Protocol C4391025

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

Statistical Analysis Plan (SAP)

Version: **3**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28 May 2024	Original 20 Mar 2024	N/A	N/A
2 9 April 2025	Original 20 Mar 2024	Preparing for data snapshot to support regulatory interaction.	Removal of language pertaining to use of dummy randomization for all data analysis prior to final analysis.
3 23 June 2025	Amendment 2, 25 November 2024	Adding details and clarification for some parts.	Sec 3.2.1. Added clarity on use of central versus local lab Ki-67 data. Sec 3.3. and 6.2.4.3. Added clarity on baseline for patients not treated. Sec 3.3. Updated ATC codes for new anti-cancer therapy. Sec 6.2.4.3. Removed analysis for parameters without CTCAE grades. Sec 6.3.1.1. Added updates required for several summary and analysis tables. Sec 6.3.3.1. Added specifications for algorithms.
		Updating modifications made to analysis plan described in the protocol.	Sec 2.1. Updated to incorporate protocol amendment changes that have incorporated previous modifications and added new modifications.
		Added definition of actual treatment arm.	Sec 3.2 Added definition of the definition to be used to assign actual treatment arm based on dose taken.
		Update and add analysis set.	Sec 4. and as applicable throughout the document: Modified to Ki-67 Analysis Set to require ≥10% Ki-67 value at baseline. Sec 4. Added ctDNA analysis set. Added PK parameter set.
		Adding ctDNA analysis	Sec 6.2.2. ctDNA is added as a secondary endpoint and details for analysis pertaining to it are added throughout the SAP.

		Addition of subgroup analysis.	Sec 6.1.1.1. Added details on addition of subgroup summaries by baseline characteristics.
		Updates to data presented in summary tables. Corrections and further details for GLM model used to study the Day14 change from baseline in Ki-67 levels.	Sec 6.2.1.1. Added information on covariates to be considered for the model and stratification factors are removed from the model.
		Update to PK Analysis	Sec 6.2.3. Added analysis set and modification to PK analysis.
		Modifications to summaries for AE	Sec 6.2.4.1. Edits and modifications made to summaries to be presented with respect to Adverse Events.
		Addition of Vital Sign summaries.	Sec 6.2.4.4. Added summaries for Vital Signs.
		Modification to ECG criteria	Sec 3.2.2.3. and 6.2.4.4. Modified categorization criteria.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4391025.

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 Kiel 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.

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 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

For lab assessments, the analyses will summarize laboratory tests on the treatment period, not the study period as mentioned in the original protocol. The correction was made in the protocol in amendment 2.

The PK concentration analysis set will include data below the lower limit of quantitation. The original protocol specified the set to include only above lower limit of quantitation which was corrected in amendment 2.

The Ki-67 evaluable analysis set is modified to require ≥10% at baseline by local assessment for the analysis set flag.

The Full analysis set will not require participants to take at least 1 dose.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Efficacy	*Evaluate the effects of PF-07220060 plus letrozole and letrozole alone, respectively, on Ki-67 expression in tumors after 2 weeks of treatment.*	*Complete cell cycle arrest (CCCA) (Ki-67 ⩽ 2.7%) rates at Day 14 (centrally assessed biopsy).*	*See Section 2.2.1.*
Safety	*Evaluate the safety and tolerability of PF-07220060 plus letrozole and letrozole alone after 2 weeks of treatment.*	*Incidence of all AEs, SAEs, and AEs leading to study drug discontinuation*	
Efficacy	*Evaluate ctDNA response on treatment after 2 weeks of treatment.*	*ctDNA measurements at baseline and Day 14.*	
PK	*To determine steady-state plasma concentrations of PF-07220060 in combination with letrozole.*	*C_{trough} and peri-biopsy plasma concentrations of PF-07220060.*	
Efficacy	*Determine changes in Ki-67 expression.*	*Ki-67 staining.*	

2.2.1. Primary Estimand(s)

The primary estimand of this study estimates the treatment effect on CCCA rates (Ki-67 ⩽ 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 ⩽ 2.7%.*
- *Intercurrent events: only participants with adequate Ki-67 results from baseline (locally) 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. 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 Wilson score-based method for each treatment arm.*

2.2.2. Secondary Estimand(s)

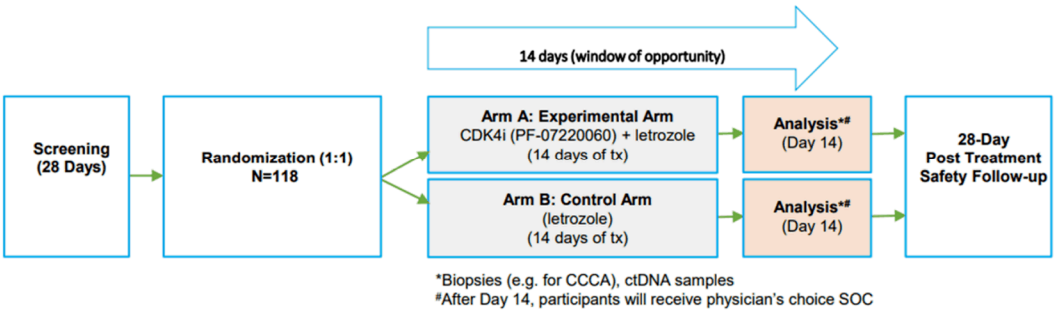
No estimands are defined for any of the secondary endpoints.

2.2.3. Additional Estimand(s)

No other estimands are defined for this study.

2.3. Study Design

Figure 1: Study Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Efficacy Endpoint(s)

The primary endpoint is CCCA (Ki-67 $\leqslant$2.7%) rates at Day 14 (centrally assessed biopsy).

*Analysis of the primary endpoint will be based on the Ki-67 evaluable analysis set. The Ki-67 evaluable participants are participants randomized to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (*locally assessed value for analysis set evaluation or where specified, centrally assessed value for all analyses*) and Day 14 (assessed centrally) visits per central lab.*

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

Analysis will be performed to study the Day14 change from baseline in Ki-67 levels using centrally assessed Ki-67 values only. Patients with only locally assessed baseline Ki-67 data but no centrally assessed Ki-67 data will not be included in this analysis.

Circulating tumor DNA (ctDNA) change from baseline to Day14 will be analyzed using Methylation tumor fraction (TF) measured by the Guardant Health Infinity methylation score. For reduction of change of ctDNA, only patients with ctDNA successfully profiled at both baseline and Day14 and at least one detectable sample (TF>0) at baseline or Day14 will be included in the analysis.

3.2.2. Safety Endpoint(s)

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

The on-treatment period is defined as the time from the first dose of study treatment through the minimum of 35 days (28 days follow-up + 7 days window) after last dose of study treatment or start of subsequent anti-cancer therapy minus 1 day, whichever occurs first. Adverse events that occurred on the same day as the first dose of any study intervention will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study intervention will be considered baseline assessments (see Section 3.4.1. for the definition of baseline).

3.2.2.1. Adverse Event

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 study treatment period. Listings of deaths will be provided.

For all the AE summaries by PT only, some PTs will be clustered. Each participant will be counted only once within each clustered term. The number of total events will be based on the individual PTs/clustered terms. Some examples of clustered terms (also referred to as Custom Queries (CQ)) are as follows:

Cluster Terms to Be Used	
NEUTROPENIA	Neutropenia, Neutrophil count decreased, Neutrophil percentage decreased, Cyclic neutropenia
LEUKOPENIA	Leukopenia, White blood cell count decreased.
LYMPHOPENIA	Lymphopenia, Lymphocyte count decreased, Lymphocyte percentage decreased
ANAEMIA	Anemia, Haemoglobin decreased, Red blood cell count decreased, Haematocrit decreased
THROMBOCYTOPENIA	Thrombocytopenia, Platelet count decreased.

FATIGUE	Asthenia, Fatigue, Malaise.
ILD (SMQ)	Includes any reported PTs that are part of the Standardized MedDRA Query Interstitial Lung Disease (narrow)
STOMATITIS	Aphthous ulcer, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Stomatitis.
RASH	Rash, Rash erythematous, Rash maculo-papular, Rash papular, Rash pruritic, Dermatitis, Dermatitis acneiform, Dermatitis contact, Rash macular, Rosacea
TRANSAMINASES INCREASED	Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased
ABDOMINAL PAIN	Abdominal pain, Abdominal pain upper
DIARRHEA	Diarrhoea, Frequent bowel movements, Defaecation urgency, Gastric hypermotility.

The clustered term definitions maybe updated based on MedDRA versions and team decisions.

Treatment-Emergent Adverse Events (TEAEs)

A conservative case approach will be taken whereby all AEs that occur on or after the first dose of study treatment and before the end of treatment (i.e., 35 days after last dose of study treatment or start of subsequent anti-cancer therapy minus 1 day, whichever occurs first) will be considered TEAEs.

TEAEs related to study drug (PF-07220060, letrozole) as judged by the investigator, i.e., treatment related AEs, are collected.

TEAEs will be characterized by type, frequency, severity as graded by NCI CTCAE Version 5.0, timing, and relationship to treatment on each arm. AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

Adverse Events of Special Interest

Hematologic toxicities such as anaemia, neutropenia and thrombocytopenia are considered AESI. AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. The following clustered terms (as defined in Section 3.2.2.1)are associated with these three AESIs.

• Anaemia(CQ)

• Neutropenia(CQ)

• Thrombocytopenia(CQ)

3.2.2.2. Laboratory Data

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 treatment period.

3.2.2.3. ECG Data

Changes from baseline for the ECG parameters QTcF, PR interval, and QRS complex will be summarized by treatment and time. QTcF will be derived based on data from CRF page for Locally Read ECG.

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

Degree of Prolongation		Mild (ms)	Moderate (ms)	Severe (ms)
Absolute Value	≤450	>450-≤480	>480-≤500	>500
Change from baseline		≤30	>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 QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. Changes from baseline will be defined as the change between the on treatment QTcF value and the average of the predose 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 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.

3.2.3. Pharmacokinetic (PK) Endpoints

C_{trough}: Pre-dose plasma concentrations of PF-07220060 on Day 14

$C_{peri\text{-}biopsy}$: Peri-biopsy plasma concentrations of PF-07220060 on Day 14

3.3. Baseline Variables

Definition of baseline for efficacy and safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for efficacy and safety analyses. If the patient is not treated, the randomization date will be used. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the

same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation.

Start and end dates of study treatment

The start date is the date (Day 1) of the first dose of any study treatment for participants on both arms. The date of last dose of any study treatment is the latest date of non-zero dosing of the study drug.

Start date of new anti-cancer treatment

Start date of new anti-cancer treatment is used to determine the end of the on-treatment period (see Section 3.2.2). The start date of new anti-cancer treatment is the earliest start date of anti-cancer drug therapy recorded in the "CONMED" eCRF pages that is after the first dose of any study treatment. A treatment with ATC Level 2 code L01 and L02 will be considered as a cancer treatment.

Study arms and duration

The study interventions are administered for 14 days. The actual treatment is PF-07220060+Letrozole if the participant takes any PF-07220060 dose during the on-treatment period, the treatment arm is Letrozole otherwise.

Study Arm(s)		
Arm Title	**Arm A** PF-07220060 + letrozole	**Arm B** Letrozole
Arm Type	Experimental	Control
Arm Description	Participants will receive: • PF-07220060 as three 100 mg tablets (i.e., 300 mg), orally, BID with food continuously for 14 days, plus • letrozole as one 2.5 mg tablet, orally, QD continuously for 14 days.	Participants will receive: • letrozole as one 2.5 mg tablet, orally, QD, continuously for 14 days.

3.4. Exploratory Endpoints

The study will be collecting ctDNA measurements at baseline and Day 14. The data will be summarized by study arm.

Study will 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 by ctDNA analyses with treatment outcome.
- Exploratory evaluations will be performed on the associations of gene expression profiles with treatment outcome by using tumor tissues.

Detailed descriptions of the exploratory biomarker endpoints and their analyses will be described in the biomarker SAP (bSAP).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	Description
Full analysis set	All participants randomized to study intervention. Study drug assignment is designated according to initial randomization, regardless of whether participants receive study drug or receive a different drug from that to which they were randomized. To be used for protocol deviation summary and may be used for baseline characteristics.
Safety analysis set	All participants randomized 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. To be used for all safety, treatment compliance and exposure.
Ki-67 evaluable analysis Set	All participants randomized to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (assessed locally with value ≥ 10%) and Day 14 (assessed

	centrally) visits per central lab. To be used for all efficacy related to Ki-67. May be used for baseline characteristics.
PK concentration set	All randomized participants, who take at least 1 dose and have at least 1 analyte concentration. To be used for PK endpoints.
PK parameter set	A subset of the PK concentration set including all participants who have a PK sample that met PK parameter evaluability criteria.
Pharmacodynamic/ Biomarker analysis set(s)	The Pharmacodynamic/Biomarker analysis population is defined as all randomized participants with at least 1 of the Pharmacodynamic/Biomarkers evaluated at pre and/or post dose. This is applicable for exploratory endpoints and will be included in the bSAP.
ctDNA analysis set	The ctDNA analysis population is defined as all randomized participants who take at least 1 dose with at least 1 ctDNA evaluated at pre or post dose. To be used for ctDNA related endpoints.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

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.

5.2. General Methods

In general, descriptive summaries will be presented for the efficacy 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.

Adequate Ki-67 value is any non-missing Ki-67 measurements from local or central lab at baseline, and any adequate Ki-67 measurements from central lab from C1D14 visit. If the value at C1D14 is reported as “0”, “<1”, or other special characters will be imputed as ‘0.1” with % as unit.

5.2.1. Analyses for Binary Endpoints

In general, binary endpoints will be summarized by frequency counts and percentages with corresponding 2-sided 95% CIs using the Wilson score method. Where applicable, the point estimate of the odds ratio between two treatment groups will be provided along with corresponding 2-sided 95% CIs. Unless otherwise specified, the calculation of percentages will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

5.2.2. Analyses for Continuous Endpoints

Continuous variables will be summarized using descriptive statistics, including the non-missing number, mean, standard deviation, median, minimum, and maximum. Descriptive statistics for PK parameters and biomarkers may also include geometric mean ± standard deviation (calculated as exp[μ±s]) and coefficient of variation (%CV).

5.2.3. Analyses for Categorical Endpoints

Categorical variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of percentages will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

5.3. Methods to Manage Missing Data

Participants may have missing data due to several reasons (missed measurement at a clinical visit, missed visit, treatment/study discontinuation, etc.). In general data points will not be imputed. Missing statistics, e.g., when they cannot be calculated, should be presented as 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'NA'.
If the value of Ki-67 at C1D14 is reported as "0", "<1", or other special characters implying the value is below quantification limits, the value will be imputed as '0.1" with % as unit.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Complete cell cycle arrest (CCCA) (Ki-67 ⩽2.7%) rates at Day 14

6.1.1.1. Main Analysis

- Estimand strategy: section 2.2.1.

- Analysis set: Ki-67 evaluable patients, participants randomized to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (assessed locally with value ≥ 10%) and Day 14 (assessed centrally) visits per central lab.

- Analysis methodology: *The rate of patients with CCCA in each group will be calculated along with the 2-sided 95% CI using the Wilson score-based method. In addition, 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. The criteria of success may be defined as follows:*

$$Posterior\ Probability\left(CCCA_{experimental\ arm} > CCCA_{control\ arm}\right) > P\%$$

The prior for the above calculation can be assumed to be a Beta (0.5, 0.5). A Beta-Binomial model, using a non-informative prior, can also be used to estimate the posterior probability, based on observed CCCA rates. The median, 95% credible interval, and the estimated posterior probability that the true CCCA rate is >45%, >60%, >68%, >70%, >80%

will be calculated within each arm. Based on the distribution of the data observed among patients enrolled, proportion of participants with CCCA will be presented by subgroups for each treatment arm. All or some subgroups as follows may be considered: histopathological classification, histological grade, TNM stage, nodal status, progesterone status, and central baseline Ki-67.

- Intercurrent events and missing data: only participants with adequate Ki-67 results from baseline (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. No missing values will be imputed.

- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed Ki-67 and change from baseline will be presented for each treatment arm.

6.2. Secondary Endpoint(s)

6.2.1. Change from baseline in Ki-67 levels

Analysis will be performed to study the change from baseline in Ki-67 levels.

6.2.1.1. Main Analysis

- Analysis set: All participants randomized to study intervention, who take at least 1 dose of study intervention, and who have adequate Ki-67 measurements from baseline (assessed locally with value ≥ 10%) and Day 14 (assessed centrally) visits per central lab. For the summary and listing of Ki-67, only the central lab value will be used.

- Analysis methodology: 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 treatment as covariate. Based on the distribution of the data observed among patients enrolled, more covariates may be considered for the model. All or some categories as follows may be considered: histopathological classification (invasive ductal carcinoma vs others), histological grade (grades 1 and 2 vs grade 3 and missing), TNM stage, nodal status, progesterone status (positive or negative), and central baseline Ki-67. 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. Data will be summarized by treatment arm along with two-sided 95% CIs and descriptive summary. 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% × [1-Ki-67 from Day 14 / Ki-67 from baseline]).

6.2.2. CtDNA analysis

- Analysis set: The ctDNA analysis population is defined as all randomized participants who take at least 1 dose with at least 1 ctDNA evaluated at pre and/or post dose.

- Analysis methodology: TF measured by methylation score from both baseline and Day14 will be used to calculate the methylation ratio:

  MR = (TF_Day14) / (TF_baseline)

  If baseline TF = 0 and Day 14 TF > 0, MR is capped at 400%. Relative change will be defined as 1-MR and will be compared between arms. Patients without detectable ctDNA (TF=0) at both baseline and Day14 will be excluded in the analysis. The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and post-baseline visits for TF and change from baseline will be presented for each treatment arm.

6.2.3. PK analysis

- Analysis set: Participants qualifying for PK concentration set.
  - Concentrations of PF-07220060 will be listed and summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by nominal timepoint and treatment
- Analysis set: Participants qualifying for PK parameter set.
  - C_{trough} and $C_{peri\text{-}biopsy}$ of PF-07220060 will be listed and summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation).
  - Box and whisker plots of individual subject PK parameters (C_{trough} and $C_{peri\text{-}biopsy}$) will be plotted by visit and overlaid with geometric mean.

6.2.4. Safety Summaries and Analyses

The safety analysis set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment arm.

6.2.4.1. Adverse Events

AEs will be classified using the latest version of MedDRA dictionary. The severity of the AEs will be graded according to the NCI CTCAE Version 5.0.

All analyses will be based on TEAEs unless otherwise specified. Treatment emergent is defined in Section 3.2.2.1. Adverse Event of Special Interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trials 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.

Unless otherwise specified, AEs will be summarized by frequency and percentage of participants with the AE in the category of interest as described above, by treatment arm, PT and Maximum CTCAE Grade in decreasing frequency based on the frequencies observed.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the worst NCI CTCAE Version 5.0 severity grade, as appropriate, will be included in the summaries for severity.

Detailed information collected for each AE will include a description of the event, severity, seriousness, causal relationship to study drug(s), and action taken.

AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE Version 5.0 Grade 3 or higher, study drug related events, and SAEs will be considered with special attention. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The percentage of participants with an event will be calculated using the number of participants in the safety analysis set as the denominator. Data will be summarized by treatment arm and overall.

Treatment related TEAEs are AEs with relationship to either study treatment (PF-07220060 or Letrozole) reported by the investigator and those of unknown relationship.

The following summaries of TEAEs will also be provided by treatment arm:

- TEAEs: Number of participants evaluable for AEs, total number of AEs (counting each unique PT across all participants), number of participants with SAEs, number of participants with Grades 3 and 4 AEs, number of participants with Grade 5 AEs, number of participants who discontinued study treatment due to AEs, and number of participants with missed doses, and/or dose interruption due to AEs. (All Causality, and Treatment Related)

- TEAEs by MedDRA Preferred Term/Cluster Term, and Maximum CTCAE Grade (All Causality, and Treatment Related)

- TEAEs by MedDRA System Organ Class/Preferred Term and Maximum CTCAE Grade (All Causality, and Treatment Related)

- TEAEs Leading to Discontinuations/Drug Withdrawn by MedDRA Preferred Term/Cluster Term and Maximum CTCAE Grade (All Causality, and Treatment Related)

- TEAEs Leading to Dose Interruptions by MedDRA Preferred Term/Cluster Term and Maximum CTCAE Grade (All Causality, and Treatment Related)

A summary of SAEs and deaths will be provided. Disease progression or hospitalization solely due to signs and symptoms of recurrence or disease progression should not be reported as an SAE, unless the death occurred within the reporting period. The number and percentage of participants with each of the following will be presented for SAEs by treatment arm:

- Serious TEAEs by MedDRA Preferred Term /Cluster Term (All Causality, and Treatment Related).

- Serious TEAEs by System Organ Class/Preferred Term (All Causality).
- Grade 5 SAEs: SAEs with fatal outcome TEAEs by MedDRA SOC, PT (All Causality).
- TEAEs by MedDRA PT and Maximum CTCAE Grade for Grade 3-5 AEs (All Causality, and Treatment Related).

6.2.4.2. Deaths

Summary of death will be presented with numbers and percentages as following:

- Deaths from start of treatment to and including 35 days after last dose of study treatment as well as primary cause of death.
- Cause of death
    - Disease under study
    - Study treatment toxicity
    - Unknown
    - Other

Deaths (during the active treatment period of the study up to 35 days after last dose of study treatment) will be listed together with the treatment arm, follow-up time, and primary cause of death.

6.2.4.3. Laboratory Data

The lab baseline value is defined as the last available value prior to the first dose of study treatment. If the patient is not treated, the randomization date will be used.

Hematology and chemistry results will be programmatically graded according to the NCI CTCAE Version 5.0 for relevant parameters. A shift summary of baseline grade by maximum postbaseline grade will be presented. The analyses will summarize laboratory tests during the entire on-treatment period. The denominator with respect to percentages for summary tables for each laboratory parameter will be all participants in the safety analysis set with post baseline data for that parameter.

6.2.4.4. Electrocardiograms

All ECGs obtained during the study will be evaluated for safety. All summary statistics and data presentations will use the average data of the triplicate ECGs or the individual data of the single ECGs, as applicable.

For all participants of the safety analysis set, individual change in QTcF will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

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 QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the pre-dose triplicate values on Day 1. If no repeated measurements are collected, then this methodology does not apply.

For all participants in the safety analysis set, categorical analysis of the QTcF data will be conducted and summarized as follows:

1. The number and percentage of participants with maximum increase from baseline in the QTcF (≤30, >30-≤60, and >60 msec).

2. The number and percentage of participants with maximum post-dose QTcF (≤450, >450-≤480, >480-≤500, and >500 msec).

3. PR changes from baseline ⩾25% if absolute baseline value was ⩾220 msec.

4. QRS changes from baseline ⩾25% if absolute baseline value was ⩾120 msec.

6.3. Baseline and Other Summaries and Analyses

6.3.1. Baseline Summaries

Baseline summaries will include (but not limited to) the following analyses based on the FAS overall and by treatment arm.

6.3.1.1. Demographic and Baseline Characteristics

Demographic characteristics and baseline characteristics will be summarized by treatment arm and overall.

- Demographic characteristics
    - Gender: Female
    - Race: White, Black (Black, African American), Asian, American Indian or Alaska Native, native Hawaiian or Pacific Islander, Not Reported, Unknown
    - Ethnicity (Hispanic or Latino or of Spanish origin vs. not, Not Reported)
    - Geographical region (US, EU, Asian, other)
    - Age (years): summary statistics, age category (<65 years, ⩾ 65 years)
    - Weight, height, body mass index: summary statistics

- Baseline disease characteristics
    - Histological hormone receptor status"
        - Estrogen receptor: ≥10%, 1-<10%, <1%

        - Progesterone receptor: positive (≥1%), negative (<1%), Not reported
        - HER2 overall status: positive, negative, equivocal, unknown.
    - Primary tumor characteristics:
        - histologic classification.
        - histologic grade, and
        - TNM stage, T-stage and N-stage.
    - ECOG Performance Status: 0, 1
    - Baseline Ki-67 value from local and central assessment: <20%, ≥20%.

6.3.1.2. Medical History and Primary Diagnosis

Medical history, and cancer history will be summarized by treatment arm and overall using the information from the 'Primary Diagnosis', 'General Medical History', and 'Molecular Biology of Disease' eCRF pages. Duration since onset of the disease will be summarized.

6.3.2. Study Conduct and Participant Disposition

Summaries will be based on the FAS overall and separately by treatment arm. An accounting of the study participants will be tabulated including screened, screened but not randomized, randomized, randomized but not treated, treated (including discontinued, ongoing at cutoff date), assessed for safety (AEs, laboratory data), and PK (including specific parameters being analyzed). Participants not meeting the eligibility criteria will be identified. Participants not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized. Randomization errors will be described.

6.3.3. Study Treatment Exposure

The following analyses will be based on the safety analysis set by treatment arm.

6.3.3.1. Extent of Exposure

The planned dose for all patients is 300 mg BID for PF-07220060, and 2.5mg QD of Letrozole.

Dose interruptions: Dose Interruption is defined as a situation when the actual dose taken during a dosing period deviated from the planned dose for that dosing period. Either actual dose being zero (e.g., dose holding regardless of reason) or the actual dose being less than the planned dose (e.g., missed doses or did not complete the planned dose) are considered as dose interruption.

Dose interruptions due to AE: Dose Interruption due to AE is defined as a situation when the actual dose taken during a dosing period deviated from the planned dose for that dosing period and the reason is due to Adverse Events. Either actual dose being zero (e.g., dose holding regardless of reason, missed dose) or the actual dose being less than the planned dose (e.g., missed doses or did not complete the planned dose due to adverse event) are considered as dose interruption. If the reason can't be identified based on the CRF data, AE would be assumed as the underlying reason.

Missed doses: Missed doses are defined as an event where the actual dose is less than planned dose due to reasons other than AE.

Intended cumulative dose: PF-07220060 will be administered as three 100 mg tablets (i.e., 300 mg), orally, twice daily, with food continuously for 13.5 days. The intended cumulative dose is 8100mg. Letrozole will be administered as one 2.5 mg tablet, orally, QD continuously for 14 days. The intended cumulative dose is 35 mg.

Intended treatment duration is 13.5 days for all participants (taking into account the schedule of treatment and the visit on day 14, participants are expected to take drug BID for PF-07220060. The intended treatment duration is 14 days for Letrozole.

Actual treatment duration (days) = the date of last non-zero dose of study drug – date of first dose of study drug +1.

Overall cumulative dose = total amount of dose administered over the full treatment period using actual treatment duration.

Actual dose intensity [DI]= [overall cumulative dose]/[intended treatment duration in days].

Relative dose intensity [RDI]: The basic intent is to evaluate dose per day factoring in dose reductions or interruptions.

Overall RDI (%) = 100 × [overall cumulative dose]/[intended cumulative dose].

The following will be summarized per treatment arm:

- Actual treatment duration (median, range and categorized to <=14 days, >14 days),
- RDI (median and range),
- Actual cumulative Dose and Actual Dose Intensity,
- Percentage of participants with dose interruptions,
- Number of participants with dose interruptions due to AE,
- Number of drug holds/ drug interruptions due to AE (1, 2,3, >3 interruptions).

6.3.4. Concomitant Medications and Nondrug Treatments

The analyses will be based on the safety analysis set by treatment arm.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period until 35 days after the last dose of study intervention or until the participant begins a new anti-cancer therapy, whichever occurs first, as well as those started during the on-treatment period.

Prior medications are medications, other than study drugs and pre-medications for study drug, which are stopped before the first dose of study treatment.

Summary of concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A

participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

7. INTERIM ANALYSES

No interim analyses are planned for this study.

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
CCCA (Ki-67 ≤2.7%) rates at Day 14 (centrally assessed biopsy).	Main analysis	Ki-67 evaluable analysis set	Only data collected are included. Missing data will not be imputed.	N/A
Changes in Ki-67 expression between baseline (centrally assessed biopsy). and Day 14 (centrally assessed biopsy).	Secondary analysis	Ki-67 evaluable analysis set	Only data collected are included. Missing data will not be imputed.	N/A
Change of ctDNA TF from baseline to Day 14	Secondary analysis	CtDNA analysis set	Only data collected are included. Missing data will not be imputed.	N/A

Appendix 2. List of Abbreviations

Abbreviation	Term
Abs	Absolute
AE	Adverse event
AESI	AE of special interest
BLQ	Below the limit of quantitation
BID	Twice daily
bSAP	Biomarker Statistical Analysis Plan
AE	Adverse event
AESI	AEs of special interest
BC	Breast Cancer

Abbreviation	Term
BP	Blood pressure
CCCA	Complete cell cycle arrest
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
C_{max}	Maximum observed concentration
CQ	Customized query
CRF	Case Report Form
CSR	Clinical Study Report
ctDNA	circulating tumor DNA
CV	Coefficient of variation
DI	Actual dose intensity
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMR	Geometric mean ratio
GMT	Geometric mean titer
ICD	Informed consent document
ICH	International Council for Harmonisation
IRC	Internal review committee
LS	Least-squares
LSM	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Pulse rate

Abbreviation	Term
PT	Preferred term
QD	Once daily
QTc	Corrected QT
QTcF	Corrected QT (Fridericia method)
qual	Qualitative
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent AE
TF	Tumor fraction
TME	Tumor microenvironment
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary