)).

c Required at screening and Day 1 pre-dose. During the study, tests will be done as clinically indicated.

d For confirmation of postmenopausal status only in participants who are <60 years of age per Inclusion Criteria.

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

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

#### 10.3.1. Definition of AE

| AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul> |

| Events <u>Meeting</u> the AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., 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:           <ul style="list-style-type: none"> <li>• Is associated with accompanying symptoms;</li> <li>• Requires additional diagnostic testing or medical/surgical intervention;</li> <li>• 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.</li> </ul> </li> <li>• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.</li> <li>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.</li> <li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>• 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.</li> </ul> |
| 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 (e.g., 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 (e.g., 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 but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study, 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 Intensity](#) 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 via PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

\* EDP (with or without an associated SAE): using the PSSA.

\*\* EDB is reported to Pfizer Safety via PSSA, which would also include details of any SAE that might be associated with the EDB.

\*\*\* Environmental or occupational exposure: AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to [Section 10.1.9](#) 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).

| 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                             |

#### Assessment of Causality

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

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the PSSA and in accordance with the SAE reporting requirements.

#### Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- 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 DCT**

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eSAE or PSSA).
- 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 electronic DCT (e.g., eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT 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 PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, e.g., 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**

All participants enrolled in this study will be postmenopausal females as defined in [Section 5.1](#), and thus contraceptive and barrier guidance does not apply.

## 10.5. Appendix 5: Genetics

### Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The 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 (see [Section 8.6.1](#)) will be stored for up to 3 years post CSR finalization or other period as per local requirements.
  - Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (e.g., 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. 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  $3 \times \text{ULN}$  (i.e., 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 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  $\geq 2$  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 (e.g., 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 Calculation Recommendations

#### 10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations<sup>1</sup>

eGFR (mL/min/1.73m<sup>2</sup>)

| 2021 CKD-EPI<br>Screat only | Screat<br>(mg/dL) | Scys<br>(mg/L) | Recommended eGFR Equation                                       |
|-----------------------------|-------------------|----------------|-----------------------------------------------------------------|
| Female                      | if ≤ 0.7          | NA             | $eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$ |
| Female                      | if > 0.7          | NA             | $eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$ |
| Male                        | if ≤ 0.9          | NA             | $eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$ |
| Male                        | if > 0.9          | NA             | $eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$ |

(Inker et al, 2021)

### 10.7.3. Kidney Function Calculation Tools

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](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). 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 (i.e., eGFR or eCrCl) will be according to CTCAE criteria.

| CTCAE Term (2017)                                                                                                                                                                                                                                  | Grade 1                                                                        | Grade 2                                                          | Grade 3                                                          | Grade 4                                                                      | Grade 5 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------|---------|
| <b>Acute Kidney Injury (AKI)</b>                                                                                                                                                                                                                   | N/A                                                                            | N/A                                                              | 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). |                                                                                |                                                                  |                                                                  |                                                                              |         |
| <b>Creatinine increased</b>                                                                                                                                                                                                                        | >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                                                                   | N/A     |
| <b>Chronic Kidney Disease (CKD)</b>                                                                                                                                                                                                                | eGFR $\geq 60$ to 89 mL/min/1.73m <sup>2</sup> OR eCrCl $\geq 60$ to 80 mL/min | eGFR 30 to 59 mL/min/1.73m <sup>2</sup> OR eCrCl 30 to 59 mL/min | eGFR 15 to 29 mL/min/1.73m <sup>2</sup> OR eCrCl 15 to 29 mL/min | eGFR <15 mL/min/1.73m <sup>2</sup> OR eCrCl <15 mL/min OR dialysis indicated | Death   |
| <b>Proteinuria</b>                                                                                                                                                                                                                                 | ADULTS: Proteinuria 1+ OR Proteinuria $\geq 0.5$ to <1.0 g/24hr                | ADULTS: Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24hr   | ADULTS: Proteinuria 4+ OR Proteinuria $\geq 3.5$ g/24hr          | N/A                                                                          | N/A     |

CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.

## 10.8. Appendix 8: ECG Findings of Potential Clinical Concern

| ECG Findings That <u>May</u> Qualify as AEs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Marked sinus bradycardia (rate &lt;40 bpm) lasting minutes.</li> <li>New PR interval prolongation &gt;280 ms.</li> <li>New prolongation of QTcF to &gt;480 ms (absolute).</li> <li>New prolongation of QTcF by <math>\geq 60</math> ms from baseline.</li> <li>New-onset atrial flutter or fibrillation, with controlled ventricular response rate: i.e., rate &lt;120 bpm.</li> <li>New-onset type I second-degree (Wenckebach) AV block of &gt;30 second duration.</li> <li>Frequent PVCs, triplets, or short intervals (&lt;30 seconds) of consecutive ventricular complexes.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| ECG Findings That <u>May</u> Qualify as SAEs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>QTcF prolongation &gt;500 ms.</li> <li>New ST-T changes suggestive of myocardial ischemia.</li> <li>New-onset LBBB (QRS complex &gt;120 ms).</li> <li>New-onset right bundle branch block (QRS complex &gt;120 ms).</li> <li>Symptomatic bradycardia.</li> <li>Asystole:               <ul style="list-style-type: none"> <li>In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses <math>\geq 3</math> seconds or any escape rate &lt;40 bpm, or with an escape rhythm that is below the AV node;</li> <li>In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.</li> </ul> </li> <li>Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate &gt;120 bpm.</li> <li>Sustained supraventricular tachycardia (rate &gt;120 bpm) ("sustained" = short duration with relevant symptoms or lasting &gt;1 minute).</li> <li>Ventricular rhythms &gt;30 seconds' duration, including idioventricular rhythm (heart rate &lt;40 bpm), accelerated idioventricular rhythm (HR &gt;40 bpm to &lt;100 bpm), and</li> </ul> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>monomorphic/polymorphic ventricular tachycardia (HR &gt;100 bpm [such as torsades de pointes]).</p> <ul style="list-style-type: none"> <li>• Type II second-degree (Mobitz II) AV block.</li> <li>• Complete (third-degree) heart block.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>ECG Findings That Qualify as SAEs</b></p> <ul style="list-style-type: none"> <li>• Change in pattern suggestive of new myocardial infarction.</li> <li>• Sustained ventricular tachyarrhythmias (&gt;30 seconds' duration).</li> <li>• Second- or third-degree AV block requiring pacemaker placement.</li> <li>• Asystolic pauses requiring pacemaker placement.</li> <li>• Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.</li> <li>• Ventricular fibrillation/flutter.</li> <li>• At the discretion of the investigator, any arrhythmia classified as an adverse experience.</li> </ul> |

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 prohibited concomitant medications listed below should not be taken with PF-07220060 for the period of time at least equal to, the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with PF-07220060 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 (e.g., emerging DDI results for 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.

The lists in the subsequent subsections are not all-inclusive lists. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

### 10.9.1. Prohibited or Cautioned Concomitant Medications Due to Potential Increase or Decrease of PF-07220060 Exposure

| Drug Category       | Drugs                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                     | Washout Period Requirement for Prohibited Medications |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| CYP3A4/5 inhibitors | Prohibited strong inhibitors:                                                                                                                                                                                                                                                                                       | Moderate inhibitors to be avoided or used with caution:                                                                                                                                                                                                                                                                             | 5 half-lives of inhibitor                             |
|                     | boceprevir<br>clarithromycin<br>cobicistat<br>conivaptan<br>danoprevir<br>elvitegravir<br>grapefruit juice DS3<br>indinavir<br>itraconazole<br>ketoconazole (excluding shampoo and topical cream)<br>lopinavir<br>mibefradil<br>mifepristone<br>nefazodone<br>nelfinavir<br>posaconazole<br>ritonavir<br>saquinavir | amprenavir<br>aprepitant<br>atazanavir<br>casopitant<br>cimetidine<br>ciprofloxacin<br>darunavir<br>delavirdine<br>diltiazem<br>dronedarone<br>erythromycin<br>fluconazole<br>fluvoxamine<br>grapefruit juice or grapefruit-related<br>citrus fruits (eg, Seville oranges, pomelos)<br>isavuconazole<br>istradefylline<br>lefamulin |                                                       |

| Drug Category                          | Drugs                                                                                                                                    |                                                                                                                                                                                                                                                                                       | Washout Period Requirement for Prohibited Medications   |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
|                                        | telaprevir<br>telithromycin<br>tipranavir                                                                                                | letermovir<br>magnolia vine (schisandra sphenanthera)<br>netupitant<br>ravuconazole<br>tofisopam<br>verapamil<br>voxelotor                                                                                                                                                            |                                                         |
| <b>CYP3A4/5 and/or UGT2B7 inducers</b> | <b>Prohibited strong inducers:</b>                                                                                                       | <b>Moderate CYP3A inducers and/or other known UGT2B7 to be avoided or used with caution:</b>                                                                                                                                                                                          | 10 days or 5 half-lives of inducer, whichever is longer |
|                                        | avasimibe<br>carbamazepine<br>lumacaftor<br>phenobarbital<br>phenytoin<br>rifabutin<br>rifampin<br>rifapentine<br>St John's Wort extract | bosentan<br>cannabinol<br>cannabis<br>cenobamate<br>daclatasvir/asunaprevir/<br>beclabuvir<br>efavirenz<br>elagolix<br>etravirine<br>lersivirine<br>lopinavir<br>modafinil<br>nafcillin<br>phenobarbital<br>rifabutin<br>telotristat ethyl<br>thioridazine<br>tipranavir<br>ritonavir |                                                         |
| <b>UGT2B7 inhibitors</b>               | <b>Prohibited known strong UGT2B7 inhibitor:</b>                                                                                         | <b>Other known inhibitors to be avoided or use with caution:</b>                                                                                                                                                                                                                      | 5 half-lives of the inhibitor                           |
|                                        | cannabidiol                                                                                                                              | eltrombopag<br>fluconazole<br>flunitrazepam<br>indomethacin<br>mefenamic acid<br>umifenovir                                                                                                                                                                                           |                                                         |
| CCI [REDACTED]                         | <b>Prohibited CCI include but are not limited to the following:</b><br>CCI [REDACTED]                                                    |                                                                                                                                                                                                                                                                                       | At least 7 days before the first dose of PF-07220060    |

| Drug Category | Drugs | Washout Period Requirement for Prohibited Medications |
|---------------|-------|-------------------------------------------------------|
|               | CCI   |                                                       |

(Drug Interaction Solutions, 2020)

#### 10.9.2. Cautioned Concomitant Medications due to Potential Increase of Exposures by PF-07220060

| Drug Category            | Drugs                 |
|--------------------------|-----------------------|
| CCI substrates with NTI  | CCI                   |
| CCI substrates with NTI  |                       |
| P-gp substrates with NTI | colchicine<br>digoxin |

(Drug Interaction Solutions, 2020)

#### 10.9.3. Prohibited CCI

| Drug Category | Drugs |
|---------------|-------|
| CCI           |       |

#### 10.9.4. Recommendations for CCI Usage With PF-07220060

| CCI | Liver Metabolism (main metabolic pathway) | Transporter(s) involved with potential DDI | Recommendation* |
|-----|-------------------------------------------|--------------------------------------------|-----------------|
| CCI |                                           |                                            | Avoid           |

| CCI | Liver Metabolism<br>(main metabolic pathway) | Transporter(s) involved with potential DDI | Recommendation *   |
|-----|----------------------------------------------|--------------------------------------------|--------------------|
| CCI |                                              |                                            | 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 and other CCI from the respective USPIs.

## 10.10. Appendix 10: Country-Specific requirements

### 10.10.1. European Union

This study will be conducted in compliance with Regulation (EU) 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:

- Any SUSAR via reporting to the EudraVigilance database
- 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

### 10.11. Appendix 11: 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 1 03 October 2024

**Overall Rationale for the Amendment:** The primary rationale for this amendment is to clarify text regarding prohibited and concomitant treatments in response to health authority feedback.

| Substantial Changes                                                                                                                 |                                                                                             |                   |
|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------|
| Change                                                                                                                              | Rationale                                                                                   | Section           |
| Added text to clarify that prohibited drugs are prohibited throughout the conduct of the study and not just prior to the first dose | In response to a regulatory request to clarify and align with Appendix 9                    | Section 6.9.1.1.1 |
| Added list of UGT2B7 inhibitors and inducers, and modified washout period requirements for prohibited drugs                         | In response to a regulatory request to include these for consistency with Section 6.9.1.1.1 | Appendix 9        |
| Added a new subsection to address concomitant medications which may result in DDI with letrozole                                    | In response to a regulatory request to include potential DDI with letrozole                 | Section 6.9.2.1   |

## 10.12. Appendix 12: Abbreviations

The following may be used in the protocol.

| Abbreviation | Term                                                        |
|--------------|-------------------------------------------------------------|
| aBC          | advanced breast cancer                                      |
| ADP          | adenosine diphosphate                                       |
| AE           | adverse event                                               |
| AESI         | adverse event of special interest                           |
| AIDS         | acquired immunodeficiency syndrome                          |
| AJCC         | American Joint Committee on Cancer                          |
| AKI          | acute kidney injury                                         |
| ALKP         | alkaline phosphatase                                        |
| ALT          | alanine aminotransferase                                    |
| ANC          | absolute neutrophil count                                   |
| ARA          | acid reducing agent                                         |
| aPTT         | activated partial thromboplastin time                       |
| ASCO         | American Society of Clinical Oncology                       |
| AST          | aspartate aminotransferase                                  |
| ARA          | acid reducing agents                                        |
| AV           | atrioventricular                                            |
| AxMP         | auxiliary medicinal product                                 |
| BC           | breast cancer                                               |
| BCS          | breast-conserving surgery                                   |
| BCRP         | breast cancer resistance protein                            |
| BID          | twice daily                                                 |
| BMD          | bone mineral density                                        |
| BP           | blood pressure                                              |
| bpm          | beats per minute                                            |
| BUN          | blood urea nitrogen                                         |
| CAP          | College of American Pathologists                            |
| CBC          | complete blood count                                        |
| CCCA         | complete cell cycle arrest                                  |
| CDK          | cyclin-dependent kinase                                     |
| CDK4         | cyclin-dependent kinase 4                                   |
| CDK4i        | cyclin-dependent kinase 4 inhibitor                         |
| CDK6         | cyclin-dependent kinase 6                                   |
| CDK4/6       | cyclin-dependent kinase 4/6                                 |
| CDK4/6i      | cyclin-dependent kinase 4/6 inhibitor                       |
| CFR          | Code of Federal Regulations                                 |
| CI           | confidence interval                                         |
| CIOMS        | Council for International Organizations of Medical Sciences |
| CK           | creatinine kinase                                           |
| CKD          | chronic kidney disease                                      |
| CKD-PI       | chronic kidney disease epidemiology                         |
| CONSORT      | Consolidated Standards of Reporting Trials                  |

| Abbreviation        | Term                                                                                           |
|---------------------|------------------------------------------------------------------------------------------------|
| CR                  | complete response                                                                              |
| CrCl                | creatinine clearance                                                                           |
| CRF                 | case report form                                                                               |
| CRO                 | contract research organization                                                                 |
| CSR                 | Clinical Study Report                                                                          |
| CT                  | clinical trial                                                                                 |
| CTCAE               | Common Terminology Criteria for Adverse Events                                                 |
| ctDNA               | circulating tumor DNA                                                                          |
| CTIS                | Clinical Trial Information System                                                              |
| C <sub>trough</sub> | lowest plasma concentration before scheduled dose                                              |
| CYP                 | cytochrome P450                                                                                |
| DCT                 | data collection tools                                                                          |
| DDI                 | drug-drug interaction                                                                          |
| DIKI                | drug-induced kidney injury                                                                     |
| DILI                | drug-induced liver injury                                                                      |
| DLT                 | dose-limiting toxicity                                                                         |
| CCI                 |                                                                                                |
| DU                  | dispensable unit                                                                               |
| eBC                 | early breast cancer                                                                            |
| EC                  | ethics committee                                                                               |
| ECG                 | electrocardiogram                                                                              |
| ECOG                | Eastern Cooperative Oncology Group                                                             |
| eCrCl               | estimated creatinine clearance                                                                 |
| eCRF                | electronic case report form                                                                    |
| EDB                 | exposure during breastfeeding                                                                  |
| EDP                 | exposure during pregnancy                                                                      |
| E-DMC               | External Data Monitoring Committee                                                             |
| eGFR                | estimated glomerular filtration rate                                                           |
| EOT                 | end of treatment                                                                               |
| ER                  | estrogen receptor                                                                              |
| eSAE                | electronic serious adverse event                                                               |
| ET                  | endocrine therapy/early termination                                                            |
| EU                  | European Union                                                                                 |
| EudraCT             | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FFPE                | formalin-fixed paraffin-embedded                                                               |
| FSH                 | follicle-stimulating hormone                                                                   |
| GCP                 | Good Clinical Practice                                                                         |
| GGT                 | gamma-glutamyl transferase                                                                     |
| GI                  | gastrointestinal                                                                               |
| GLM                 | general linear model                                                                           |
| GLP                 | Good Laboratory Practice                                                                       |
| HBV                 | Hepatitis B virus                                                                              |
| HDI                 | human development index                                                                        |

| Abbreviation | Term                                                                                                |
|--------------|-----------------------------------------------------------------------------------------------------|
| HER2         | human epidermal growth factor receptor 2                                                            |
| HCV          | Hepatitis C virus                                                                                   |
| HIV          | human immunodeficiency virus                                                                        |
| HR           | heart rate/hormone receptor                                                                         |
| HRT          | hormone replacement therapy                                                                         |
| IB           | Investigator's Brochure                                                                             |
| ICD          | informed consent document                                                                           |
| ICH          | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID           | identification                                                                                      |
| IHC          | immunohistochemistry                                                                                |
| ILD          | interstitial lung disease                                                                           |
| IMP          | investigational medicinal product                                                                   |
| IMPACT       | The Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen                       |
| IND          | Investigational New Drug                                                                            |
| INR          | international normalized ratio                                                                      |
| IP           | investigational product                                                                             |
| IPM          | investigational product manual                                                                      |
| IPAL         | Investigational Product Accountability Log                                                          |
| IRB          | Institutional Review Board                                                                          |
| IRT          | Interactive Response Technology                                                                     |
| ISH          | in situ hybridization                                                                               |
| IV           | intravenous                                                                                         |
| Ki-67        | antigen Kiel 67                                                                                     |
| LBBC         | left bundle branch block                                                                            |
| LFT          | liver function test                                                                                 |
| LHRH         | luteinizing hormone-releasing hormone                                                               |
| LSM          | least squares method                                                                                |
| CCI          |                                                                                                     |
| mBC          | metastatic breast cancer                                                                            |
| mCRPC        | metastatic castration resistant prostate cancer                                                     |
| MedDRA       | Medical Dictionary for Regulatory Activities                                                        |
| MOI          | medically qualified individual                                                                      |
| CCI          |                                                                                                     |
| MTD          | maximum tolerated dose                                                                              |
| NA           | not applicable                                                                                      |
| NCI          | National Cancer Institute                                                                           |
| NCT          | neoadjuvant chemotherapy                                                                            |
| NET          | neoadjuvant endocrine therapy                                                                       |
| NIMP         | non-investigational medicinal product                                                               |
| nsAI         | nonsteroidal aromatase inhibitor                                                                    |
| NTI          | narrow therapeutic index                                                                            |
| CCI          |                                                                                                     |

| Abbreviation | Term                                              |
|--------------|---------------------------------------------------|
| CCI          |                                                   |
| OR           | objective response                                |
| ORR          | objective response rate                           |
| OS           | overall survival                                  |
| PACL         | protocol administration clarification letter      |
| PD           | pharmacodynamics(s)                               |
| PDx          | patient derived xenograft                         |
| PE           | physical examination                              |
| PFS          | progression-free survival                         |
| P-gp         | p-glycoprotein                                    |
| PK           | pharmacokinetic(s)                                |
| CCI          |                                                   |
| PR           | progesterone receptor/partial response/pulse rate |
| PS           | performance status                                |
| PSSA         | Pfizer's Serious AE Submission Assistant          |
| PT           | prothrombin time                                  |
| PVC          | premature ventricular contraction                 |
| QD           | every day                                         |
| QTc          | corrected QT interval                             |
| QTcF         | QTc corrected using Fridericia formula            |
| QTL          | quality tolerance limit                           |
| RB           | retinoblastoma                                    |
| RDE          | recommended dose for expansion                    |
| RECIST       | Response Evaluation Criteria in Solid Tumors      |
| RP3D         | recommended phase 3 dose                          |
| SAE          | serious adverse event                             |
| sAI          | steroidal aromatase inhibitor                     |
| SAP          | Statistical Analysis Plan                         |
| SAS          | safety analysis set                               |
| SCreat       | serum creatinine                                  |
| Scys         | serum cystatin C                                  |
| SmPC         | Summary of Product Characteristics                |
| SoA          | schedule of activities                            |
| SOC          | standard of care                                  |
| SOP          | standard operating procedure                      |
| SRSD         | Single reference Safety Document                  |
| SUSAR        | Suspected Unexpected Serious Adverse Reaction     |
| T bili       | total bilirubin                                   |
| TEAE         | treatment-emergent adverse events                 |
| TME          | tumor microenvironment                            |
| TNM          | tumor, nodes, metastases                          |
| UGT          | uridine 5' diphosphate-glucuronosyltransferase    |

| Abbreviation | Term                                  |
|--------------|---------------------------------------|
| UK           | United Kingdom                        |
| ULN          | upper limit of normal                 |
| UPCR         | urine protein:creatinine ratio        |
| US           | United States                         |
| USPI         | United States Prescribing Information |
| WBC          | white blood cell                      |
| WHO          | World Health Organization             |
| WOCBP        | woman/women of childbearing potential |

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