PHASE 1/2a DOSE ESCALATION AND EXPANSION STUDY EVALUATING SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMICS AND ANTI-TUMOR ACTIVITY OF PF-06873600 AS A SINGLE AGENT AND IN COMBINATION WITH ENDOCRINE THERAPY

Investigational Product Number:	PF-06873600
Investigational Product Name:	N/A (Not applicable)
United States (US) Investigational New Drug (IND) Number:	134457
European Clinical Trials Database (EudraCT) Number:	2020-001757-40
Protocol Number:	C3661001
Phase:	1/2a
NCT#	NCT03519178

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 9	03 March 2023	The primary purpose of this amendment is to define the primary completion date (PCD), end of study date, and clarify continued access to study intervention for eligible patients who continue to derive a clinical benefit from study treatment. • Section 13.2 added to define primary completion date, clarify end of trial and access to the investigational product for the patients who continue to derive clinical benefit. Section 13.1 revised to define end of trial for all countries. • Appendix 8 added to detail study procedures after PCD and until end of study. • An additional SoA table SCHEDULE OF ACTIVITIES Following Amendment 09: Treatment and Follow-up added to detail study activities after PCD and to replace ALL other SoA tables. • Text added in Section 7 to clarify the SoA after PCD. Updates from Protocol Administrative Change Letter (PACL) dated 21 February 2022 pertaining to safety include the following: • Added text to clarify that hematology labs for C1 and C2D8, D15 and D21 for Part 2 are required in footnote 11 of SCHEDULE OF ACTIVITIES (Part 1, Part 2 and J-LIC). • Clarification of the dose modification guidelines for PF-06873600 related hematologic toxicity in Section 5.4.3.4 Table 3. Additional updates to incorporate changes per PACLs dated 03 October 2022 and 21 February 2022: <u>Per PACL 03 October 2022:</u> • Removal of scheduled PK and select biomarker sampling for participants in Part 2 in Section 7.3.5 and footnotes b and e in Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments – Immediate release formulation in Part 2 (Arms A ,B and C) and footnote f in Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments - Modified Release Formulation in Part 2. • Remove long term follow-up for Part 2 in Section 7.7 and footnote 14 in SCHEDULE OF ACTIVITIES (Part 1, Part 2 and J-LIC).

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		Per PACL 21 February 2022: • Remove mandatory skin biopsy requirement for patients in the mandatory paired biopsy subset in Part 2 in footnote d in Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments – Immediate release formulation in Part 2 (Arms A, B and C) and footnote e in Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments - Modified Release Formulation in Part 2, and in Section 1.5.1. In addition, clarifications, administrative and typographical modifications were made.
Amendment 8	08 July 2021	The primary purpose of this amendment is to incorporate feedback received from PMDA which is applicable to Japan only. **Appendix 7 Country-Specific Requirement, Appendix 7.1 Japan Specific Requirements**: The following sections were updated or added. • Japan Participation: Japan Lead-in Cohort. • Figure 10 and Japan Lead-in Cohort statement were updated. • Exclusion Criterion was added: Current or history of idiopathic interstitial pneumonias (IIPs), drug-induced pneumonitis or radiation pneumonitis. In some cases, imaging with scarring may be observed in asymptomatic patients resulting from prior treatments. These cases (eg, if the scarring is identified at baseline and not considered clinically significant and/or active disease) may be eligible at the discretion of the PI, following a discussion and agreement with the Sponsor. Hepatitis B Viral monitoring: • Corrected typo. Added text for Granulocyte-colony stimulating factors: • Clarified the definition of use of G-CSF. Interstitial lung disease (ILD) and pneumonitis: • Added the screening for ILD. • Dose interruption and discontinuation related ILD.

Document	Version Date	Summary of Changes and Rationale

		Pregnancy Testing:
		• Clarified the pregnancy testing requirements.
		
		In addition, clarifications, administrative and typographical modifications were made:
		• 3.1.5 Criteria for Dose Escalation
		  • Language around a DLT period of 28 days for Part 2 was removed from the text, as this is not applicable.
		  • Language around 28-count blister packs for Letrozole has been added SOA and Section 5.3.1.2.

Amendment 7	07 June 2021	The primary purpose of this amendment is to add Arm C in Part 2 of the study (ie, PF-06873600 in combination with fulvestrant in HR-positive HER2-negative locally advanced or mBC (naïve to CDK4/6 inhibitors). In addition, a Japan lead-in cohort (J-LIC) has been added to confirm the safety of PF-06873600 monotherapy in Japanese participants (Appendix 7 was added to provide all the J-LIC details).
		The following clarifications were added to the SCHEDULE OF ACTIVITIES (PART 1 AND PART 2) • Addition of 'and J-LIC' in the title. • Footnote 11: addition of 'and Cycle 2'. • Footnote 12: addition of 'For Japan only, participants with HBsAb and HBcAb should be monitored with HBV viral load (refer to Appendix 7).
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (PART 1– EXCEPT MODIFIED RELEASE SELECTION COHORT WITHIN PART 1C*– QD AND BID DOSING REGIMEN • Addition of 'AND J-LIC**' and removal of 'QD'in the title; • Addition in the footnote of: • The necessity of hospitalization and its duration of DLT assessment period for Japanese participants in J-LIC are based on the investigator's decision • Addition in footnote j of the sentence 'Exceptions may be granted after consultation with the Sponsor'.

Document	Version Date	Summary of Changes and Rationale
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - IMMEDIATE RELEASE FORMULATION IN PART 2 (ARMS A ANDB) • Addition of' ARM C' in the title and removal of the row 'PF-06873600 PK Urine collectionb' in the table. • The row 'PF-06873600 PK Urine collection', the row 'Semm Biomarkers' and the footnote **h** were removed this was an en-or and should have be.en removed in the previous protocol amendment. • Footnote c and d: the wording 'Arms A and B' was replaced by 'each aim'. • Footnote g: addition of the sentence 'A sample is also to be collected when patient develops progressive disease'.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - MODIFIED RELEASE FORMULATION IN PART 2 • The row' Se11llllBiomarkers' and the footnote i were removed. • Footnotes d and e: the wording 'Anus A and B' was replaced by 'each rum'. • Footnote h: addition of the sentence: 'A sample is also to be collected when patient develops progressive disease'. CCI [redacted] I [redacted] I [redacted] Section 2. Study Objectives and Endpoints • The additional group of patients (ie, Alm C) was described in Pait 2 of the primary objective: HR-positive HER2-negative locally advanced or mBC (PF-06873600+fulvestrant) (nai've to CDK4/6 inhibitors).

Document	Version Date	Summary of Changes and Rationale
		Section 3.1. Study Overview • A brief explanation for the addition sub-cohort (the Japan lead-in cohort) was provided. • The number of patients in the last sentence of this section has been changed from '70' to '100'.
		Section 3.1. Study Overview • Figure 8 has been modified to reflect the addition of the extra groups of patients.
		Section 3.2. Part 2 PF-06873600 Combination Dose Expansion • In Section 3.2.2, the wording 'Arm A prior to initiating this dose expansion arm' was removed. The wording 'who have not previously received' was replaced by 'who have not received any prior treatment with a'. The word available was added in front of 'preliminary'. The information '(prior adjuvant therapy with AI is permitted)' was added after metastatic setting. • Addition of 'Section 3.2.3 Part 2/Arm C- PF-06873600 in Combination with Fulvestrant in HR-Positive HER2-Negative Locally Advanced or mBC (naïve to CDK4/6 inhibitors)' describing the evaluation PF-06873600 in this Arm C.
		Section 3.3.1. Tumor Biopsy • The number of patients was changed from 12 patients to 10 patients and the wording 'Arms A and B' was replaced by 'the dose expansion arm'.
		3.3.2. Skin Biopsy • Deletion of the wording 'Arms A and B'.
		Section 4.1. Inclusion Criteria • In Part 2, Arm A: Addition of the sentence 'Participants with only non-measurable disease may be enrolled if a compelling clinical rationale is provided by the investigator and approved by the sponsor' to allow for increased patient access. In addition, more than one line of chemotherapy may be allowed following a discussion with SPONSOR. • In Part 2, Arm B: Addition of the wording 'as treatment' in the 2nd bullet point and addition of the sentence 'Have not received an aromatase inhibitor

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		in the advanced or metastatic setting (prior adjuvant therapy with AI is pennitted). Addition of the sentence 'Participants with only non-measurable disease may be enrolled if a compelling clinical rationale is provided by the investigator and approved by the sponsor' to allow for increased patient access in the 5th bullet point • Addition of the inclusion criteria of the Alm C. • Addition of the wording 'c:::20 years in Japan in the 3rd bullet. • Addition of the sentence 'When there is a high FSH level, it should be confinned that there is no other medical cause'.
		Section 4.3. Lifestyle Requirements • A clarification in the first paragraph was added: 'as approved by local regulatory authority'.
		• Section 5.7.3. Hematopoietic Grov.rth Factors • A clarification and a note were added; • For Japan only: since the indication and dosage of G-CSF compounds approved in Japan may differ from ASCO guidelines, refer to Japanese package insert and local clinical guideline. • Note: erythropoietin is not approved for anemia caused by chemotherapy in all local regions, nor is it cwTently approved in Japan.
		Section 7.1.3. Laboratory Safety Assessments • Table 4: Addition of 'or aPTT' in the platelet-coagulation row and addition of 'or Bicarbonate' next to carbon dioxide in the Chemistry colwnn.
		CCI [redacted] I [redacted]

Document	Version Date	Summary of Changes and Rationale
		CCI [redacted] I [redacted] Section 7.3.3. Skin Biopsy • The wording 'AmlSA and B' was removed.
		Section 9.3.2. Pait 2 • The number of patients has been changed from 70 to 100. • The sample size determination for the Ann C was added.
		Section 9.7. Data Monitoring Committee • Addition of the sentence 'These data would also include all treated paiticipants'.
		Appendix 7 was added to provide the infoimation for the Japanese cohoit: Appendix 7 Japan Country-Specific.
Amendment6	15 December 2020	The primaiy purpose of this amendment is to delete Pait **1** Alm D and Pait 2 Alms A, B, and C, which will no longer be studied as a result of focused development of PF-06873600 in combination with fulvestrant in patients who have received a prior CDK4/6 inhibitor and a nonsteroidal aromatase inhibitor (ie, Pait 2 Alm E) and PF-06873600 in combination with letrozole in patients who have not been previously treated for their advanced or metastatic HR+/HER2- breast cancer (ie, Pait 2 Alm D). These changes were made to align with a change in development strategy by the SPONSOR. In addition, clarifications, administrative and typographical modifications were made.
		SCHEDULE OF ACTIVITIES (PART **1** AND PART 2) and SCHEDULE OF ACTMTIES (MODIFIED RELEASE SELECTION COHORT WITHIN PART lC) • Deleted reference to Pait lD (Dose Titration Alm). • Added COVID-19 to Viral disease screening tests footnote.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (PART **1**- EXCEPT MODIFIED RELEASE SELECTION

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		COHORT WITHIN PART lC)-QD AND BID DOSING REGIMEN: • Footnoted: Clarified that C2Dl biopsy should be taken at 4hr post the moming dose in the C2D1±3 days window. • Footnote e: Allowed a ±2 days window for the ClD15 skin biopsy, and clarified that biopsies should be taken at the specified hours post the moming dose. • Footnote j: Clarified that tumor tissue from cytologic sampling and bone biopsy specimens are not adequate and should not be submitted.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - IMMEDIATE RELEASE FORMULATION IN ARM A AND ARM B IN PART 2: • CCI [redacted] • Footnoted: Clarified that the C2Dl biopsy can be collected within ±3 days from C2D1 at 4 hr post the moming dose. • CCI [redacted] • Urine PK assessments have been removed from the SOA table.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY ANDBIOMARKERASSESSMENTS: PART 1D and SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - ARM A (STUDY PARTICIPANTS ASSIGNED TO THE FOOD EFFECT ASSESSMENT ONLY) IN PART 2

Document	Version Date	Summary of Changes and Rationale
		• Deleted Prut lD and coITesponding Schedule of Activities Table. • Deleted food effect substudy in Pait 2 and coITesponding Schedule of Activities Table.
		Section 1.5.1 Rationale for Pre-, On- and End of Treatment Biopsies r [redacted] • Clarified the patient population in Prut 2 of the study, which will enroll 2 different dose expansion anns.
		Section 2. Study Objectives and Endpoints: Paits lA and lC: Single agent dose escalation and Pait **lB:** Combination dose finding: CCI [redacted] I [redacted] I [redacted] Pait 2: PF-06873600 Combination Dose Expansion: • Changed secondary endpoint of PD modulation from following treatment with PF-06873600 to PF-06873600 in combination with fulvestrant or letrozole. CCI [redacted] I [redacted] I [redacted]
		Section 3.**1** Study Design • Updated overall study schema and deleted the Pait **lD** PF-06873600 dose titration cohoit. • The term recommended dose for expansion (RDE) replaces recommended Phase 2 dose (RP2D).

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		• Clarified that both available formulations of PF-06873600 at the respective RDE will be studied in combination with endocrine therapy in Part 1B (approximately 12 patients to be dosed in the respective endocrine therapy combinations, with approximately 6 patients receiving PF-06873600 IR + endocrine therapy and approximately 6 patients receiving PF-06873600 MR + endocrine therapy in both the fulvestrant and letrozole arms). • Updated the approximate number of patients expected to be enrolled in the dose escalation/finding safety cohorts is 75 patients and approximately 70 patients are expected to be enrolled in Part 2.
		Section 3.1.4 Part 1D PF-06873600 Dose Titration Cohort • Deleted Part 1D dose titration cohort, as well as information pertaining to dose-escalation, minimum safety criteria, and dose de-escalation.
		Section 3.2 changed to Part 2 PF-06873600 Combination Dose Expansion • Deleted Arms A, B, and C in Part 2, and renamed Part 2/Arm E to Arm A, and added Part 2/Arm B (PF-06873600 in Combination with Letrozole in HR-positive HER2-negative Locally Advanced or mBC (first-or second-line setting).
		Section 3.2.1 changed to Part 2/Arm A – PF-06873600 in Combination with Fulvestrant in HR positive HER2 negative Locally Advanced or mBC (second or third line setting). • The sample size for Part 2A has been increased from 30 patients (formally Part 2E) to approximately ~40 patients to allow for additional flexibility to test either formulation being studied.
		Section 3.3.1 Tumor Biopsy • Editorial changes/clarifications.
		Section 3.4 Food Effect Substudy in Part 2 Arm A • Deleted single agent dose expansion cohort in Part 2 to examine the effect of food on the PK of PF-0687360) which was previously planned as part of the monotherapy arm in Part 2, which is no longer being studied.

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		Section 4.1 Inclusion Criteria • Clarified that in Pait lB, measurable disease per RECIST 1.1 is required. • Deleted inclusion criteria peitaining to deleted Arms A, B, and C in Pait 2. • Changed Arm E to Alm A (Patients with HR-positive HER2-negative locally advanced or mBC (second- or third-line setting [histologically or cytologically proven]). • Added criteria for added Arm B in Pait 2 (Patients with HR-positive HER2-negative locally advanced or mBC who are nai've to CDK4/6 inhibitors [histologically or cytologically proven]).
		Section 5.4.3.4 Dose Reductions • Deleted instmctions for dose reduction guidelines for pruticipating in the Pait lD.
		Section 5.4 Administration • Deleted TID dosing regimen information. • Deleted requirements for the food effect cohort (Pait 2 Arm A).
		Section 7.2.2 Deleted urine for analysis of PF-06873600 concentration from the protocol due to the absence of monotherapy anus.
		Section 7.3 Biomarker and Phannacodynrunic Assessments • Deleted duplicate and unnecessru-yparagraphs.
		CCI [redacted] I [redacted] I [redacted]

Document	Version Date	Summary of Changes and Rationale
		• Removed unnecessary sentences.
		CCI [redacted] • Other editorial changes/clarifications.
		Section 9.3 Sample Size Detennination • Updated samples sizes for Part 1 and Pait 2 Ann A PF-06873600 + fulvestrant (second or third line setting) and Prut 2 Arm B PF-06873600 + letrozole ann (first line setting).
		Section 7.6.1 Additional Research • Editorial changes.
		Section 9.5.1.1 Single-Dose and Steady-State PF-06873600 Phaimacokinetic Analysis • Deleted analysis of urine drng concentrations.
		Section 9.5.1.2 Effect of Food on PF-06873600 Phannacokinetics • Deleted assessment of PK pru·ameters from food effect substudy.
Amendments	25 August 2020	The primary purpose of this amendment is to add Pait lD, which will use a dose titration design to allow patients the opportunity to titrate up to a higher dose of PF-06873600 on C2Dl to maximize efficacy following a thorough review of safety parameters. In addition, clarifications, administrative, and typographical modifications were made. Updated reference and abbreviation lists as applicable.
		SCHEDULE OF ACTIVITIES (PART 1 AND PART 2): • 12-Lead ECG row: Added "and C2 Pait lD only" on Day 8 of Cycles 1 and 2 for clarity. • Added timing of CT/MRI scans for Pait lD in table during active treatment phase. • Footnote# 9: Added bullet for tirning of ECG for Pait lD only.

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		• Footnote #16: Added clarifying language for patients in Part lD (Dose Titration Ann) only, patients may titrate up their dose to three times a day (TID) starting in Cycle 2. Added specifics for tablet counts for PF-06873600 for sites to consider when scheduling drug dispensing visits. • Footnote #17: Added specifics for tablet counts for letrozole for sites to consider when scheduling chug dispensing visits.
		SCHEDULE OF ACTIVITIES (MODIFIED RELEASE SELECTION COHORT WITHIN PART lC) • Footnote 14: Added specifics for tablet counts for PF-06873600 for sites to consider when scheduling chug dispensing visits.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (PART 1-EXCEPT MODIFIED RELEASE SELECTION COHORTWITHINPARTlC*ANDPARTlD)-QD AND BID DOSING REGIMEN: • Added Prut lD to the title. • Made ClD15 6 hour post-dose skin biopsy optional for all patients. • Added a 4-hour post-dose assessment column (including allowable window) for C2Dl. Moved PF-06873600 PK blood sampling and skin biopsy biospecimen collections from C2D1 0 hours post-dose to 4 hours post-dose. • Footnote c: Added instructional text for PK samples for Cl5Dl and C2Dl. • CCI [redacted] • Footnote e, Skin Biopsy Biospecimen: Indicated that screening and C2D1 skin punch biopsies are mandatory for patients enrolled in the biomarker cohorts of Prut 1 and optional for other patients, and that ClD15 biopsy is optional for all patients. Added reference to Laboratory Manual for details.

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		• CCI [redacted]
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS- PART 1D • Added new table with footnotes for Patt lD.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (PART 1*) - TID DOSING REGIMEN • Title: Added (NOT PART **1** D- DOSE TITRATION ARM) for clarification. • Made ClD15 6 hour post-dose biopsy optional for all patients. • Added a 4 hour post-dose assessment column (including allowable window) for C2Dl. Moved PF-06873600 PK blood sampling and skin biopsy biospecimen collections from C2D1 0 hours post-dose to 4 hours post-dose. • CCI [redacted] • Footnote e, Skin Biopsy Biospecimen: Indicated that screening and C2D1 skin punch biopsies are mandatory for patients enrolled in the biomarker cohorts of Patt **1** and optional for other patients, and that ClD15 biopsy is optional for all patients. Added reference to Laboratory Manual for details. • CCI [redacted]
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - ARM A, ARM B (STUDY PARTICIPANTS NOT ASSIGNED TO THE FOOD EFFECT ASSESSMENT), ARM C, ARM D AND ARM E IN PART 2 • Added a 4 hour post-dose assessment column (including allowable window) for Cycles :?:2. Moved PF 06873600 PK blood sam lino and skin

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		biopsy biospecimen collections from C2Dl O hours post-dose to 4 hours post-dose. • Added an assessment ofthymidine kinase on ClD8. • Updated footnotes c, d. and i with biopsy requirements. • Footnote k: Removed Cycle 3.
		SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - ARM B (STUDY PARTICIPANTS ASSIGNED TO THE FOOD EFFECT ASSESSMENT ONLY) IN PART 2 • Deleted (Ann) B from title and table row, replaced with A. • Added column for ClD8, 0 hours post-dose for thymidine kinase assessment. • CCI [redacted] • Updated footnotes d, f, and k with biopsy requirements. • Footnote h: Removed Cycle 3.
		Section 1 Introduction: • Section 1.5.1 Rationale for Pre, On, and End of Treatment Biopsies: • Indicated that serial and skin biopsy samples will be collected and indicated the number of patients in each coho1t of Pait **1.** Added "and skin punch biopsy" to the mandato1y tumor collections for a subset of patients in Anns A and B. • CCI [redacted]

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		• CCI [redacted] • Section 1.6 Overview ofLetrozole (Femara®) updated USPI to most cwTent version (2020). • Section 1.7 Overview ofFulvestrant (Faslodex®) updated USPI to most cwTent version (2020).
		Section 2. Study Objectives and Endpoints: • Added Pait lD as applicable to objectives and endpoints.
		Section 3 Study Design: • Section 3.1: Added description of Pait lD as applicable, updated Figw-e 8 to include Pait lD, added Figure 10: Part lD Dose Titration Study Schema. Added descriptive text for dosing frequency for patients in Prut lD. • Updated patient numbers for the dose escalation/finding safety cohorts and biomarker cohorts in Paits lA and lB. • Added Section 3.1.4: Pait lD PF-06873600 dose titration cohoit. • Section 3.1.6 Criteria for Dose Escalation: Updated paragraph under Table 2 for clarity; replaced "unless related to treatment emergent toxicity" with "unless the patient has experienced a DLT prior to receiving 75% of the planned dose", and added In Pait lD, a patient is considered evaluable for the up-titration if he/she receives at least 75% of the planned doses of the study intervention dw-ing cycle 1 and cycle 2. • Section 3.3.1 Tumor Biopsy: Specified the number of patients. Deleted "and skin" from last paragraph as it is not applicable. • Section 3.3.2 Skin Biopsy: Added details for skin biopsy requirements.

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		• Section 3.4 Food Effect Substudy in Part 2 Arm A: Changed Arm B to Arm A.
		• Section 4.2 Exclusion Criteria: Criterion #10, added text for SARs-CoV2 testing and infections and added a reference/hyperlink to Appendix 6 for SARs-CoV2 infection eligibility.
		Section 5 Study Treatments: Listed letrozole and fulvestrant as investigational products rather than standard of care. • Section 5.2 Patient Compliance: Indicated that fulvestrant will be administered at the investigational site and PF-06873600 and letrozole will be distributed to the patient. • Section 5.3 Investigational Product Supplies: Indicated that letrozole and fulvestrant will be supplied by Pfizer, • Section 5.3.1.1 PF-06873600: Updated strengths for the immediate and modified-release (MR) tablets and added details regarding table counts. • Section 5.3.1.2 Letrozole: • Removed “and Fulvestrant” from section title. • Added new section: Section 5.3.1.3 Fulvestrant • Section 5.4.1, PF-06873600: Added bullet for Part 1D only. Added instructions for the administration of letrozole and fulvestrant. • Section 5.4.2. 5.4.2.2. Requirements for the Food Effect Cohort (Part 2 Arm A): Replaced Arm B with Arm A. • Added new section: 5.4.3.2 Dose Interruption of Patients with Presumed or Active COVID-19/SARs-CoV2 Infection. • Section 5.4.3.4 Dose Reductions: Added instructions for patients in Part 1D and added that at the discretion of the investigator or Sponsor based on emerging safety data patients may be asked to reduce their dose within the DLT window. • Table 3 Dose Modifications for PF-06873600-Related Toxicity. Added instructions for patients in

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		Pait lD with Grade 3 nonhematologic and hematologic toxicities.
		Section 6.4: Updated text regarding permanent discontinuation of study intervention and the study with text to comply with updated protocol template language effective December 2019/May 2020.
		CCI [redacted]
		Section 8 Adverse Event Repoiting • Section 8.1.4 Time Period for Collecting AE/SAE Infonnation: Added details for long-term follow-up collection period for Prut 2 only.
		Sections 9.2.2/9.3.1/9.3.2 Prut **1** and Pait 2: Updated number of patients to be enrolled.
		Section 9.5.1.1 Single Dose and Steady State PF 06873600 Phannacokinetic Analysis: Added PK sampling for patients in Part **ID** added specifics for samples on C2D8.
		Appendix 4. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines: Best Overall Response section, Stable disease bullet: changed timing after randomization from 8 weeks to 6 weeks.
		Added Altemative Measures During Public Emergencies appendix (Appendix 6), with hyperlinks to appendix in

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		the schedule of activities section as well as Sections 4.2 (exclusion criterion # 10) and 7 as appropriate.
Amendment4	08 April 2020	The purpose of this amendment is to add the Schedule of Phannacokinetic, Biopsy and Biomarker Assessments for Pait 2 of this study. Pait 2 dose expansion is an open-label, multi-center, non-randomized study to assess the preliminaiy anti-tumor activity and the safety and tolerability of PF-06873600. PF-06873600 will be administered at the RP2D in 28 day cycles as a single agent in 2 separate dose expansion arms and in combination with endocrine therapy in 3 separate dose expansion arms. In addition, clarifications, administrative and typographical modifications were made.
		• CCI [redacted] I [redacted] • Schedule of Phaimacokinetic, Biopsy and Biomarker Assessments - Ann A, Alm B (Study Paiticipants Not Assigned to the Food Effect Assessment), Alm C, Alm D and Alm E in Pait 2 has been added. • Schedule Of Phannacokinetic, Biopsy Alld Biomarker Assessments - Ann B (Study Paiticipants Assigned To The Food Effect Assessment Only) In Part 2 Has Been Added.
		Section 1.5.1 Rationale for Pre-, On- and End of Treatment Biopsies - Clarification around Part 2, I -- biopsies has been added: • CCI [redacted]

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		Section 2 Study Objectives and Endpoints - Part 2 Seconda1y Endpoint (Phannacokinetic parameters have been clarified): Phannacokinetic parameters of PF-06873600, including but not limited to: • SD - Cmax, $T_{max,}$ • MD (asswning steady state is achieved) - Css,max, $T_{ss,max,}$ Css,minand $R_{ae,}$
		CCI [redacted] I [redacted]
		CCI [redacted] I [redacted]
		Section 5.5 Investigational Product Storage: Modified text to clarify storage for immediate release and modified release. PF-06873600 should be stored at 15-25°C for the immediate release fonnulation and at 2-8°C for the modified release formulation, which has been coITected in the protocol.
		Section 7.2.2 Urine for Analysis of PF-06873600 Concentrations: More detailed info1mation around the collection, storage and processing of Urine PK samples has been added to the protocol.
		Section 7.3 Biomarker and Phannacodynamic Assessments: All patients in Pait 2 will have the option to provide pre-, on-, end of treatment tumor biopsies, but mandato1y pre- and on-treatment biopsies will be collected for up to 12 paired biopsies to yield a minimwn of 6 evaluable pairs in each of the dose expansion Arms A and B.

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		Section 9.5.1.1 Single-Dose and Steady-State PF-06873600 Pharmacokinetic Analysis: Urine concentration data will be analyzed to estimate the fraction of drug excreted unchanged in urine (Ae%) and renal clearance (CLr) for PF-06873600.
		Section 9.5.2 Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling: Section has been updated to reflect the analysis that will be conducted.
Amendment 3	29 April 2019	The purpose of this amendment is to add additional cohorts of patients to evaluate a modified release formulation of PF-06873600, as indicated, based on emerging and available preliminary clinical data, including safety/tolerability, laboratory, PK and PD findings. In addition, clarifications, administrative and typographical modifications were made.
		SCHEDULE OF ACTIVITIES: • Added Modified Release Dose Selection Cohort Within Part 1C SOA table. • Added Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Modified Release Selection Cohort in Part 1C) SOA table. • Modified the title and PK footnote for SOA table "Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1 – Except Modified Release Selection Cohort within Part 1C) – QD and BID Dosing Regimen.
		Section 1.5.1. Rationale for Pre-, On- and End of Treatment Biopsies: Qualitative language added.
		Section 2. Study Objectives and Endpoints: Study Objectives and Endpoints were updated to reflect the addition of Part 1C.
		Section 3.1 Study Design:

Document	Version Date	Summary of Changes and Rationale
		• Addition of Part 1C description. • Overall Study Schema updated to include Part 1C. • Addition of Figure 9: MR Selection Cohoit Study Schema (within Part 1C through Cycle 1).
		Section 3.1.3. Pait 1C PF 06873600 MR F01mulation: Addition of MR Foimulation lead-in and MR escalation rationale including starting doses.
		Section 3.1.5. Criteria for Dose Escalation: • Addition of Part 1C included.
		Section 3.1.6. DLT Definition (added): • Significant adverse events considered to be related to the investigational product for treatment under investigation that occur during the DLT observation period in the MR Selection Cohoit will be reviewed in context of all safety data available. That review may involve re-evaluation of the dosing level or regimen.
		CCI [redacted] Administrative clarifications made.
		Section 4 Patient Eligibility Criteria: • Clarifications made to include Pait 1C. • Clarification made to include "cytotoxic" in the inclusion criteria, "Received 1 or 2 prior lines of **cytotoxic** chemotherapy in the advanced or metastatic setting."
		Section 5.3.1 Dosage Foims and Packaging: • The description of the modified release fonnulations were added.
		Section 7.3. Biomarker and Phannacodynamic Assessments: • Clarifications made to include Pait 1C.

Document	Version Date	Summary of Changes and Rationale
		Table 5: Administrative clarifications made.
		CCI [redacted] Administrative clarifications made.
		CCI [redacted] Administrative clarifications made.
		CCI [redacted] Administrative clarifications made.
		Section 9.5.1.1 Single Dose and Steady State PF 06873600 Phrumacokinetic Analysis: • Clarifications made to include Patt 1C.
Amendment2	26 October 2018	The primaty purposes of the amendment are to adjust the approach to selection of the dose level increases during dose escalation and to incotporate the option to evaluate an alternative dosing regimen (eg, QD or TID) which may be considered during the course of dose escalation or after determination of the MTD for the BID regimen based on emerging and available preliminary clinical data, including safety/tolerability, laboratory, PK and PD findings. In addition, clarifications, administrative and typographical modifications were made.
		Protocol Cover Page: NCT number added per Pfizer template update.
		SCHEDULE OF ACTMTIES (Patt 1 and Prut 2) PF-06873600 administration: • Removed the words "twice daily (BID)" from the description of dosing in the table as well as footnote. • Added reference to Section 5 to the dosing footnote (Footnote: 16).
		SCHEDULE OF ACTMTIES (Patt 1 and Prut 2); Footnote 19:

Document	Version Date	Summary of Changes and Rationale
		• The words "with HR-positive HER2-negative advanced or mBC" was added to the requirement for treatment with an LHRH agonist in women who are pre or peri menopausal at study entry.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B*) – "QD and BID Dosing Regimen" was added to the table to differentiate it from a new table developed for the potential three times a day (TID) dosing regimen.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B*) – QD and BID Dosing Regimen; FOOTNOTE f: • Added the words "such as" to description of pharmacodynamic markers to be analyzed for added flexibility.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B) – QD and BID Dosing Regimen; FOOTNOTE j: • Minor modification, in the description of the assessments to be conducted on tumor tissue, was made for additional clarity and flexibility.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B) – TID Dosing Regimen: • New table and accompanying footnotes added for potential TID dosing regimen.
		Section 1.3.2. Nonclinical Pharmacokinetics (PK): • A PF-06873600 oral dosing regimen of TID may be evaluated during dose escalation based on the continued evaluation of preliminary PK from the BID dose escalation. In addition, an accelerated dose escalation (as utilized for the initial dose levels) may be adopted until the observation of clinically relevant adverse events or the dose levels approaching the projected pharmacologically active dose (PAD). • Rationale: If a suboptimal half-life is observed at 10 mg BID and higher, a PF 06873600 oral dosing regimen of three times daily (TID) may be evaluated during dose escalation. In addition, a higher than predicted clearance could result in a higher PAD than the originally predicted 10-15 mg BID and therefore require an accelerated dose

Document	Version Date	Summary of Changes and Rationale
		escalation in order to minimize the number of patients exposed to sub-therapeutic dose levels.
		Section 1.5.1. Rationale for Pre, On and End of Treatment Biopsies: • CCI [redacted] • Rationale: The modification better reflects the biomarker analysis plan.
		CCI [redacted] I [redacted] I [redacted] I [redacted]
		Section 3.1. Study Overview: • A description of how and when the potential of a PF-06873600 oral dosing regimen ofTID may be evaluated during dose escalation based on the continued evaluation of preliminary PK from the BID dose escalation. • Added language to provide an example of how the MTD would be detennined if the TID regimen is evaluated.
		Section 3.1 Study Overview: Study Scheme was modified to clarify that the initiation of the biomarker cohorts will not strut at Dose Level 3 as previously depicted but potentially occwring at a subsequent dose level to be detennined.

Document	Version Date	Summary of Changes and Rationale
		Section 3.1.4. Criteria for Dose Escalation: • The description for dose escalation increments was modified to approximate 100%-150% increases, beyond dose level 4, based on emerging available clinical data, including safety/tolerability, laboratory, PK and PD findings. • Additionally, the total daily dose will be administered in divided doses of either two (BID) or three times a day (TID).
		Section 3.1.4. Criteria for Dose Escalation; Table 2: PF-06873600 Dose Levels: • Table was updated to add a column for "Total Daily Dose" to reflect the dose escalation increment modifications made earlier in the section.
		Section 3.1.4. Criteria for Dose Escalation and Section 9.1 Analysis Sets: • Modified the percentage requirement for planned doses from 70 to 75% based in order to be evaluable for DLT assessment. This modification is based on Institutional Review Board (IRB) feedback.
		Section 3.1.4. Criteria for Dose Escalation: • Repetitive text removed from list of bullets describing criteria for stopping the study.
		Section 4.1. Inclusion Criteria: • #8: The words "or liver" was added to the criteria for defining adequate alkaline phosphatase levels based on investigator feedback.
		Section 4.1. Inclusion Criteria: • #11: The words "with HR-positive HER2-negative advanced or mBC" was added to the requirement for treatment with an LHRH agonist in women who are pre or peri menopausal at study entry. This requirement doesn't apply to patients with ovarian cancer or TNBC. • #3 and #4 for gender requirements were combined.
		Section 4.2. Exclusion Criteria:

Document	Version Date	Summary of Changes and Rationale
		• #3: The addition of "that has an external component such as those used for… or central venous catheter that is externally exposed (eg, perphierally inserted central catheter (PICC line)" was added to the description of indwelling catheters. This change also clarified that indwelling catheters that are fully internalized (eg, PORT-A-CATH®) *are permitted.*
		Section 4.2. Exclusion Criteria: • #7: The addition of washout criteria for antibody based agent(s) (approved or investigational) was added based on protocol template updates.
		Section 4.2. Exclusion Criteria: • #8: The addition of "or 5 half-lives, whichever is shorter" was added to the washout for prior investigational drug(s) based on protocol template updates.
		Section 5.4.1. PF-06873600 Administration: • TID was added to the potential dosing regimens. • Dosing intervals for QD, BID and TID were delineated. • Administrative updates were made.
		Section 5.4.2. Food Requirements: • TID was added to the potential dosing regimens for food effect requirement studies.
		Section 5.8. Luteinizing Hormone Releasing Hormone (LHRH) Agonist: • The words "with HR-positive HER2-negative advanced or mBC" was added to the requirement for treatment with an LHRH agonist in women who are pre or peri menopausal at study entry.
		Section 7.2.2. Urine for Analysis of PF 06873600 Concentrations: • Given the potential for TID dosing, modifications to the section were made in the event the urine PK evaluations are necessary in the TID dosing regimen.

Document	Version Date	Summary of Changes and Rationale
		Section 7.3. Biomarker and Pharmacodynamic Assessments: Table 5. Biomarker and Phannacod_ynamic Assessments; and Section CCI [redacted] and Section 7.5. Tumor Markers. Updates in the above sections were required after modifications were made to: • The footnote description of the evaluations in the "Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Pait lA and lB)-QD and BID Dosing Regimen and TID Dosing Regimen"; and • CCI [redacted]
		Section 9.2.2. Statistical Method for Estimating the MTD: Text was added to clarify that if the TID dosing regimen is evaluated, the MTD will be determined independently based on dose escalation following the mTPI method.
		Appendix 1. Abbreviations: • New abbreviations added.
Amendment 1	22 January 2018	The primaiy purpose of the amendment is to incoiporate feedback received from the United States (US) Food and Drug Administration (FDA). In addition, clarifications, administrative and typographical modifications were made.
		Protocol Title and Section 3.1: • The "a" was added for consistency with Phase of study described on the cover page of the protocol.
		SCHEDULE OF ACTMTIES (Pait 1 and Pait 2); Footnote 9: • For patients enrolled in dose level 1 and 2 that undergo intra patient dose escalation, as described in Section 3.1.4, triplicate ECGs should be perfonned on Day 8 and Day 15 in the first cycle at the escalated dose of PF-06873600.

Document	Version Date	Summary of Changes and Rationale
		SCHEDULE OF ACTIVITIES (Part 1 and Part 2); Footnote 12: • Typographical error.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B*): • The window period for the 12-hour PK sample on Cycle 1 Day 1 and 15 was extended to 120 minutes to allow flexibility for clinical site and patient convenience.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B*): • The additional clarification that the 24-hour PK sample on Cycle 1, Day 1 and Day 15, if indicated, would correspond to Day 2 and Day 16.
		Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1A and 1B*); FOOTNOTE d and e: • Part 1 of the study includes a dose escalation (Part 1A) and dose finding (de-escalation, Part 1B) component. The addition of "dose finding" was added for clarity.
		Section 1.1. Mechanism of Action/Indication: • The section was modified to include female and male patients.
		Section 1.2.2 Hormone Receptor (HR) Positive Breast Cancer: • Statistics for male breast cancer were added.
		Section 1.3.3. Nonclinical Safety: • Nonclinical safety findings for compounds with CDK 4/6 inhibition was added to the nonclinical safety summary due to the addition of male patients with breast cancer in Part 1A of the study.
		Section 1.5.1 Rationale for Pre-, On- and End of Treatment Biopsies: • Clarification that Part 1 contains a dose escalation (Part 1A) and a dose finding (Part 1B) component.

Document	Version Date	Summary of Changes and Rationale
		• Part 1A description modified to include female and male patients.
		Section 2 Study Objectives and Endpoints, Primary Objective, Part 1B: • Table header updated to "1B: Combination Dose Finding". • The last sentence of the 3rd bullet under primary Objective for Part 1A was moved out for clarity. • Part 1B of the study is designed to assess the safety and tolerability of PF-06873600 at the single agent MTD in combination with letrozole and in combination with fulvestrant, in a de-escalation manner, if indicated. The reference to "increasing doses" was removed.
		Section 3.1 Study Overview: • Clarification that Part 1A only will evaluate successive cohorts of escalating doses of PF-06873600) and that Part 1 contains a dose escalation (Part 1A) and a dose finding (Part 1B) component.
		Section 3.1 Study Overview, Figure 8 Overall Study Schema: • The study figure section header for Part 1 was modified from "Part 1B PF-06873600 + ET Combination Dose Escalation" to "Part 1B PF-06873600 + ET Combination Dose Finding". • The figure and legend were updated to differentiate the dose escalation safety cohorts (Part 1A) from the dose finding safety cohort (Part 1B).
		Section 3.1 Study Overview: • Part 1A description modified to include both female and male patients. • Part 1B and Part 2 will only evaluate women patients in an effort to evaluate a more homogenous study population and minimize variability in response rates.

Document	Version Date	Summary of Changes and Rationale
		• Language to describe the patient population for Part 1B was added to the study overview for consistency and clarity.
		Section 3.1.1 Part 1A PF-06873600 Single Agent Dose Escalation: • Part 1A description modified to include female and male patients.
		Section 3.1.2 Part 1B PF-06873600 Dose Finding in Combination with Endocrine Therapy: • Language to describe the patient population for Part 1B was added for consistency and clarity.
		Section 3.1.4 Criteria for Dose Escalation: • Part 1 of the study includes a dose escalation (Part 1A) and dose finding (de-escalation, Part 1B) component. The addition of "dose finding" was added for clarity. • Table 1: the title was modified to include "de-escalation" since the actions described in the table apply to both escalation and de-escalation.
		Section 3.1.5 DLT Definition: • The addition of "dose finding" was added for clarity. • Grade 3 thrombocytopenia will include clinically significant bleeding as indicated by ≥ Grade 2 bleeding. • Grade 3 nausea, vomiting, or diarrhea will only be considered a DLT if it persists for ≥72 hours despite optimal supportive care. • Grade 5 event will be considered a DLT unless attributed to a cause clearly not related to study treatment.
		Section 3.1.6 MTD Definition: • The addition of "dose finding" was added for clarity.

Document	Version Date	Summary of Changes and Rationale
		Section 3.3.1 Tumor Biopsy: • Text was added to differentiate the Part-1A single-agent dose escalation safety cohorts from the Part 1B combination dose de-escalation safety cohorts. • The reference to women was removed since Part 1A will now include female and male patients.
		Section 3.3.2. Skin Biopsy: • Part 1 of the study includes a dose escalation (Part 1A) and dose finding (de-escalation, Part 1B) component. Text was removed for clarity. • The reference to women was removed since Part 1A will now include female and male patients.
		Section 4.1 Inclusion Criteria: • Part 1A and Part 2, Arm B: Ovarian Patients: To clarify platinum resistance, language was added that each line of therapy that includes platinum, as a single agent or in combination, will be considered a unique treatment line. • Part 2, Arm A: Bullet point for measurable disease per RECIST 1.1 requirement was removed since it is already stated in Inclusion #10 (previously inclusion #8). • New criterion #2 was added: All patients in Part 1 must be refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. • New criterion #4 was added: Male patients age ≥18 years old will be included in Part 1A only. • Inclusion #7 (previously inclusion #5): Adequate renal function will be defined as Estimated creatinine clearance ≥60 mL/min for Part 1 and ≥50 mL/min for Part 2 as calculated using the method standard for the institution. • Inclusion #11 (previously inclusion #9): If female patients of nonchildbearing potential meet one of the criteria listed, a screening serum pregnancy test will not be required.

Document	Version Date	Summary of Changes and Rationale
		• Inclusion #11 (previously inclusion #9): Clarified that patients are to be without chemotherapy, endocrine therapy, or other cause for amenorrhea in order to determine that 12 months of amenorrhea is consistent with determination of menopausal status.
		Section 4.2 Exclusion Criteria: • New criterion #3 was added to exclude patients with an indwelling catheter used for drainage of effusion(s) due to the possibility of increased infection risk. • Exclusion #17 (previously #16): Modified to exclude fertile male patients in Part 1A that are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
		Section 4.3 Lifestyle Requirements: • The addition of fertile male patients in Part 1A was added to the requirement for use of 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product. • Text was deleted from the bullet point describing male or female condoms to avoid confusion.
		Section 5.7.2 Supportive Care: • Text was added to clarify that the description of the use of a gonadotropin-releasing hormone agonist (GnRH agonist) in this section is relevant for female patients currently being treated with a GnRH prior to study enrollment.
		Section 5.8 Luteinizing Hormone Releasing Hormone (LHRH) Agonist: • To avoid confusion with Section 5.7.2., text was added to clarify that this section refers to patients not currently receiving an LHRH agonist prior to study entry.
		Section 7.1.3 Laboratory Safety Assessment:

Document	Version Date	Summary of Changes and Rationale
		• The table for Other: Pregnancy test was modified to indicate that a negative "sernm" assessment is required at screening only. On study assessments can include a semm or mine pregnancy assessment.
		Section 7.3 Biomarker and Phannacodynamic Assessments: • Pait **1** of the study includes dose escalation safety cohorts (Pait lA) and dose finding safety cohorts (de-escalation, Pait **lB).** Text was removed for clarity.
		CCI [redacted] I [redacted]
		Section 9.2.1 Statistical Methods for Dose Escalation/De-Escalation: • Pait **1** of the study includes a dose escalation (Pait lA) and dose finding (de-escalation, Part lB) component. The addition of"dose finding" and de-escalation was added for clarity. • A clarification was made that the mTPI is a rnle-based system. • The abbreviation for the decision to remain at a given dose level was modified from "R" to"S" for consistency with other areas of the protocol and the decision mies were moved from Section 9.2.2. to 9.2.1.
		Section 9.2.2 Statistical Methods for Estimating the MTD: • Pait **1** of the study includes a dose escalation (Pait lA) and dose finding (de-escalation, Part lB) component. The addition of"dose finding" and de-escalation was added for clarity. • Duplicate text was removed.
		Section 9.3.1 Pait **1:** • The addition of"dose finding" and de-escalation was added for clarity.

Document	Version Date	Summary of Changes and Rationale
		REFERENCES: Several new references were included.
Original protocol	30 October 2017	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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APPENDICES

SCHEDULE OF ACTIVITIES (PART 1, PART 2 AND J-LIC)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS 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 schedule of activities in order to conduct evaluations or assessments required to protect the well-being of the patient.

See Appendix 6 for alternative measures during public emergencies including the COVID-19 pandemic.

Protocol Activity	**Screening**	**Active Treatment Phase[†]- One Cycle = 28 days**					**End of Treatment/ Withdrawal[§]**	**Post-Treatment Follow-Up[*]**
		Cycles 1 and 2				**Cycles ≥3**		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window			**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**
Informed Consent[1]	X							
Medical/Oncological History[2]	X							
Baseline Signs/Symptoms[3]		X						
Physical Examination[4]	X						X	
Abbreviated Physical Examination[5]		X	X	X	X	X		X
Vital Signs[6]	X	X	X	X	X	X	X	X
Contraception Check[7]	X	X				X	X	
ECOG Performance Status[8]	X	X				X	X	X
12-Lead ECG[9]	X	X	X C1[9] and C2[9]	X C1 only		X	X	
Laboratory Studies[10]								
Hematology	X	X	X	X	X	X	X	(X)
Blood Chemistry	X	X	X[11]	X[11]	X[11]	X	X	(X)
Coagulation	X	X						(X)
Urinalysis	X						X	(X)
Pregnancy test	X	X				X	X	
Viral disease screening[12]	X							
Disease Assessment								
Tumor markers (for breast cancer: CA 15-3 and CEA; Part 1 only for ovarian cancer: CA 125)	X	X				X	X	
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, and then every 12 weeks (±7 days)					X[13]	

Protocol Activity	**Screening**	**Active Treatment Phase[†]- One Cycle = 28 days**					**End of Treatment/ Withdrawal[§]**	**Post-Treatment Follow-Up[*]**
		Cycles 1 and 2				**Cycles ≥3**		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window			**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**
disease, and of bone lesions; Clinical evaluation of superficial disease[13]		thereafter for up to 2 years. After 2 years, performed every 4 months thereafter.						
Follow up for Overall Survival (OS)								
Study Treatment								
Registration[14]	X							
PF-06873600[15]		◀--▶ Orally on Days 1 to 28 of each Cycle						
Letrozole[16]		◀--▶ Orally 2.5 mg once daily as continuous daily dosing						
Fulvestrant[17]		X		X C1 only		X		
For pre-/peri-menopausal patients with HR-positive HER2-negative advanced or mBC only: LHRH agonist[18]		Administration according to package insert						
Other Clinical Assessments								
Adverse Event Reporting[19]	◀--▶							
Concomitant Medications/Treatments[20]	◀--▶							

Protocol Activity	Screening	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal§	Post-Treatment Follow-Up*
		Cycles 1 and 2				Cycles ≥3		
Study Day	Within 28 days prior to registration unless specified otherwise	Day 1‡	Day 8	Day 15	Day 21	Day 1		
Visit Window			±3 days	±3 days	±3 days	±5 days		±7 days

Abbreviations: ◄--►= ongoing/continuous event; C = cycle; CA 125 = cancer antigen 125; CA 15-3 = cancer antigen 15-3; carcinoembryonic antigen = CEA; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; LHRH = luteinizing hormone releasing hormone; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

After Cycle 1, Day 1, tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.

For Pharmacokinetics and additional sampling requirements, please see Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Part 1– Except Modified Release Selection Cohort within Part 1C*, AND J-LIC**) – BID Dosing Regimen Table.

† **Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. **Day 1 of any cycle visit should coincide with the day the PF-06873600 treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06873600.

‡ **Cycle 1/Day 1:** Blood chemistry, hematology, coagulation tests, and physical examination are not required if acceptable screening assessment is performed within 7 days prior to registration.

§ **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).

▫ **Post Treatment Follow-up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity 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.

1. **Informed Consent**: Informed consent must be obtained prior to any protocol required assessments.
2. **Medical/Oncological History**: To include information on oncology disease including details of diagnosis and prior anticancer treatments (systemic treatment, prior surgery and radiotherapy, etc). When available primary diagnosis history should also include known molecular characteristics of the patient's tumor including mutations, amplifications, etc.
3. **Baseline Signs/Symptoms**: Baseline tumor related signs and symptoms will be recorded at the Cycle 1, Day 1 (C1D1) visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
4. **Physical Examination (PE)**: A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, as acceptable according to local regulation. Physical examinations will be carried out at Screening and the End of Treatment.
5. **Abbreviated PE**: A symptom directed exam and an assessment for emergent toxicities or changes from prior visits conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.
6. **Vital Signs**: blood pressure and heart rate should be recorded after approximately 5 minutes of rest.

Protocol Activity	Screening	Active Treatment Phase[†]- One Cycle = 28 days					End of Treatment/ Withdrawal[§]	Post-Treatment Follow-Up[*]
		Cycles 1 and 2				Cycles ≥3		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window			**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**

7. **Contraception Check**: The investigator/designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient (and her partner(s)) from the permitted list of contraception methods and will confirm the patient has been instructed in their consistent and correct use. Assessment should be performed within 7 days of C1D1, and Day 1 of every other cycle and at the EOT visit.
8. **Performance Status**: ECOG scale to be assessed within 14 days prior to the first dose of PF-06873600, and as indicated in the table above.
9. **Triplicate 12-lead Electrocardiography (ECG)**:

   Triplicate 12-lead ECG **measurements** will be performed at the following time points (single ECG is acceptable, as indicated below):

   - Screening (single ECG);
   - Cycle 1, Day 1: pre-dose (within 6 hours prior to the morning dose of PF-06873600), and 1 hour after the morning dose of PF-06873600;
   - Cycle 1, Day 8: within 30 min prior to the morning dose of PF-06873600;
   - Cycle 1, Day 15: pre-dose (within 30 min prior to the morning dose of PF-06873600), and 1 hour after the morning dose of PF-06873600;
   - Cycle 2 and subsequent cycles, Day 1: within 30 min prior to the morning dose of PF-06873600;
   - Cycle 2, Day 8: pre-dose (within 30 mins prior to the morning dose of PF-06873600);
   - EOT (single ECG).

   At each time point, (except those with single ECGs) 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

   For patients enrolled in dose level 1 and 2 that undergo intra patient dose escalation (Section 3.1.5), triplicate ECGs should be performed on Day 8 (within 30 min prior to the morning dose of PF-06873600) and Day 15 (within 30 min prior to the morning dose of PF-06873600 and 1 hour after the morning dose of PF-06873600) in the first cycle at the escalated dose of PF-06873600 and then on Day 1 (within 30 min prior to the morning dose of PF-06873600) of each subsequent cycle.
10. **Laboratory Studies:** Screening labs to be performed within 7 days of C1D1. Laboratory assessments can be performed earlier but will have to be repeated to be done within 7 days of C1D1. For subsequent cycles, pre-dose labs may also be drawn up to 3 days (-3 days/72 hours) in advance of scheduled dosing in order to obtain results prior to visit.
    - See Table 4 in Section 7.1.3 for a full list of safety laboratory assessments.
    - For Urinalysis, dipstick is acceptable but microscopic analyses is required if dipstick abnormal. Additional tests may be performed as clinically indicated.
    - Pregnancy test at screening and Day 1 of every other cycle only for women of childbearing potential. Test may be repeated as per request of institutional review board/independent ethics committee (IRB/IECs) or if required by local regulations. See Section 7.1.1.
11. **Cycle 1 and Cycle 2, Day 8, 15 and 21:** Not required for patients in Part 2.
12. **Viral disease screening tests**: Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), (HbcAb), hepatitis B surface antibody (anti-HBs), hepatitis C virus antibodies (HCVAb), human immunodeficiency virus testing (HIV), and COVID-19 to be conducted by local laboratory where required by local regulations or if warranted by patient history. For Japan only, participants with HBsAb and HBcAb should be monitored with HBV viral load (refer to Appendix 7).

Protocol Activity	Screening	Active Treatment Phase[†]- One Cycle = 28 days					End of Treatment/ Withdrawal[§]	Post-Treatment Follow-Up[*]
		Cycles 1 and 2				Cycles ≥3		
Study Day	Within 28 days prior to registration unless specified otherwise	Day 1[‡]	Day 8	Day 15	Day 21	Day 1		
Visit Window			±3 days	±3 days	±3 days	±5 days		±7 days

13. **CT/MRI Scans of Chest, Abdomen, and Pelvis:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Patients with a history of CNS metastases or cord compression are eligible if there is no evidence of progression at time of study enrollment (baseline MRI required). Tumor assessment should be repeated at the end of study visit if more than 8 weeks have passed since the last evaluation.
14. **Registration (enrollment):** Patient enrollment, dose level allocation (if applicable) and arm (if applicable) will be assigned by Pfizer or designee.
15. **PF-06873600:** To be administered orally twice per day as continuous dosing schedule from Day 1 through Day 28. Study drug will initially be administered orally on a continuous basis. If indicated by emerging data, an alternative intermittent dosing regimen may be considered eg, 5 days of continuous dosing and 2 days without dose administration. Patients will be required to return all bottles of PF-06873600 as well as the completed patient diary for drug accountability. PF-06873600 immediate release tablets are supplied in 68-count bottles, modified release tablets are supplied in 62-count bottles; sites should take this into consideration when scheduling drug dispensing visits. See Section 5.4.1 for further information.
16. **Letrozole:** To be administered according to the prescribing information. Commercial letrozole comes in a 30-count bottle or 28-count blister pack; sites should take this into consideration when scheduling drug dispensing visits.
17. **Fulvestrant:** Fulvestrant is given on Day 1, Day 15 of Cycle 1, Cycle 2, Day 1 and monthly thereafter (±3 days) to accommodate dosing on Day 1 of each cycle. Refer to the prescribing information for more information.
18. **Luteinizing hormone-releasing hormone (LHRH) agonist**: Treatment with a LHRH agonist (eg, goserelin and leuprolide acetate) should be used according to the prescribing information for all women with HR-positive HER2-negative advanced or mBC who are pre- or peri-menopausal at study entry. Patients must have commenced treatment with LHRH agonist at least 1 week prior to C1D1 for the monthly administration form and at least 3 weeks prior to C1D1 for an LHRH that is administered on an every 3 month schedule.
19. **Adverse Events (AEs)**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
20. **Concomitant Treatments:** All concomitant medications and treatments, blood products, as well as nondrug interventions received by patients swill be recorded in the CRF.

SCHEDULE OF ACTIVITIES (MODIFIED RELEASE SELECTION COHORT WITHIN PART 1C)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS 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 schedule of activities below in order to conduct evaluations or assessments required to protect the well-being of the patient.

See Appendix 6 for alternative measures during public emergencies including the COVID-19 pandemic.

Protocol Activity	**Screening**	**Lead-in**				**Active Treatment Phase[†]- One Cycle = 28 days**					**End of Treatment/ Withdrawal[§]**	**Post-Treatment Follow-Up[*]**
						Cycles 1 and 2				**Cycles ≥3**		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day -7**	**Day - 6**	**Day -4**	**Day -3**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window							**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**
Informed Consent[1]	X											
Medical/Oncological History[2]	X											
Baseline Signs/Symptoms[3]		X		X		X						
Physical Examination[4]	X										X	
Abbreviated Physical Examination[5]		X		X		X	X	X	X	X		X
Vital Signs[6]	X	X		X		X	X	X	X	X	X	X
Contraception Check[7]	X	X				X				X	X	
ECOG Performance Status[8]	X	X				X C1 only				X	X	X
12-Lead ECG[9]	X	X		X		X	X C1 only	X C1 only		X	X	
Laboratory Studies[10]												
Hematology	X	X				X	X	X	X	X	X	(X)
Blood Chemistry	X	X				X	X	X	X	X	X	(X)
Coagulation	X	X				X						(X)
Urinalysis	X	X				X					X	(X)
Pregnancy test	X	X								X	X	
Viral disease screening[11]	X											

Protocol Activity	**Screening**	**Lead-in**				**Active Treatment Phase†- One Cycle = 28 days**					**End of Treatment/ Withdrawal§**	**Post-Treatment Follow-Up***
						Cycles 1 and 2				**Cycles ≥3**		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day -7**	**Day - 6**	**Day -4**	**Day -3**	**Day 1‡**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window							**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**
Disease Assessments												
Tumor markers (for breast cancer: CA 15-3 and CEA for ovarian cancer: CA 125	X	X				X C2 only				X	X	
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease[12]	X					Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, and then every 12 weeks (±7 days) thereafter for up to 2 years. After 2 years, performed every 4 months thereafter.					X	
Study Treatment												
Registration[13]	X											
PF-06873600[14]		X		X		◄--► Orally on Days 1 to 28 of each Cycle						
For pre-/peri-menopausal patients with HR-positive HER2-negative advanced or mBC only: LHRH agonist[15]						Administration according to package insert						
Other Clinical Assessments												
Adverse Event Reporting[16]	◄--►											
Concomitant Medications/Treatments[17]	◄--►											

Abbreviations: ◄--►= ongoing/continuous event; C = cycle; CA 125 = cancer antigen 125; CA 15-3 = cancer antigen 15-3; carcinoembryonic antigen = CEA; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; LHRH = luteinizing hormone releasing hormone; MR = Modified Release; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

After Cycle 1, Day 1, tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.

For Pharmacokinetics and additional sampling requirements, please see Schedule of Pharmacokinetic, Biopsy and Biomarker Assessments (Modified Release Selection Cohort in Part 1C) Table below.

† Active Treatment Phase: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. Day 1 of any cycle visit should coincide with the day the PF-06873600 treatment begins. If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06873600. Prior to Cycle 1 only, a single QD dose of PF-06873600 will be administered on Day -7 and Day -4 in the AM in the MR lead in cohort.

‡ Cycle 1/Day 1: Blood chemistry, hematology, coagulation tests, and physical examination are not required if acceptable screening assessment is performed within 7 days prior to registration.

Protocol Activity	Screening	Lead-in				Active Treatment Phase[†]- One Cycle = 28 days					End of Treatment/ Withdrawal[§]	Post-Treatment Follow-Up[*]
						Cycles 1 and 2				Cycles ≥3		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day -7**	**Day - 6**	**Day -4**	**Day -3**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window							**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**

§ End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).

[*]Post Treatment Follow-up: At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity 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.

1. **Informed Consent:** Informed consent must be obtained prior to any protocol required assessments.
2. **Medical/Oncological History:** To include information on oncology disease including details of diagnosis and prior anticancer treatments (systemic treatment, prior surgery and radiotherapy, etc). When available primary diagnosis history should also include known molecular characteristics of the patient's tumor including mutations, amplifications, etc.
3. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded in the Lead-in period for Cycle 1 (Day -7 and Day -4) and on Day 1 (C1D1) visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
4. **Physical Examination (PE)**: A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, as acceptable according to local regulation. Physical examinations will be carried out at Screening and the End of Treatment.
5. **Abbreviated PE**: A symptom directed exam and an assessment for emergent toxicities or changes from prior visits conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.
6. **Vital Signs**: blood pressure and heart rate should be recorded after approximately 5 minutes of rest.
7. **Contraception Check:** The investigator/designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient (and her partner(s)) from the permitted list of contraception methods and will confirm the patient has been instructed in their consistent and correct use. Assessment should be performed within 7 days of C1D-7, and Day 1 of every other cycle and at the EOT visit.
8. **Performance Status:** ECOG scale to be assessed within 14 days prior to the first dose of PF-06873600, and as indicated in the table above.
9. Triplicate 12-lead Electrocardiography (ECG):

   Triplicate 12-lead ECG measurements will be performed at the following time points (single ECG is acceptable, as indicated below):

   - Screening (single ECG);
   - Lead-in, Day -7: pre-dose (within 6 hours prior to the morning dose of PF-06873600), and 6 hour after the morning dose of PF-06873600;
   - Lead-in, Day -4: pre-dose (within 6 hours prior to the morning dose of PF-06873600), and 6 hour after the morning dose of PF-06873600; Cycle 1, Day 1: pre-dose (within 6 hours prior to the morning dose of PF-06873600), and 1 hour after the morning dose of PF-06873600;
   - Cycle 1, Day 8: within 30 min prior to the morning dose of PF-06873600;

Protocol Activity	Screening	Lead-in				Active Treatment Phase[†]- One Cycle = 28 days					End of Treatment/ Withdrawal[§]	Post-Treatment Follow-Up[*]
						Cycles 1 and 2				Cycles ≥3		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day -7**	**Day - 6**	**Day -4**	**Day -3**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window							**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**

- Cycle 1, Day 15: pre-dose (within 30 min prior to the morning dose of PF-06873600), and 1 hour after the morning dose of PF-06873600;
- Cycle 2 and subsequent cycles, Day 1: within 30 min prior to the morning dose of PF-06873600;
- EOT (single ECG).

At each time point, (except those with single ECGs) 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

10. **Laboratory Studies:** Screening labs to be performed within 7 days of C1D-.7, assessments can be performed earlier but will have to be repeated to be done within 7 days of C1D1. For subsequent cycles, pre-dose labs may also be drawn up to 3 days (-3 days/72 hours) in advance of scheduled dosing in order to obtain results prior to visit.
    - See Table 4 in Section 7.1.3 for a full list of safety laboratory assessments.
    - For Urinalysis, dipstick is acceptable but microscopic analyses is required if dipstick abnormal. Additional tests may be performed as clinically indicated.
    - Pregnancy test at screening and Day 1 of every other cycle only for women of childbearing potential. Test may be repeated as per request of institutional review board/independent ethics committee (IRB/IECs) or if required by local regulations. See Section 7.1.1.
11. **Viral disease screening tests:** Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), (HbcAb), hepatitis B surface antibody (anti-HBs), hepatitis C virus antibodies (HCVAb), human immunodeficiency virus testing (HIV) and COVID-19 to be conducted by local laboratory where required by local regulations or if warranted by patient history.
12. **CT/MRI Scans of Chest, Abdomen, and Pelvis:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Patients with a history of CNS metastases or cord compression are eligible if there is no evidence of progression at time of study enrollment (baseline MRI required). Tumor assessment should be repeated at the end of study visit if more than 8 weeks have passed since the last evaluation.
13. **Registration (enrollment):** Patient enrollment, dose level allocation (if applicable) and arm (if applicable) will be assigned by Pfizer or designee.
14. **PF-06873600:** To be administered orally twice per day as continuous dosing schedule from Day 1 through Day 28. Patients will be required to return all bottles of PF-06873600 as well as the completed patient diary for drug accountability. See Section 5 for further information. PF-06873600 doses of the modified release formulations (with two different release rates) will be administered during the lead-in period. During the Lead-in period, a single dose of PF-06873600 with the modified release formulation will be administered on Day -7 and Day -4 in the AM. Starting from Cycle 1 Day 1, PF-06873600 tablets of the immediate-release formulation will be administered orally on a continuous basis. If indicated by emerging data, an alternative intermittent dosing regimen may be considered eg, 5 days of continuous dosing and 2 days without dose administration. PF-06873600 immediate release tablets are supplied in 68-count bottles, modified release tablets are supplied in 62-count bottles; sites should take this into consideration when scheduling drug dispensing visits.
15. **Luteinizing hormone-releasing hormone (LHRH) agonist:** Treatment with a LHRH agonist (eg, goserelin and leuprolide acetate) should be used according to the prescribing information for all women with HR-positive HER2-negative advanced or mBC who are pre- or peri-menopausal at study entry. Patients must have commenced treatment with LHRH agonist at least 1 week prior to C1D-7 for the monthly administration form and at least 3 weeks prior to C1D1 for an LHRH that is administered on an every 3 month schedule.

Protocol Activity	Screening	Lead-in				Active Treatment Phase[†]- One Cycle = 28 days					End of Treatment/ Withdrawal[§]	Post-Treatment Follow-Up[*]
						Cycles 1 and 2				Cycles ≥3		
Study Day	**Within 28 days prior to registration unless specified otherwise**	**Day -7**	**Day - 6**	**Day -4**	**Day -3**	**Day 1[‡]**	**Day 8**	**Day 15**	**Day 21**	**Day 1**		
Visit Window							**±3 days**	**±3 days**	**±3 days**	**±5 days**		**±7 days**

16. **Adverse Events (AEs):** AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
17. **Concomitant Treatments:** All concomitant medications and treatments, blood products, as well as nondrug interventions received by patients will be recorded in the CRF.

SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (PART 1-EXCEPT MODIFIED RELEASE SELECTION COHORT WITHIN PART 1C*, AND J-LIC**)-BID DOSING REGIMEN

		Cyclel																			Cycle 2		Cycle 3	EOT
		Day 1								Day8				Day15							Dayl		Day 1	
Hours Post-Dose* **	**creening**	**0•**	**0.25[1]**	**0.5[1]**	**1**	2	3	4	6	12b	**0•**	**0•**	0.25[1]	0.5[1]	**1**	2	3	4	6	12b	**0•**	4	**0•**	
Visit Window†			±3 min	±3 min	±6 min	**±15** min	±20 min	±25 min	±40 min	±120 min			±3 min	±3 min	±6 min	±15 min	±20 min	±25 min	±40 min	±120 min		±60 min		
PF-06873600 PK blood sampling[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	xc	X	X
CCI																								
Serum Biospecimen for Thymidine Kinase assay[f]		X							X	X		X							X		X			X
Blood Sample for Circulating Nucleic Acid (CNA) Profiling[h]		X										X												X
Serum Biomarkers[i]		X										X												X
CCI																								

Abbreviation: CNA = circulating nucleic acid; PK= pha1macokinetic; EOT = End of Treatment; (X)= optional.

*Table for Pait 2 will be created prior to initiation of enrolhnent in any Anu of Pait 2. Table for Part lC MR Fo1mulation lead in is below.

**The necessity of hospitalization and its duration ofDLT assessment period for Japanese participants in J-LIC are based on the investigator's decision (See Appendix 7).

***Collection Time: Sampling times are related to the **morning** dose.

tSample collection windows: All other sampling should be within the protocol specified window in the table above.

12 hour sampling: 12 hour assessments will shift to 24 hours (ie, Day 2 and Day 16-not shown in table above) in patients treated on PF-06873600 QD regimen; sample should be collected within 30 min prior to the moming dose of PF-06873600 (See Section 3).

Details for handling of all specimens including processing, storage, and shipment, will be provided in the Laboratory Manual.

a. Pre-dose sample collection:
   - Cycle 1, Day **1:** within 6 hotu·s prior to the moming dose of PF-06873600);
   - Cycle 1, Day 8, Day 15 and Day **1** of subsequent cycles: within 30 min prior to the moming dose of PF-06873600.

b. Prior to the evening dose for BID regimen.

c. **Pharmacokinetics (PK):** Blood samples of 3 mL each (to obtain at least 1 mL of plasma) for detemtination of plasma PF-06873600 drug concentrations will be collected at the time points above (NOTE: PK sampling time points may change, pending PK data from early dose levels). Additional PK blood samples may be collected at time of occtu1·ence of nnexpected or serious adverse events. On days when patients require pre-dose PK sampling assessments, the moming dose of PF-06873600 should be held *(NOT* taken) prior to the study visit. On those days, the PF-06873600 moming dose can then be taken after the pre-dose PK sampling is obtained. After C15Dl, no additional PK samples will be collected with the exception of the EOT sample. On C2D1, the 4-hotu· PK sample will be collected in patients who have consented to C2D1 on-treatment biopsies only.

		Cyclel																		Cycle 2		Cycle 3	EOT
		Day 1								Day8	Day 15									Dayl		Day 1	
Hours Post-Dose* **	**Screening**	o•	0.25[1]	o.5[1]	1	2	3	4	6	12h	o•	o•	0.25[1]	o.5[1]	1	2	3	4	6	12[b]	O•	4	O•	
Visit Window†			±3 min	±3 min	±6 min	±15 min	±20 min	±25 min	±40 min	±120 min			±3 min	±3 min	±6 min	±15 min	±20 min	±25 min	±40 min	±120 min		±60 min		
[redacted]																								

£ **ernm 1ospec1men or ym1 me nase assay:** ne ooo specimen optimized for semm preparation will be collected and analyzed for phanuacodynamic markers, such as thym.idine kinase (TK) activity. If the PK assessments are postponed, this associated blood sample should also be postponed as well, and resume with the PK collection.

g. **Cycle 3 only:** (pre-dose, aligned with the first tumor assessment on treatment).

h. **Blood Sample for Circulating Nucleic Acid (CNA) Profiling:** A IO mL-blood specimen optimized for plasma preparation for circulating nucleic acid analysis will be collected.

ı. **Serum Biomarkers:** In addition one 3 mL-blood s ecimen o ti.mi.zed for semm re aration will be collected and anal ed for levels of semm biomarkers.

J· [redacted]

I. odified Release (MR) dose escalation coho11s only, there will be no 0.25 and 0.5 hotu·s post-dose PK samples taken in Cycle I on Day I and Day I5, this includes MR dosing in Pait IB.

SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS (MODIFIED RELEASE SELECTION COHORT IN PART lC)

		Lead-in (Part lC)																
		Day-7							Day-6		Day-4							Day-3
Hours Post-Dose**	**Screening**	**0[a]**	**1**	**2**	**3**	**4**	**6**	**12b**	**18**	**24**	**O•**	**2**	**3**	**4**	**6**	**12**	**18**	**24**
Visit Window†			**±6 min**	**±15 min**	**±20 min**	±25 **min**	±40 **min**	**±120 min**	**±120 min**	±40**min**		**±6 n**	**±15 min**	±20 min	±25 min	±40 **min**	**±120** min	**±120min**	±40**min**
PF-06873600 PK blood sampling[c]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
CCI																			

Abbreviation: CNA = circulating nucleic acid; **PK=** phannacokinetic; EOT = End of Treatment; (X) = optional.

****Collection Time:** Sampling times are related to the **morning** dose.

tSample collection windows: All other sampling should be within the protocol specified window in the table above.

12 hour sampling: 12 hour assessments will shift to 24 hours (ie, Day 2 and Day 16 -not shown in table above) in patients treated on PF-06873600 QD regimen; sample should be collected within 30 min prior to the morning dose of PF-06873600 (See Section 3).

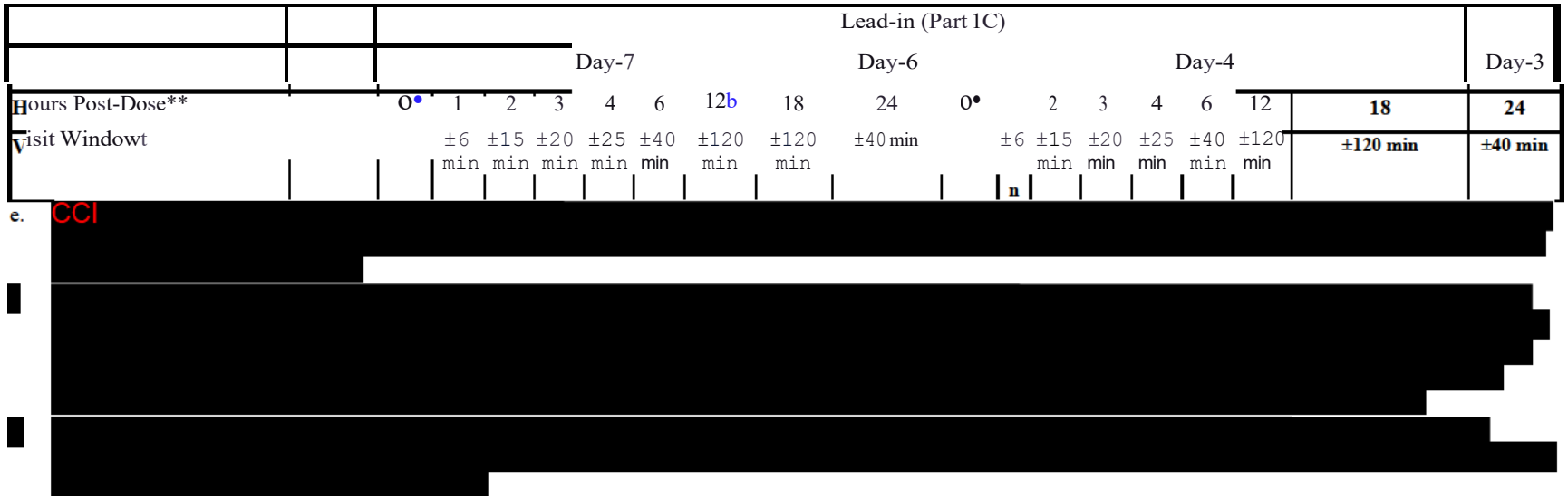
Details for handling of all specimens including processing, storage, and shipment, will be provided in the Laboratory Manual.

a. Pre-dose sample collection:
   - Lead-in, Day -7 and Day -4: within 6 hours prior to the morning dose of PF-06873600;
   - Cycle I, Day I: within 6 hours prior to the morning dose of PF-06873600;
   - Cycle I, Day 8, Day 15 and Day I of subsequent cycles: within 30 min prior to the morning dose of PF-06873600.

b. Prior to the evening dose for BID regimen.

c. **Pharmacokinetics (PK):** Blood samples of 3 mL each (to obtain at least I mL of plasma) for detennination of plasma PF06873600 dmg concentrations will be collected at the time points above (NOTE: PK sampling time points may change, pending PK data from earlydose levels). Additional PK blood samples may be collected at time of occtm·ence of unexpected or serious adverse events. On days when patients require predose PK sampling assessments, the morning dose of PF-06873600 should be held (NOT taken) prior to thestudy visit. On those days, the PF-06873600 morning dose can then be taken after the predose PK sampling is obtained.

I [redacted]


Lead-in (Part 1C)
Day-7
Day-6
Day-4
Day-3
Hours Post-Dose**
Visit Windowt
0•
1
2
3
4
6
12b
18
24
0•
2
3
4
6
12
18
24
±6 min
±15 min
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±120 min
±40 min
±6 min
±15 min
±20 min
±25 min
±40 min
±120 min
±120 min
±40 min
n
e.
CCI

		Cycle 1 (Part lC)											Cycle 2	Cycle :C,3	EOT
			Day 1								Day8	Day 15	Day 1	Dayl	
Hours Post-Dose**	creening	○ •	0.25	0.5	1	2	3	4	6	12b	○ •	○ •	○ •	○ •	
Visit Window†			±3 min	±3 min	±6 min	±15 min	±20 min	±25 min	±40 min	±120 min					
PF-06873600 PK blood sampling[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]															
[redacted]															

Abbreviation: CNA = circulating nucleic acid; PK= phannacokinetic; EOT = End of Treatment; (X) = optional.

****Collection Time:** Sampling times are related to the **morning** dose.

t**Sample collection windows:** All other sampling should be within the protocol specified window in the table above.

12 hour sampling: 12 hour assessments will shift to 24 hours (ie, Day 2 and Day 16 -not shown in table above) in patients treated on PF-06873600 QD regimen; sample should be collected within 30 min prior to the morning dose of PF-06873600 (See Section 3).

Details for handling of all specimens including processing, storage, and shipment, will be provided in the Laboratory Manual.

a. Pre-dose sample collection:
   - Lead-in, Day-7 and Day-4: within 6 hours prior to the morning dose of PF-06873600;
   - Cycle **1,** Day 1: within 6 hours prior to the morning dose of PF-06873600;
   - Cycle **1,** Day 8, Day 15 and Day 1 of subsequent cycles: within 30 min prior to the morning dose of PF-06873600.

b. Prior to the evening dose for BID regimen.

c. **Pharmacokinetics (PK):** Blood samples of3 mL each (to obtain at least 1 mL of plasma) for detennination of plasma PF-06873600 dmg concentrations will be collected at the time points above (NOTE: PK sampling time points may change, pending PK data from earlydose levels). Additional PK blood samples may be collected at time of occtm·ence of unexpected or serious adverse events. On days when patients require predose PK sampling assessments, the morning dose of PF-06873600 should be held (NOT taken) prior to thestudy visit. On those days, the PF-06873600 morning dose can then be taken after the predose PK sampling is obtained.

d. CCI [redacted]

I [redacted]

SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - IMMEDIATE RELEASE FORMULATION IN PART 2 (ARMS A, BAND C)

		Cyclel											Cycle		EOT
		Dayl					Day8	Day15					Dayl		
Hours Post-Dose**	**Screening**	**O•**	**1**	**2**	**4**	**6**	**O•**	**O•**	**1**	**2**	**4**	**6**	**O•**	**4**	
Visit Windowt			**±6min**	**±15 min**	**±25 min**	**±40 min**			**±6min**	**±15 min**	**±25 min**	**±40 min**		**±60 min**	
PF-06873600 **PK** blood samplingb		X	X	X	X	X	X	X	X	X	X	X			
FoodDia1y		X					X	X							
	I													I	
	■													■	
Blood Sample for Circulating		X						X							
	■														
		I													

Abbreviation: CNA = circulating nucleic acid; PK= pharmacokinetic; EOT = End ofTreatment; (X) = optional.

****Collection Time:** Sampling tintes are related to the **morning** dose.

tSample collection windows: All other sampling should be within the protocol specified window in the table above.

Details for handling of all specimens including processing, storage, and shipment, will be provided in the Laboratory Manual.

a. Pre-dose sample collection:
   - Cycle I, Day 1: within 6 hours prior to the moming dose of PF-06873600);
   - Cycle I, Day 8, Day I5 and Day 1 of subsequent cycles: within 30 min prior to the moming dose of PF-06873600.

b. **Pharmacokinetics (PK):** Blood samples of3 mL each (to obtain at least 1 mL of plasma) for detenuination of plasma PF-06873600 dmg concentrations may be collected at tinte of occtm·ence of unexpected or serious adverse events.

		Cyclel										Cycle	
		Dayl				Day8			Day15			Dayl	
ours Post-Dose**	Screening	O•	1	2	4	6	O•	O•	1	2	4	6	O•	4
isit Windowt			±6min	±15 min	±25 min	±40 min			±6min	±15 min	±25 min	±40 min		±60 min

EOT

c. CCI

[redacted]

e. **Blood Sample for Circulating Nucleic Acid (CNA) Profiling: A** 10 mL blood specimen optimized for plasma preparation for circulating nucleic acid analysis will be collected.

f. CCI

I [redacted]

SCHEDULE OF PHARMACOKINETIC, BIOPSY AND BIOMARKER ASSESSMENTS - MODIFIED RELEASE FORMULATION IN PART 2.

		Cyclel								Cycle 2:2							EOT
		Dayl					Day8		DaylS						Day 1		
Hours Post-Dose**	Scl'eening	O•	1	2	4	6	12b	O•	O•	1	2	4	6	12b	O•	4	
Visit Window†			±6 min	±15 min	±25 min	±40 min				±6 min	±15 min	±25 min		±180 min		±60 min	
PF-06873600 PK blood sampling[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	xc,f	X
Food Diary		--															
CCI																	
Blood Sample for Circulating Nucleic Acid (CNA) Profiling[g]		X							X								
CCI																	

Abbreviation: CNA = circulating nucleic acid; **PK=** phannacokinetic; EOT = End of Treatment; (X) = optional.

****Collection Time:** Sampling times are related to the **morning** dose.

tSample collection windows: All other sampling should be within the protocol specified window in the table above.

Details for handling of all specimens including processing, storage, and shipment, will be provided in the Laboratory Manual.

a. Pre-dose sample collection:
   - Cycle I, Day I: within 6 hours prior to the moming dose of PF-06873600;
   - Cycle I, Day 8, Day I5 and Day I of subsequent cycles: within 30 min prior to the moming dose of PF-06873600.

b. Prior to the evening dose for BID regimen.

c. **Pharmacokinetics (PK):** Blood samples of3 mL each (to obtain at least I mL of plasma) for detenuination of plasma PF-06873600 dmg concentrations will be collected at the time points above (NOTE: PK sampling time points may change, pending PK data from earlydose levels). Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when patients require predose PK sampling assessments, the moming dose of PF-06873600 should be held (NOT taken) prior to the study visit. On those days, the PF-06873600 moming dose can then be taken after the predose PK sampling is obtained. After CI SDI no additional PK samples will be collected. On C2Dl, the 4-hour PK sample will be collected in patients who have consented to C2Dl on-treatment biopsies only.

I

		Cycle!												Cycle 2:2	EOT
		Dayl					Day8	DaylS						Day 1	
Hours Post-Dose**	Scl'eening	O[e]	1	2	4	6		1	2	4	6			4	
Visit Windowt			±6 min	±15 min	±25 min	±40 min	±180 min	±6 min	±15 min	±25 min	±40 min	±180 min		±60 min	

CCI

[redacted]

f. Cycle 2 only.

g. **Blood Sample for Circulating Nucleic Acid (CNA) Profiling:** A 10 mL blood specimen optimized for plasma preparation for circulating nucleic acid analysis will be collected.

[redacted]

SCHEDULE OF ACTIVITIES FOLLOWING AMENDMENT 09: TREATMENT AND FOLLOW-UP

Protocol Activity	**Active Treatment Phase One Cycle = 28 days**	**End of Treatment[§]**	**Post-Treatment Follow-Up[*]**
Study Day	**Cycle X Day 1**		
Visit Window	**±7 days**		**±7 days**
PF-06873600[1]	Orally on Days 1 to 28 of each Cycle		
Fulvestrant[2]	X		
Adverse Event Reporting[3]	X	X	X

[§] **End of Treatment:** Visit to be performed as soon as possible from the last dose of investigational products

[*] **Post-Treatment Follow-up:** At least 28 days, and no more than 35 days after discontinuation of treatment. Patients continuing to experience toxicity 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.

1. **PF-06873600**: To be administered orally twice per day as continuous dosing schedule from Day 1 through Day 28. Patients will be required to return all bottles of PF-06873600 as well as the completed patient diary for drug accountability.
2. **Fulvestrant** is given monthly to accommodate dosing on Day 1 of each cycle. Refer to the prescribing information for more information
3. **Adverse Events (AEs)**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

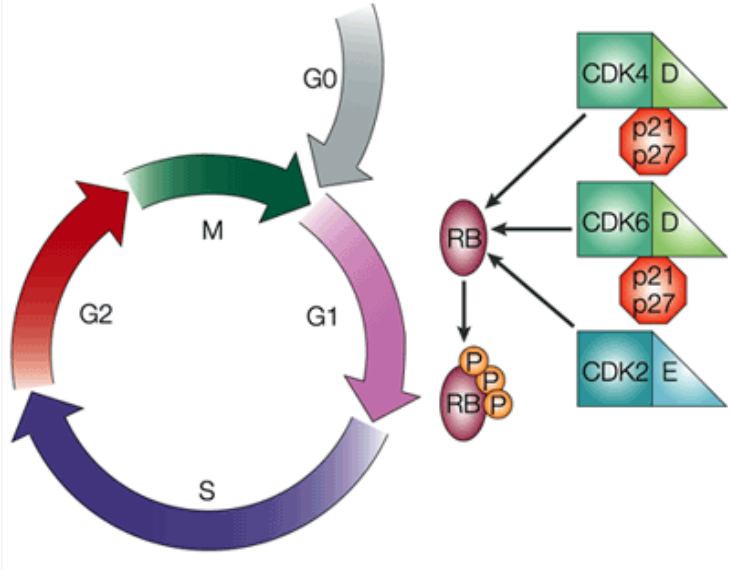
PF-06873600 is an inhibitor of cyclin-dependent kinases (CDK) 2, 4 and 6 that is being investigated in women of any menopausal status and men with hormone receptor (HR) positive human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer (mBC) and patients with other tumor types that have potential to have increased Cyclin E expression/CDK 2 activity, including locally recurrent/advanced or metastatic triple negative breast cancer (women and men) and women with advanced platinum resistant ovarian cancer.

1.2. Background and Rationale

1.2.1. CDK 2/4/6

Cell division is a highly regulated, conserved process by which normal cells only divide when appropriate and checkpoint requirements have been met (Kastan & Bartek, 2004).[1] The cell cycle involves distinctive phases for mitosis and deoxyribonucleic acid (DNA) synthesis with growth phases interspersed (Figure 1, M. L. Coleman, et al, 2004).[2] During the Gap 1 phase (G1), cells normally require CDK4/6-cyclin D1 (CCND1), then CDK2-cyclin E1 (CCNE1) to phosphorylate the retinoblastoma (Rb) tumor suppressor releasing E2F transcription factors to regulate gene expression leading to S-phase and subsequent entry into Gap 2 phase (G2) and subsequent cell cycle progression (Choi & Anders, 2014).[3] Cancer cells have circumvented these checkpoints with mutations in many of these proteins resulting in amplification of CCND1 or CCNE1, Rb deletion, etc (Herrera-Abrue et al, 2016).[4] Thus, selectively-targeted cell cycle CDKs have been considered logical targets as cancer therapies (Malumbres & Barbacid, 2009).[5]

Figure 1. Schematic Representation of the CDK 2/4/6 Rb pathway



1.2.2. Hormone Receptor (HR) Positive Breast Cancer

It is estimated that by the year 2015, there were more than 3.5 million women living in the United States with a history of invasive breast cancer. Seventy-five percent of breast cancer survivors (more than 2.6 million women) are ages 60 years or older, while 7% are younger than 50 years. The median age of women at diagnosis is 61 years and approximately 19% of breast cancers are diagnosed in women ages 30 to 49 years, and 44% occur among women who are age 65 years or older (Miller, 2016).[6] Male breast cancer is rare, with fewer than 1% of all breast carcinomas reported in men with an estimated 2470 new cases reported in the United States in 2017. The disease can occur in men of any age; however, the median age at diagnosis is between 60-70 years old. The risk increases with age and those with high estrogen levels or diseases associated with hyperestrogenism, radiation exposure to the breast/chest or a family history of breast cancer.[34] Overall mortality associated with metastatic breast cancer remains high (Shah & Cristofanilli, 2017).[7]

Approximately 70-80% of new breast cancers express the estrogen (ER) and/or progesterone receptor (Yee and Potter, 2009; Turner, NC et al, 2015).[8,9] It was reported that 92% of male breast cancers were estrogen-receptor-positive.[35] Up to 60% of patients with ER-positive tumors may benefit from hormonal therapy (Pietras, 2006).[10] Unfortunately, the majority of these women will develop resistance to endocrine therapy at some point during treatment (Dawood and Cristofanilli, 2007).[11] Cancer develops through unchecked progression of the cell cycle where checkpoint controls are lost subsequently permitting uncontrolled cellular proliferation. Multiple genetic lesions have been identified that augment this process in various tumor types. For instance, CCND1 and CCNE1 amplification are common, as are deletions of Rb and the endogenous CDK4-CCND1 inhibitor p16 (INK4a, encoded by the CDKN2A gene). The prediction that specific pharmacological targeting of the CDK4/6-Rb axis would be efficacious in cancer was borne out by the clinical success of the first CDK4/6 inhibitor palbociclib in combination with anti-estrogens in ER-positive breast cancer (Cristofanilli et al, 2016).[12]

A more contemporary approach to treat HR-positive advanced or metastatic breast cancer involves combining novel agents with existing endocrine therapy to block pathways enabling partial or complete endocrine resistance. Palbociclib was the first selective CDK4/6 inhibitor proven clinically efficacious in HR-positive breast cancer in combination with anti-hormonal therapy in both the first and second line settings (DeMichele et al, 2015; Finn et al, 2016; Cristofanilli et al, 2016).[13,33,12] More recently additional CDK4/6 inhibitors have been approved including ribociclib in combination with anti-hormonal therapy in the first line setting along with abemaciclib in combination with anti-hormonal therapy in a second line setting and as monotherapy in a third line setting. (https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf. Accessed October 04, 2017);[14] (https://www.verzenio.com/hcp/. Accessed October 04, 2017).[15]

While presenting valuable treatment options, these targeted therapies may experience initial clinical benefit followed by acquired resistance through mutation or activation of orthologous pathways (Chong & Janne, 2013).[16] Resistance to CDK4/6 inhibition in preclinical cellular models can be overcome by adding CDK2 inhibition (Herrera-Abrue et al, 2016).[4] Therefore, a CDK2/4/6 inhibitor with the ability to treat both intrinsic and acquired resistance to CDK4/6, such as treatment with PF-06873600, may have the potential to fill a very high unmet medical need for breast cancer patients requiring therapy.

1.2.3. Other Cancers

Activation of CDK2 is observed where Cyclin E (encoded by CCNE1 or CCNE2 genes) is amplified, representing a common event in triple negative breast cancer (TNBC) and ovarian cancer (90-100% of triple negative breast cancer (TNBC) and ~30% of serous ovarian carcinoma based on current TCGA data) (The Cancer Genome Atlas Network, 2012, Nakayama et al, 2010).[17,18] In addition, the genetic predisposition of pancreatic adenocarcinoma, head and neck squamous cell carcinoma, and non-small cell lung cancer to lose the tumor suppressor CDKN2A (p16) through mutation or deletion (>90%, 22% and 80% respectively) also implies a CDK2 driven mechanism of growth (Makohon-Moore and Iacobuzio-Donahue 2016, Kalu and Johnson 2016, Cooper et al 2013).[19,20,21] Further Cyclin D1 amplifications are also common in head and neck squamous carcinoma (31%) implicating the CDK 2/4/6 axis as a credible target across multiple tumor types.

While currently no CDK4/6 inhibitors are approved for treatment of the malignancies mentioned above, specific targeting of CDK2 in addition to CDK4 and CDK6 represents a novel approach to address additional high unmet medical need indications. Importantly, preclinical models testing PF-06873600 in pancreatic, non-small cell, head and neck, triple negative breast, and ovarian cancer have all shown evidence of anti-tumor activity. Further, translation of these in vitro findings to in vivo models has been successful in triple negative breast, ovarian and head and neck cancer. In these models, significant tumor growth inhibition has been observed at doses predicted to be achievable and tolerable in humans.

1.3. Overview of PF-06873600

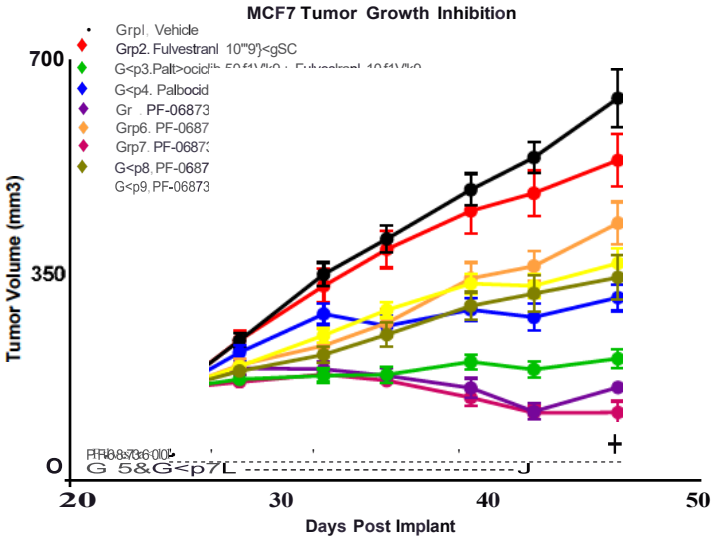
PF-06873600 is a potent, small molecule inhibitor of CDK2/4/6 that attenuates phosphorylation of the tumor suppressor retinoblastoma (Rb) resulting in prevention of cell cycling and tumor growth. During cell cycle progression, growth signals allow cyclin D to form a complex with CDK 4 or 6 and Cyclin E with CDK2. Subsequently, Rb becomes hyperphosphylated, and bound E2F is released. By inhibiting CDK2 in addition to CDK4/6, PF-06873600 may potentially provide additional benefit by further regulating and attenuating cell cycle progression to S-phase and disrupting malignant proliferation.

1.3.1. Nonclinical Efficacy

1.3.1.1. In Vivo Tumor Growth Inhibition (MCF7 Tumor Model)

The MCF7 cell line derived from ER positive HER2 negative breast adenocarcinoma is commonly used as a model of response and resistance to ER-targeted therapy (Adrian V. Lee et al 2015).[22] Oral administrntion of PF-06873600 was efficacious in the ER-positive breast cancer mouse xenograft model MCF7 as shown in Figure 2. Significant tumor growth inhibition (TGI) compared to vehicle was observed at a minimllllll dose of 10 mg/kg PF-06873600 administered twice daily (BID) in combination with 10 mg/kg fulvestrant, administered subcutaneous (SC) (Day 46, 57% TGI; p=0.0001, Pfizer internal data). Further, a dose-dependent relationship was observed where TGI was observed at the lowest dose (10 mg/kg PF-06873600 administered twice daily (BID) in combination with 10 mg/kg fulvestrant, administered SC) and the greatest TGI was observed in the highest dose (50 mg/kg PF-06873600 administered BID in combination with 10 mg/kg fulvestrant, administered SC). Palbociclib was efficacious in this model as both a single agent and in combination with fulvesti·ant albeit with better anti-tumor activity in the combination than as a single agent.

Figure 2. Tumor Growth Inhibition in MCF7 Tumor Xenograft Model

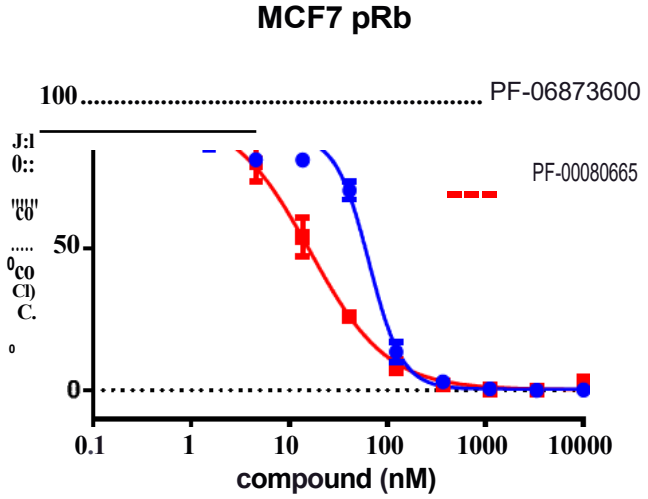


Mice propagating MCF7 ER-positive breast cancer cell tumor xenografts were dosed orally BID with the CDK2/4/6 inhibitor PF-06873600 staiting on Day 25 post cell implant at 50 mg/kg (100 mg/kg total daily dose) and 25 mg/kg (50 mg/kg total daily dose) or in combination with 10 mg/kg fulvestrant delivered SC at 50 mg/kg (100 mg/kg total daily dose), 25 mg/kg (50 mg/kg total daily dose) and 10 mg/kg (20 mg/kg total daily dose). Dosing regimens ai·e illustrated with a1wws for fulvestrant, solid black line for PF-06873600 and dashed line for 50 mg/kg dose of PF-06873600 (in single agent [Gip5) and combination [Gip7]). Control coho1ts of mice were dosed with palbocicl.ib 50 mg/kg QD, Fulvestrant 10 mg/kg SC, palbociclib (50 mg/kg QD)/Fulvestrant (10 mg/kg SC) in combination or vehicle sta1ting 25 days post cell implant. Tumor growth was measured on 28, 32, 35, 39, 42 and 46 days as indicated. Error bars represent standard error of the mean tumor volume.

1.3.1.1.1. In Vivo PF-06873600 Inhibits pRb in MCF7 ER-positive Breast Cancer Cells

The cellular activity of PF-06873600 was initially evaluated in ER positive MCF7 cells in multiple independent in vitro experiments and compared to palbociclib. Activity was determined by phospho1ylation of Rb protein following 24 hour inhibitor treatment. PF-06873600 demonstrated inhibition of cellular activity in the phospho-Rb enzyme-linked immunosorbent assay (ELISA) assay, shown relative to palbociclib (Figure 3). PF-06873600 had a mean half maximal inhibito1y concentration (ICso) of 64 nM while palbociclib had a mean ICsoof 17 nM.

Figure 3. PF-06873600 Inhibits pRb in MCF7 Cells



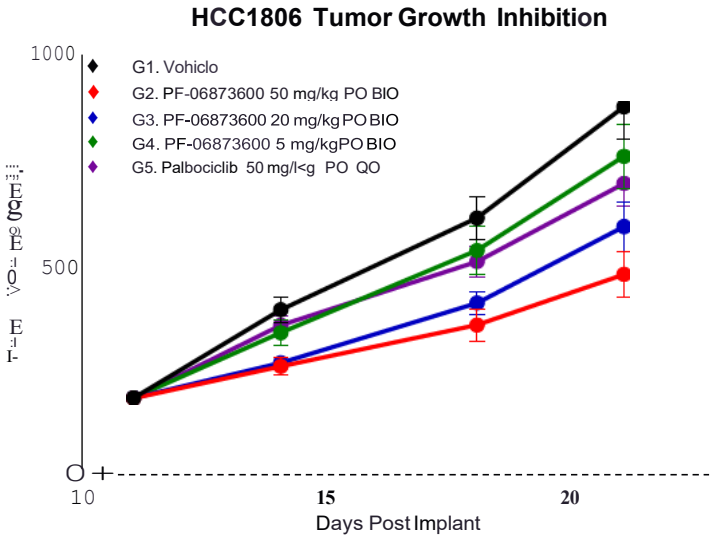
Representative IC50ctuves for pRb biomarker modulation in MCF7 ER-positive breast cancer cells. MCF7 cells were treated for 24 hour with PF-06873600 or palbociclib (PF-00080665, PD-0332991). Cell lysates were subjected to pRb ELISA and data nonualized as percent pS807/811 Rb. Data points are the mean of duplicates and en-or bars are standard deviation. pRb = Phospho1ylated retinoblastoma.

1.3.1.2. Tumor Growth Inhibition (HCC1806 Tumor Model)

Oral administration of PF-06873600 was efficacious in the Cyclin E-amplified triple negative breast cancer tumor model HCC1806, as shown in Figure 4 and Figure 5. Significant tumor growth inhibition compared to vehicle control (Day 21, 41% TGI; p <0.01) was observed in at the Inid-level dose of20 mg/kg PF-06873600 adininistered BID as well as at the highest dose of 50 mg/kg PF-06873600 adininistered BID (Day 21, 58% TGI; p <0.001) (Figure 4). Fmther, a dose-dependent relationship was observed where minimal TGI was observed at the lowest dose (5 mg/kg PF-06873600 administered BID) and the greatest TGI was observed in the highest dose (50 mg/kg PF-06873600 adininistered BID). Significant tumor growth inhibition compared to vehicle control (51% TGI; p <0.001) was also observed in a second study with a dose of 30 mg/kg BID (Figure 5) with maximal tumor growth inhibition occuning at a dose of 50 mg/kg BID.

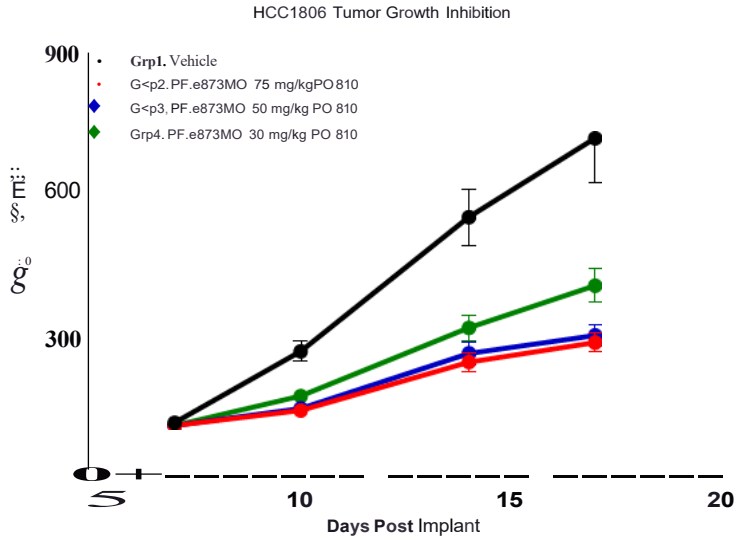
A lack of distinction between the 50 mg/kg BID and 75 mg/kg BID dosing coho1is suggests that saturation of the mechanism driving anti-proliferation is achieved at the 50 mg/kg dose. The HCC1806 model is intrinsically resistant to the CDK4/6 inhibitor palbociclib as illustrated by the minimal tumor growth inhibition observed when administered at a clinically relevant dose (Figure 4). This is likely due to the CCNEl amplification in this model which results in elevated CDK2 activity.

Figure 4. Tumor Growth Inhibition in HCC1806 Tumor Xenograft Model including Palbociclib



Mice propagating HCC1806 triple negative breast cancer cell tumor xenografts were dosed orally BID with the CDK2/4/6 inhibitor PF-06873600 at *5* mg/kg (10 mg/kg total dailydose), 20 mg/kg (40 mg/kg tot.al dailydose) or *50* mg/kg (100 mg/kg total daily dose), palbociclib *50* mg/kg QD or vehicle starting 11 days post cell implant. Tumor growih was measured on 14, 18 and 21 days as indicated. EiTor bars represent standard en-or of the mean tumor volume.

Figure 5. Tumor Growth Inhibition in HCC1806 Tumor Xenograft Model

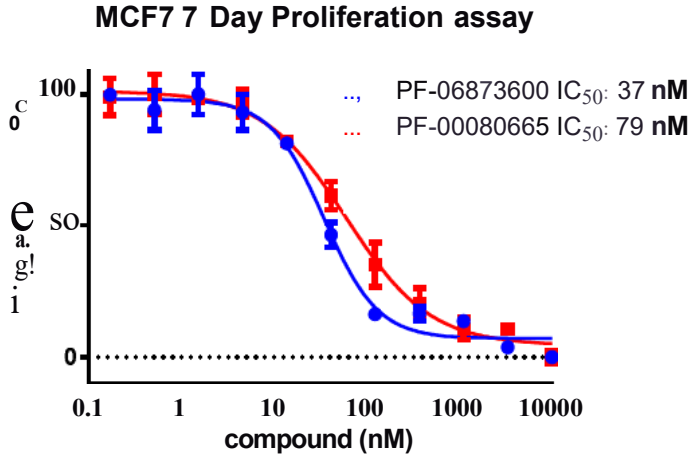


Mice propagating HCC1806 triple negative breast cancer cell tumor xenografts were dosed orally BID with the CDK2/4/6 inhibitor PF-06873600 at 30 mg/kg (60 mg/kg total dailydose), *50* mg/kg (100 mg/kg total dailydose) or 75 mg/kg (150 mg/kg total daily dose), palbociclib *50* mg/kg QD or vehicle starting 11 days post cell implant. Tumor growih was measured on 14, 18 and 21 days as indicated. EiTor bars represent standard e!l'or of the mean tumor volume.

1.3.1.3. PF-06873600 Inhibits the Proliferation of Drug Nai've and Resistant ER-positive Human Breast Cancer Cells

To examine the effect of PF-06873600 on the cell proliferation, different types of breast cancer cell lines were tested. Figure 6 illustrates representative data of the dose response relationship of PF-06873600 to proliferation in the ER-positive breast cancer, palbociclib sensitive MCF7 model. The dose-response relationship of palbociclib (PF-00080665, PD-0332991) is included as a CDK4/6 inhibitor benchmark.

Figure 6. PF-06873600 and Palbociclib Inhibit the Proliferation of MCF7 ER-positive Breast Cancer Cells



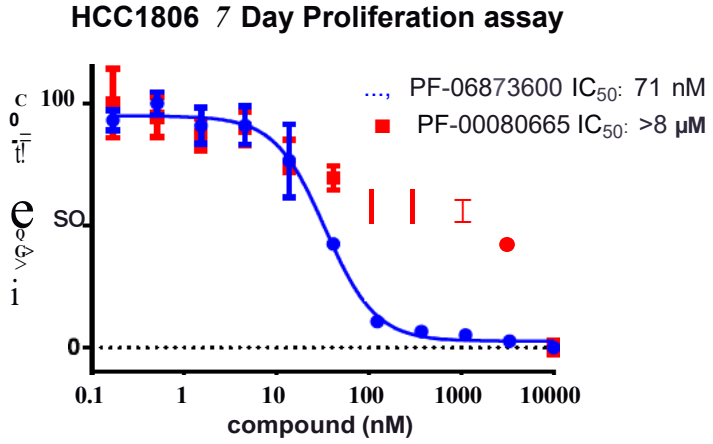
Proliferation ofMCF-7 cells relative to vehicle control were assayed across a concentration gradient of the compounds indicated (PF-00080665, PD-0332991 =palbociclib).

ICsodata from other ER positive breast cancer cell models including parental T47D, CAMAl, and HCC1428, as well as PF-06873600, palbociclib, tamoxifen, and fulvestrant drng resistant variants were generated. PF-06873600 had ICsovalues ranging from 53 to 277 nM in parental breast cancer cell lines. PF-06873600 ICsoranged from 40 to 146 nM in cell lines resistant to ER inhibitors fulvestrant and tamoxifen as well as the CDK4/6 inhibitor palbociclib. These data illustrate the anti-proliferative effect of PF-06873600 in both parental and dmg resistant models of ER-positive breast cancer.

1.3.1.4. PF-06873600 Inhibits the Proliferation of CCNE1 High Cancer Cells Inherently Resistant to Palbociclib

Oncogenic CCNEl amplification is predicted to activate CDK2 thereby rendering cells insensitive to CDK4/6 inhibitors (ie, palbociclib). To address this hypothesis we assessed the proliferation ICsoof PF-06873600 and palbociclib in four CCNEl amplified cell lines; HCC1806, OvCar3, COV362 and CAOV3. In each case, PF-06873600 was effective at inhibiting proliferation with ICsobetween 18.7 to 63.5 nM, while palbociclib had no significant anti-proliferative effect at doses relevant to free drng exposure achieved in patient (ie, below 100 nM). Representative results from the ti·iple negative breast cancer cell line HCC1806 are shown in Figure 7 as a dose response relationship of PF-06873600 to cell proliferation, in conti·ast to palbociclib.

Figure 7. PF-06873600 is an Inhibitor of CCNE1 High HCC1806 Cell Proliferation Where Palbociclib is Ineffective



Proliferation ofHCC1806 cells relative to vehicle control were assayed across a concentration gradient of the compounds indicated (PF-00080665, PD-0332991 =palbociclib).

ICso data from the HCC1806 and 3 ovarian cancer cell lines, OvCar3, COV362 and CAOV3 were generated. In each case, PF-06873600 was effective at inhibiting cell proliferation between 18.7 to 63.5 nM, while palbociclib had no anti-proliferative effect.

1.3.2. Nonclinical Pharmacokinetics (PK)

Following intrnvenous (IV) administration, the non-clinical PK of PF-06873600 was characterized by low plasma clearance (CLp) in rat, dog and monkey (8 to 13 mL/min/kg) and high in mouse (63 mL/min/kg). PF-06873600 exhibits a volume of distribution at steady state (Vss) of between 0.6 to 1.3 L/kg across species. PF-06873600 exhibits moderate to rapid abso1ption (time to maximum concentration (Tmax) = 0.5 to 4 hours) after oral administration in preclinical species. The oral bioavailability of PF-06873600 was moderate and observed to range between 29% to 59% in the relevant preclinical species. Following repeat oral dosing in Inice and dogs, systeinic exposure increased with an increase in dose with no evidence of sex-related differences in exposure in either species. There was no accumulation of exposure after multiple doses on Day last when compared to the exposure on Day 1 in either species.

In vitro studies suggest PF-06873600 is a substrate for the efflux transporters human pe1meability glycoprotein, (P-gp) and human breast cancer resistance protein (BCRP). As a result of the high passive pe1meability exhibited by PF-06873600 and moderate % F observed in relevant preclinical species (rat, dog, and monkey), the oral abso1ption of PF-06873600 in humans is predicted to be moderate.

Renal and/or bilia1y excretion of PF-06873600 in rats and dogs was minimal. In vitro studies using Sandwich Cultured Human Hepatocytes (SCHH) demonstrate that PF-06873600 does not exhibit bilia1y excretion and therefore biliaiy excretion is predicted to be minimal in humans.

Following in vitro evaluation, the primary mechanisms of clearance for PF-06873600 in preclinical species and humans appears to be oxidation mediated primarily by cytochrome P450 (CYP) enzymes, predominantly CYP3A4. No unique human metabolites were identified. Mean IC_{50} values for inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2D6, and 3A4/5 were >100 μM, while the IC_{50} value for CYP2C19 was 92.8 μM. PF-06873600 demonstrated time-dependent inhibition (TDI) of CYP3A4 enzymes but did not exhibit induction of CYP1A2, CYP3A4, or CYP2B6. PF- 06873600 is not likely to demonstrate drug-drug interaction (DDI) with MDR1, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2; however, PF-06873600 may exhibit DDI mediated by inhibition of BCRP, MATE1, or MATE2K.

In humans, PF-06873600 is predicted to have a low CLp (1.0 mL/min/kg) and a low Vss, (0.8 L/kg) resulting in a half-life of approximately 9 hours. In addition, PF-06873600 is expected to be moderately absorbed in humans with a projected oral bioavailability of approximately 40%. The oral plasma clearance (CLp/F) and the apparent volume of distribution (Vd/F) are predicted to be 2.5 mL/min/kg and 2 L/kg for PF-06873600 respectively. A dose response relationship was established between plasma exposure of PF-06873600 and the proximal biomarker of phosphorylated Rb serines 807/811/total Rb in the tumor. A pharmacologically active dose (PAD) for PF-06873600 is estimated at 10 mg BID with a predicted unbound efficacious concentration (C_{eff}) (equal to minimal concentration (C_{min})) of approximately 33 nM (15.6 ng/mL) in HCC1806 tumors (triple negative breast cancer) and a PAD of 15 mg BID is estimated with a predicted unbound C_{eff} (equal to C_{min}) of approximately 50 nM (23.6 ng/mL) in MCF 7 tumors (metastatic ER-positive breast cancer).

If a suboptimal half-life is observed at 10 mg BID and higher, a PF-06873600 oral dosing regimen of three times daily (TID) may be evaluated during dose escalation. In addition, a higher than predicted clearance could result in a higher pharmacologically active dose (PAD) than the originally predicted 10-15 mg BID. To minimize the number of patients exposed to sub-therapeutic dose levels, an accelerated dose escalation with potential for larger dose increments (as utilized for the initial dose levels) may be adopted until the observation of clinically relevant adverse events or the dose levels approaching the projected PAD.

1.3.3. Nonclinical Safety

Consistent with the intended pharmacologic activity of PF-06873600 (ie, cell cycle inhibition), the primary target organ systems identified included the hematopoietic and gastrointestinal systems. In addition, pancreas and liver findings were identified in exploratory toxicity studies, and cardiovascular effects were observed in ex vivo and in vivo assessments in dogs. In the pivotal 1-month Good Laboratory Practice (GLP) dog and mouse toxicity studies, PF-06873600 was not tolerated at the highest dose tested and was associated with clinical signs of body weight loss, dehydration, inappetence, liquid feces, emesis (dog) and hypoactivity leading to unscheduled euthanasia. Intolerance to PF-06873600 in the mouse and dog was primarily ascribed to adverse gastrointestinal effects. Hematology changes in mice correlated with non-adverse microscopic changes of decreased cellularity in bone marrow, spleen, thymus and lymph node. Conversely, in the dog, the observed changes in hematology, and microscopic pathology of bone marrow and lymphoid organs were

considered adverse. The hematolymphopoietic changes observed with PF-06873600 are consistent with those observed with other cell cycle inhibitors, palbociclib and ribociclib, and are considered a consequence of the primary pharmacology of CDK 4/6 inhibition. Changes in the pancreas and liver were observed only in a single species in the 14-Day exploratory toxicity studies, were not observed in the 1-month GLP studies, and lack any specific mechanistic link; therefore, the relevance of these findings to patients is uncertain. In addition, a non-dose limiting decrease in blood pressure, increase in heart rate, and decrease in PR interval, were observed in dogs at expected clinically relevant exposures. The observed in vivo hypotensive effect was consistent with the decrease in vascular tone observed in ex vivo studies. Reversibility was established for all PF-06873600-related target organ toxicities identified in the 1-month GLP studies with recovery arms (gastrointestinal tract, hematopoietic, lymphoid).

In exploratory in vitro genetic toxicity assays, PF-06873600 was not mutagenic or clastogenic, but was observed to be aneugenic. PF-06873600 absorbs light in the 280 nm to 500 nM range with the greatest molar extinction coefficient of 20,643 L/mol•cm at 351 nM, and therefore has the potential to cause phototoxicity. Developmental and reproductive toxicity studies specific for fertility and teratology have not been conducted with PF-06873600 but toxicity to reproductive organs was not observed in the 1-month mouse and dog GLP general toxicity studies. However, based on the mechanism of action, male reproductive and embryo fetal toxicity are potential risks. Adverse effects of other CDK 4/6 inhibitors, including ribociclib, abemaciclib, and palbociclib,[14,15,34] on male reproductive organs, function and fertility in animal studies were observed and partially reversible in some instances. In addition, effects on fetal growth, survival and morphology were also observed with CDK 4/6 inhibitors in animal studies.

The nonclinical safety findings related to oral administration of PF-06873600 represent toxicities that can be monitored and/or are considered clinically manageable or acceptable risks in the intended advanced cancer patient population.

1.4. Starting Dose Rationale

The selection of the starting dose and regimen for this first-in-patient (FIP) study was based on the nonclinical toxicology and PK results in accordance with the International Conference on Harmonization (ICH) S9 Guidance.[23] Results from nonclinical toxicity studies indicate that the dog is the most sensitive species, and the highest non-severely toxic dose (HNSTD) of PF-06873600 in dog was 0.6 mg/kg after daily oral administration. The human equivalent dose for the HNSTD of 0.6 mg/kg/day in dog is approximately 20 mg daily (assuming a body weight of 60 kg). Per Guidance S9, one-sixth of the HNSTD can be considered as the appropriate starting dose. Given the predicted human disposition of half-life of approximately 9 hours, the starting dose has been selected to be 1 mg administered orally BID. The human area under the curve (AUC) of PF-06873600 at the proposed starting oral dose of 1 mg BID (by mouth 2 mg/day) is predicted to be ~26% of the observed $AUC_{0\text{-}24}$ at HNSTD in dog (PO 0.6 mg/kg/day), and ~1% of the observed $AUC_{0\text{-}24}$ at the (severely toxic dose in 10% of animals) STD10 (severely toxic dose in 10% of animals) of 50 mg/kg/day in mouse.

Additional infonnation for PF-06873600 may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

1.5. Study Rationale

Modulating the cell cycle by inhibiting CDK4/6 in combination with endocrine therapy has been shown to provide significant clinical benefit in patients with HR-positive HER2-negative advanced or mBC (Finn et al, 2016; Cristofanilli et al, 2016).[33,12] Despite the proven clinical response observed with this class of diugs, some patients may have intrinsic or adaptive resistance to ti·eatment with combined CDK4/6 and endocrine therapy. Preclinical studies have shown that resistance to CDK4/6 inhibition in preclinical cellular models can be overcome with the addition of CDK2 inhibition to the inhibition of CDK4 and 6 (Henera-Abme et al, 2016).[4] As such, the inhibition ofCDK2/4/6 may provide an impo1tant new therapeutic sti·ategy to overcome resistance to combined CDK4/6 and endocrine therapy. This study will evaluate the effect of PF-06873600, as a single agent and in combination with endocrine therapy, in patients with HR-positive HER2-negative advanced metastatic breast cancer, who have failed prior combination CDK4/6 inhibitor and endocrine therapy.

In addition, the effects of PF-06873600 will be explored in tumor types that have potential for increased Cyclin E expression and/or CDK2 or 4/6 activity including locally recunent/advanced or metastatic TNBC and advanced platinum resistant ovarian cancer. Utilizing biomarker coho1ts, the mechanism of action of PF-06873600 as well as putative di·ivers for resistance (eg, amplified CCNEl) will also be studied.

CCI

CCI

[redacted]

1.5.2. Banked Biospecimens

Banked biospecimens will be collected for the pm-pose of conductin g research; specific uses are described in the Banked Bios ecimens section. CCI [redacted] and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most a ro riate ·ou of atients in which to tar et a iven treatment. CCI [redacted]

Banked biospecimens retained in the BBS also can be used in research in advanced or mBC and ovarian cancer. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or institution review board (IRB)/ethics committee (EC) decision.

1.6. Overview of Letrozole (Femara®)

Letrnzole (Femara®)is an oral nonsteroidal aromatase inhibitor and it is approved worldwide for the first and second line treatment of postmenopausal women with ho1mone receptor positive advanced breast cancer. Common side effects include hypercholesterolemia, hot flashes/flushing, aiihralgia/arthritis, night sweats, bone fractures, weight increase, nausea, fatigue, myalgia, edema, weight decrease, vaginal bleeding, back pain, osteoporosis not othe1wise specified (NOS), and bone pain (Nova1iis Phannaceuticals Corporation, United States package inse1i (USPI), 2020).[14]

Complete info1mation for this compound may be found in the SRSD, which for this study is the Novaitis USPI, Femai·a®(letrozole), East Hanover, New Jersey.

1.7. Overview of Fulvestrant (Faslodex®)

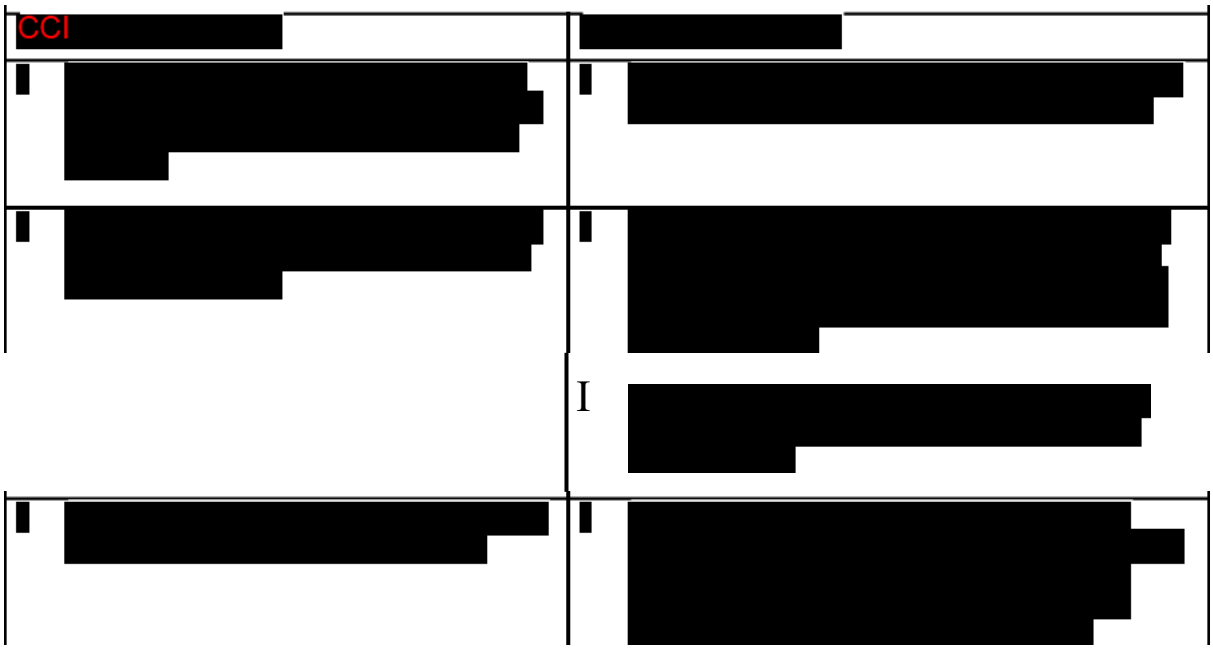
Fulvestrant (Faslodex®) is a competitive ER antagonist with an affinity comparable to estradiol. It blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity, and is currently indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The mechanism of action is associated with down-regulation of ER protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER-positive tumors compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg/month downregulates ER and the proliferation marker Ki67 to a greater degree than fulvestrant 250 mg/month in breast tumors in the postmenopausal neoadjuvant setting. Fulvestrant is comparable to aromatase inhibitors (AIs) in terms of efficacy and tolerability for women who have progressed on prior tamoxifen therapy (AstraZeneca Pharmaceuticals USPI, 2020).[25]

Complete information for fulvestrant may be found in the SRSD, which for this study is the AstraZeneca Pharma USPI, Faslodex® (fulvestrant) injection, Wilmington, DE.[25]

2. STUDY OBJECTIVES AND ENDPOINTS

Parts 1A and 1C: Single Agent Dose Escalation and Part 1B: Combination Dose Finding	
Primary Objective(s):	**Primary Endpoint(s):**
Parts 1A and 1C: To assess the safety and tolerability of increasing doses of PF-06873600 in patients with: • HR-positive HER2-negative advanced or mBC patients (third or fourth line setting). • Locally recurrent/advanced or metastatic TNBC. • Advanced platinum resistant epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer • In order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Dose for Expansion (RDE) for PF-06873600 as a single agent (Part 1A and Part 1C only). Part 1B: To assess the safety and tolerability of PF-06873600 at the single agent RDE in combination with letrozole and in combination with fulvestrant (in a de-escalation manner, if indicated) in patients with: • HR-positive HER2-negative advanced or mBC (third or fourth line setting) in order to establish the RDE for PF-06873600 in combination with letrozole and in combination with fulvestrant, respectively.	Parts 1A, Part 1B, and Part 1C: • Dose-Limiting Toxicities (DLTs). • Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital sign abnormalities. • Heart rate corrected QT interval (eg, QTcF).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the single- and multiple- dose PK of PF-06873600 when given as a single agent (Part 1A, and Part 1C), in combination with letrozole, and in combination with fulvestrant (Part 1B).	Pharmacokinetic parameters of PF-06873600: • Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and as data permit, AUC_{inf}, CL/F, V_z/F, and $t_{1/2}$. • Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, CL_{ss}/F, and as data permit, V_{ss}/F, $t_{1/2}$, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).
• To document any preliminary evidence of anti-tumor activity of PF-06873600.	• Objective Response (OR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. • Time-to-event endpoints: eg, Duration of Response (DoR), Progression-Free Survival (PFS), Time to Progression (TTP).
• To evaluate the pharmacodynamic (PD) biomarkers of CDK pathway modulation following treatment with PF-06873600 in tumor.	• Modulation of PD biomarkers (eg, pRb, Ki67) of CDK in tumor.

Parts lA and lC: Single Agent Dose Escalation and Part 1B: Combination Dose Finding



Part 2: PF-06873600 Combination Dose Expansion	
Primary Objective(s):	**Primary Endpoint(s):**

• To evaluate the preliminary antitumor activity and confinu the safety and tolerability of PF-06873600:
 	
In combination (at the RDE from Pait lB) in patients with:
• HR-positive/HER2-negative advanced or mBC (PF-06873600 + fulvestrant) - (second or third line setting).
• HR-positive/HER2-negative advanced or mBC (PF-06873600 + a nousteroidal aromatase inhibitor) (CDK4/6i naive).
• HR-positive HER2-negative advanced or mBC (PF-06873600+fulvestrant) (CDK4/6i nai:ve).
	• Preliminary antitumor activity meastu·e for efficacy includes ORR, as assessed using RECIST 1.**1.**
	• Safety and tolerability:
	  • Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Tenuinology. Criteria for Adverse Events (NCI CTCAE v 4.03) timing, seriousness and relationship to study therapy.
	  • Lab abnonualities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.
	  • Vital sign abno1malities.
	  • Heart rate con-ected QT interval (eg, QTcF).

Secondary Objective(s):	**Secondary Endpoint(s):**
• To further explore preliminary antittuuor activity of PF-06873600.	• Time-to-event endpoints: eg, DOR, PFS, overall smvival (OS) and TIP.
• To further evaluate the **PK** of PF-06873600 in combination with letrozole, and in combination with fulvestrant at the respective RDE.	Phrumacokinetic parameters of PF-06873600, including but not limited to: • SD - Cmax, Tmax.

Part 2: PF-06873600 Combination Dose Expansion	
	• MD (assuming steady state is achieved) - Css,max, Tss,max, Css,minand Rac,Cmax.
• To evaluate phanuacodynam.ic (PD) biomarkers of CDK pathway modulation following treatment with PF-06873600 in combination with fulvestrant or letrozole in ttuuor.	• Modulation of PD biomarkers (eg, pRb, Ki67) ofCDK in tumor.
CCI [redacted]	[redacted]
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3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1/2a, open-label, multi-center, non-randomized, multiple dose, safety, tolerability, phaimacokinetic, and phannacodynamic study of PF-06873600 administered as a single agent in sequential dose levels and then in combination with endocrine therapy. In Pait IA, successive coho1ts of patients will receive escalating doses of PF-06873600 staiting at I mg BID dosed on a continuous basis and then in dose finding (Pait IB) with immediate release fo1mulations of PF-06873600 in combination with endocrine therapy (ET) in an outpatient setting. In Pait IC, successive coho1ts of patients will receive escalating doses of PF-06873600 testing a modified release (MR) fo1mulation in a MR coho1t evaluation and then in dose finding (Pali IB) with modified release fo1mulations of PF-06873600 in combination with endocrine therapy (ET) in an outpatient setting.

This study contains 2 pa1ts, dose escalation with single agent (Pait IA and IC) and then dose finding with PF-06873600 in combination with endocrine therapy (letrozole and fulvestrant, independently with both immediate and modified release fonnulations) (Pait IB) followed by dose expansion aims in combination with endocrine therapy (Pait 2). The decision to initiate Pait 2 with either the immediate release fonnulation or the modified release fo1mulation will

be made following a careful review of all available data from Part 1 (1A, 1B, and 1C) and in consultation with the C3661001 Safety Team.

The Japan lead-in cohort (J-LIC) will be added separately as a sub-cohort in order to assess the safety of monotherapy of PF-06873600 in Japanese population. Detailed information is provided in the Appendix 7. Japanese participants will be able to enroll into Part 2 after safety and tolerability of monotherapy of PF-06873600 in Japanese participants is confirmed.

The overall study design is depicted in Figure 8 below.

Figure 8. Overall Study Schema

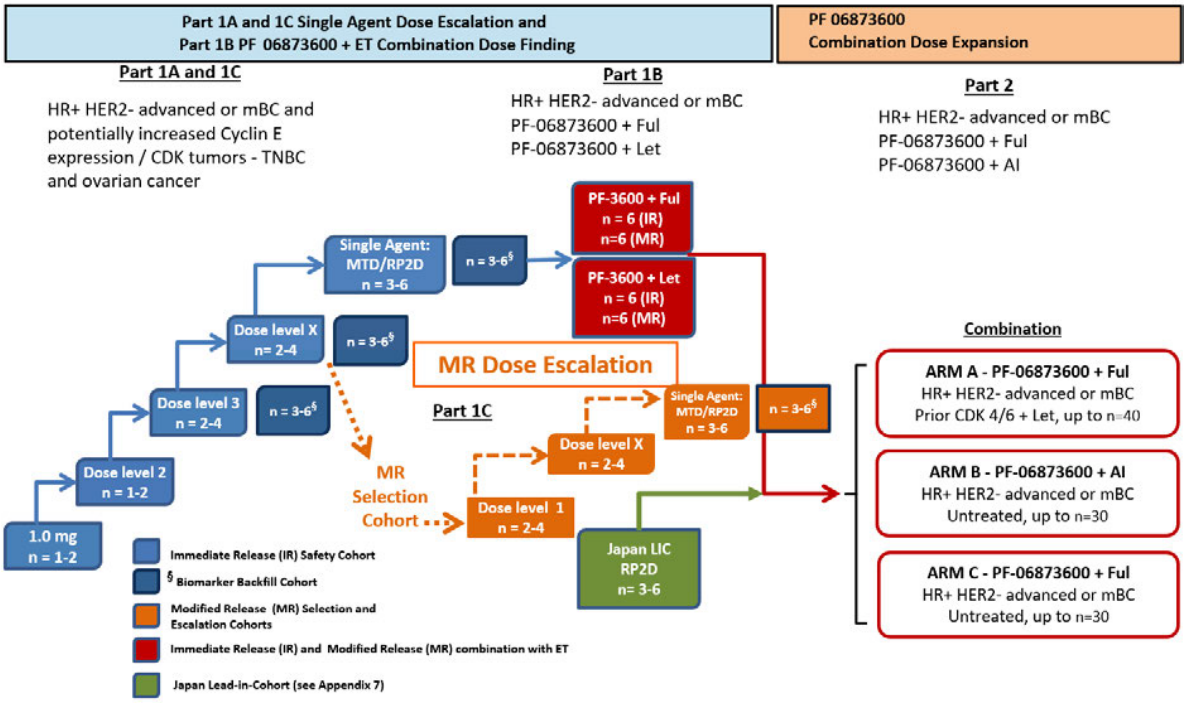
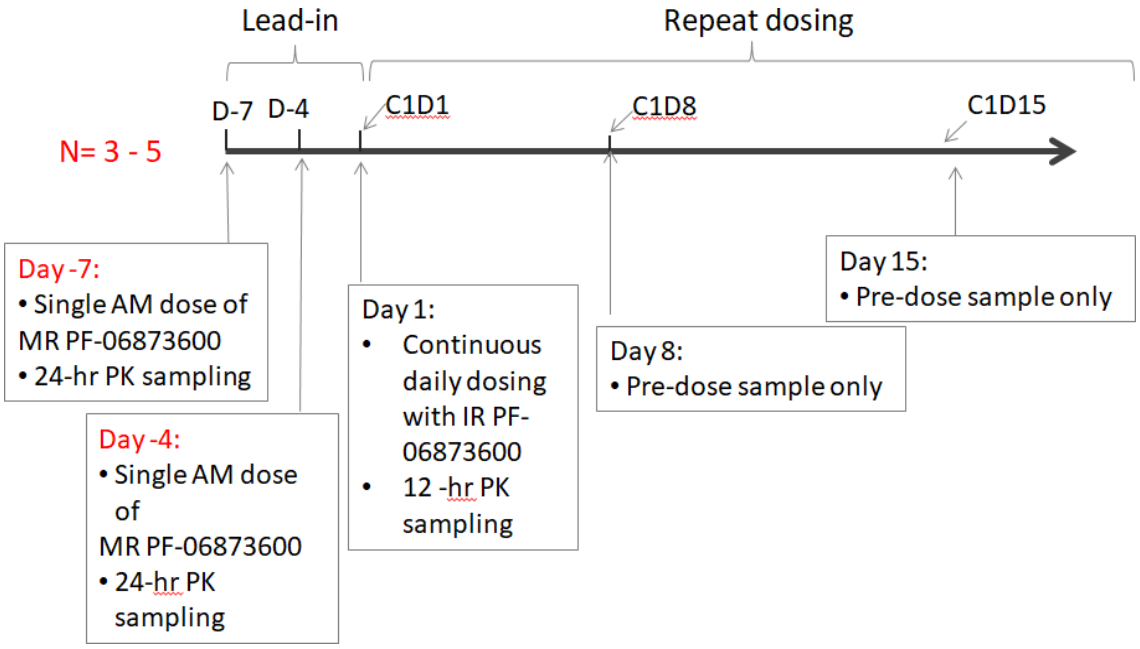


Figure 9. Modified Release Selection Cohort Study Schema (within Part 1C through Cycle 1):



Part 1A will estimate the maximum tolerated dose/recommended Phase 2 dose/recommended dose for expansion (MTD/RDE) in sequential dose escalation safety cohorts for PF-06873600 as a single agent in women of any menopausal status and men with HR-positive HER2-negative advanced or mBC (third or fourth line setting) and in women/men with locally recurrent/advanced or metastatic TNBC and women with advanced platinum resistant ovarian cancer.

Any given PF-06873600 dose in Part 1A (or Part 1C) may be escalated or de-escalated at full or intermediate dose levels, depending on emerging clinical data. Parallel biomarker cohorts may be initiated for HR-positive HER2-negative advanced or mBC patients only, once the respective preceding dose escalation safety cohort has cleared (see Section 3.1.1).

After the MTD/RDE for PF-06873600 as a single agent has been identified in Part 1A (or Part 1C) based on safety and clinical observations, initiation of combination dose de-escalation with PF-06873600 in combination with letrozole and PF-06873600 in combination with fulvestrant independently (Part 1B) will be initiated at the single agent MTD or RDE in women of any menopausal status with HR-positive HER2-negative advanced or mBC. In Part 1B, the PF-06873600 dose can be de-escalated at full or intermediate dose levels. In addition both available formulations of PF-06873600 at the respective RDE will be studied in combination with endocrine therapy in Part 1B. Approximately 12 patients will be dosed in the respective endocrine therapy combinations, with approximately 6 patients receiving PF-06873600 IR + endocrine therapy and approximately 6 patients receiving PF-06873600 MR + endocrine therapy in both the fulvestrant and letrozole arms.

Part 2 will evaluate the dose selected (RDE) in combination with endocrine therapy (letrozole and fulvestrant in independent dose expansion arms) depending on clinical observations from Part 1B (See Section 3.2).

PF-06873600 will initially be administered orally BID on a continuous basis. If emerging PK data from initial dose levels in Part 1A (or Part 1C), demonstrate the feasibility of once daily (QD) dosing, the dose escalation may continue with QD dosing, following the dose escalation schema with the same total daily dose as planned for BID dosing. The evaluation of an alternative dosing regimen (eg, QD) may be considered during the course of dose escalation or after determination of the MTD for the BID regimen based on emerging and available preliminary clinical data, including safety/tolerability, laboratory, PK and PD findings. If an alternative dosing regimen (eg, QD) assessment occurs after determining the MTD of the BID regimen, it will be initiated with a dose level at a comparable total daily dose determined from the MTD of the BID regimen.

Intermittently administered PF-06873600 dosing schedules may also be evaluated if indicated based on emerging clinical data. As an option, PF-06873600 may be administered continuously for three weeks followed by one week off if indicated by emerging clinical safety and PK data.

All cycles are 28 days in length and treatment will continue until progression of disease, uncontrollable toxicity, a decision by the patient or investigator to discontinue treatment or the study is terminated. Patients experiencing toxicity including a dose limiting toxicity (DLT) may be managed with dose modification or discontinuation from treatment. The proposed doses, schedule(s) and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. It is estimated that each patient may remain on treatment for approximately 6-8 cycles, making total study duration approximately 32-36 weeks. Actual duration can be longer, if a patient derives benefit from study treatment.

Approximately 75 patients are expected to be enrolled in the dose escalation/finding safety cohorts and an additional 6-12 patients are expected in the biomarker cohorts in Parts 1A and 1C. The actual number of patients enrolled will depend on the tolerability of PF-06873600 and the number of dose levels required to identify the MTD/RDE. Approximately 100 patients are expected to be enrolled in Part 2.

3.1.1. Part 1A PF-06873600 Single Agent Dose Escalation

Part 1A consists of single agent dose escalation in dose escalation safety cohorts as well as biomarker cohorts. The dose escalation safety cohorts will be initiated in 1-2 patients for the first 2 planned dose levels starting at 1 mg BID orally on a continuous basis and dose escalation will proceed according to the modified toxicity probability interval (mTPI) method. When a dose level is deemed safe following a DLT observation period of 28 days and based on the discussion by the safety review team (comprised of the Investigators and the Sponsor), dose escalation will occur to the next dose level (Table 2).

While patients enrolled in the dose escalation safety cohorts are being evaluated, patients may enroll into additional biomarker cohorts (approximately 6 patients in each cohort) requiring mandatory pre- and -on treatment tumor and skin biopsies. An end of treatment tumor biopsy is optional but encouraged. Initiation of enrollment into the first biomarker cohort will be based on observations of key pharmacodynamic (PD) findings (eg, neutropenia, gastrointestinal toxicities, and/or other PK/PD markers) and/or reaching a predicted active dose (noted in Figure 8 as [§]Biomarker Cohort). Enrollment into a biomarker cohort can occur after the dose level is deemed safe for escalation to a higher dose level or at the MTD. Biomarker cohorts will enroll women and men with HR-positive HER2-negative advanced or mBC. Because these additional patients will receive a dose lower than the concurrent dose escalation safety cohort or will be enrolled at a dose following the DLT evaluation period in the first 2-4 dose escalation safety cohort patients enrolled, their potential DLT observations may not be strictly used in the mTPI method for the ongoing dose finding. However, the safety profile from these additional patients will be used to establish the MTD or RDE.

3.1.2. Part 1B PF-06873600 Dose Finding in Combination with Endocrine Therapy

After the single-agent PF-06873600 MTD/RDE has been determined for both the IR and MR formulations, enrollment will be initiated into Part 1B which will evaluate the PF-06873600 in combination with letrozole and in combination with fulvestrant in independent cohorts in women with HR-positive HER2-negative advanced or mBC. PF-06873600 will be administered orally on a continuous basis (unless the dose schedule has changed during Part 1A or Part 1C), while letrozole and fulvestrant will be administered per standard of care. Available safety and clinical data will be reviewed by the safety review team. The PF-06873600 dose in combination with letrozole may be decreased if determined to not be tolerable. The PF-06873600 dose de-escalation in combination with letrozole will follow the mTPI method. Similarly, the PF-06873600 dose in combination with fulvestrant may be decreased if determined to not be tolerable. The PF-06873600 dose de-escalated in combination with fulvestrant will follow the mTPI method. The MTD/RDE of each of the PF-06873600 formulations (IR and MR) in combination with the respective endocrine therapy (letrozole and fulvestrant) will be declared when at least 6 patients have been enrolled at a dose level that is predicted to be the MTD/RDE for each of the respective combination per the mTPI. Once the MTD/RDE of PF-06873600 in combination with letrozole and the MTD/RDE of PF-06873600 in combination with fulvestrant have been confirmed, a recommended dose for expansion for each combination will be declared and enrollment into Part 2 may be initiated. The decision to dose either the MR or IR or MR and IR formulation in Part 2 will be made following a careful review of all available clinical data and in alignment with C3661001 Safety Team.

Similar to Part 1A and/or Part 1C, dose escalation, all safety, PK and PD information from safety cohorts in Part 1B available will be used to determine the PF-06873600 MTD/RDE for the respective combination treatments.

3.1.3. Part 1C PF06873600 MR Formulation

"A MR formulation with two designed release rates shorter duration (eg, 6 -hour) and longer duration (eg, 12-hour) release, respectively, has been developed for PF-06873600 and were studied in the Part 1C MR Selection Cohort only." Compared to the Immediate Release (IR) formulation, the MR formulation has the potential to achieve more prolonged effective target inhibition during a dose interval. Emerging pharmacokinetics and safety data for the IR formulation suggest there is a large peak-to-trough fluctuation in steady-state concentrations and that a lower maximal concentration (C_{max}) could potentially improve tolerability. Therefore, the MR formulation with the two release rates were evaluated in an MR selection cohort in this study.

The MR selection cohort enrolled 3 to 5 evaluable patients. These patients received two single doses of the MR formulation during a 7-day lead-in period (Day -7 to Day -1), prior to receiving the IR formulation of PF-06873600 twice daily in 28-day cycles. During the 7-day lead-in period, patients first received a single dose of the shorter release tablets on Day -7, and then another single dose of the longer release tablets on Day -4. The dose for the shorter and longer release MR tablets were administered during the lead-in period, as well as the IR dose administered starting from Cycle 1 Day 1, were no higher than the highest nominal dose tested found to be safe from the IR dose escalation. Serial PK sampling was performed for 24 hours following each of the MR formulation doses on Day -7 and Day -4, and for 12 hours following the IR formulation morning dose on Cycle 1 Day 1. PK was compared between the shorter and longer release MR tablets, and also between each of the two release rate MR tablets and IR. Based on the PK data from the MR selection cohort, 12-hour release rate provides a slower release compared to the 6-hour release rate, thus achieves more prolonged drug coverage during a dosing interval. Therefore, 12-hour release rate was selected to be further investigated during MR dose escalation.

The MR dose escalation, proceeded with one of the selected MR formulation release rates according to the mTPI method until a MTD/RDE is determined. The starting dose for the MR dose escalation was selected to achieve similar steady-state AUC during one dose interval ($AUCss,\tau$) as the highest safe IR dose based on prediction. The dose increment will be no more than a 50% increase. After MTD/RDE is determined, a biomarker cohort may be open to enroll patients with HR-positive HER2-negative advanced or mBC requiring mandatory pre- and on-treatment tumor and skin biopsies.

During the Part 1C dose escalation, all available safety, PK and PD information from dose escalation safety and biomarker cohorts in will be used to determine the PF-06873600 MTD/RDE as a single agent.

3.1.4. Starting Dose for Part 1A

The starting dose of PF-06873600 will be 1 mg administered orally BID on a continuous basis in 28 day cycles.

3.1.5. Criteria for Dose Escalation

Compared to the traditional mTPI method, the proposed mTPI method for this protocol includes stopping rules and dose escalation/finding criteria, which prevents the target DLT rate to reach ≥33% for determining the MTD. This proposed mTPI method, targeting a DLT rate of 27.5% and an acceptable DLT interval (22.5% to 32.5%), will be utilized in Part 1 dose escalation/finding phase, and will also be used to monitor the DLTs so as not to cross toxicity boundaries in the expansion of a cohort. In this process, the upper limit of the DLT rate to determine a MTD will be <33%. This proposed mTPI method is more conservative than the traditional toxicity probability interval (TPI) method.

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 1-4 patients, or the trial should be terminated (Table 1).

Table 1. Dose Escalation/De-Escalation Decision Rules

DLT	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E
2	D	D	D	S	S	S	S	S	S	S	E
3		U	U	D	D	S	S	S	S	S	S
4			U	U	U	U	D	S	S	S	S
5				U	U	U	U	U	D	S	S
6					U	U	U	U	U	U	U
7						U	U	U	U	U	U
8							U	U	U	U	U
9								U	U	U	U
10									U	U	U
11										U	U
12											U

Actions to be taken: D = De-escalate the dose; E = Escalate the dose; S = Stay at the dose. U = Unacceptable toxicity.

Initially, dose cohorts may consist of 1-2 patients in the single agent dose escalation in Part 1A. When a DLT is observed, additional patients will be enrolled and dose escalation decision will follow the mTPI criteria. Table 2 showing escalating doses with a 100% to 150% increase from the previous dose in dose levels (DLs). In later cohorts it is anticipated that total daily dose level increases may approximate 100% or less depending on emerging available clinical data, including safety/tolerability, laboratory, PK and PD findings.

The total daily dose will be administered once a day (QD) or in divided doses of either two (BID) or three times a day (TID).

Initial dose levels are provided in Table 2 and intermediate dose levels may be considered as indicated. Intra-patient dose escalation for patients enrolled in dose level 1 and 2 may be considered in consultation with the sponsor. Once the respective dose level has been declared safe, patients who have completed at least 2 Cycles of treatment at the original enrolled dose level may escalate to the next higher dose level that has cleared the DLT observation period of 28 days.

Table 2. PF-06873600 Dose Levels (Immediate Release Formulation)

DOSE LEVEL (DL)*	DOSE	TOTAL DAILY DOSE***
DL 1**	1 mg BID	2 mg
DL 2	2 mg BID	4 mg
DL 3	5 mg BID	10 mg
DL 4	10 mg BID	20 mg
DL 5 and Beyond		Escalation to continue to the MTD or desired pharmacological activity

*The proposed doses, schedule(s), and PK time points may be reconsidered or amended during the study based on the emerging safety and PK data. Intermediate doses may be considered when deemed necessary based on on-going evaluation of safety and toxicity data.
** Starting dose DL1.
*** Total daily dose may be administered in up to 3 divided doses.

In principle, all patients must be evaluated for a minimum DLT observation period of 28 days in Part 1. However, in order to be evaluable for DLT assessment patients need to have received at least 75% of planned doses unless the patient has experienced a DLT prior to receiving 75% of the planned dose.

The dose escalation in Part 1A, and 1C, dose finding in Part 1B, and each arm of the dose expansion in Part 2 of the study will stop as the applicable following criteria are met:

- The maximum sample size has been achieved (approximately 75 patients in Part 1, excluding patients enrolled in biomarker cohorts, and approximately 70 patients in Part 2);

- 6 to 12 evaluable patients (for Parts 1A, Part 1B, and Part 1C) that have been enrolled at a PF-06873600 dose level (as a single agent, in combination with letrozole, and in combination with fulvestrant, each)) that is predicted to be the MTD per the mTPI method;

- All dose levels explored appear to be overly toxic, and the MTD cannot be determined.

3.1.6. DLT Definition

Severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For the purpose of dose escalation/finding, any of the following AEs occurring in the first cycle of treatment (28 days) which are attributable to one, the other, or both agents in the combination will be classified as DLTs:

Hematologic

- Grade 4 neutropenia lasting >7 days;

- Febrile neutropenia defined as an absolute neutrophil count (ANC) <1.0 x 109/L with a single temperature of >38.3°C, or 101°F, or a sustained temperature of ≥38°C, or 100.4°F, for more than one hour;

  - Grade ≥3 neutropenia with associated infection;

- Grade 3 thrombocytopenia with clinically significant bleeding as indicated by ≥ Grade 2 bleeding;

  - Grade 4 thrombocytopenia.

Nonhematologic:

- Confirmed case of DILI (Hy's Law) as per Section 8.4.1.

- Grade ≥3 AEs that are clinically significant with the following exceptions:

  - Grade 3 nausea, vomiting, or diarrhea for ≥72 hours despite optimal supportive care will be considered a DLT;

  - Grade 3 fatigue for ≥5 days will be considered a DLT;

  - Grade 5 event unless attributed to a cause clearly not related to study treatment.

All DLTs need to represent a clinically significant shift from baseline.

Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae or are corrected with supplementation/appropriate management, if indicated, within 72 hours of onset will not be adjudicated as DLTs. However, isolated Grade 4 laboratory abnormalities that are clinically significant will be considered as DLTs. Abnormal objective test findings should be reported as AEs as per Section 8.2.2.

Significant adverse events considered to be related to the investigational product for treatment under investigation that occur during the DLT observation period in the MR Selection Cohort will be reviewed in context of all safety data available. That review may involve re-evaluation of the dosing level or regimen.

3.1.7. MTD Definition

The MTD is defined as the highest dose associated with a DLT rate of 27.5% with an equivalence interval of (22.5%, 32.5%) following the mTPI method. During dose escalation/finding, patients will be enrolled in dose cohorts of 1-4 patients in Part 1A and 2-4 patients in Part 1B and Part 1C in dose cohorts other than the MTD/RDE. Each MTD/RDE including single-agent and combination treatments will enroll 6-12 patients. Each patient will receive continuous doses of PF-06873600 every 28 days. The dose finding decision will be based on 1-cycle (28 days) DLT observation period. DLTs observed after the Cycle 1 (28-day) may also be considered in the final determination of the MTD as a single agent, in combination with letrozole, and in combination with fulvestrant.

3.1.8. Recommended Dose for Expansion (RDE) and Recommended Phase 2 Dose (RP2D) Definition

The RDE is the dose chosen for further investigation based on Part 1 study results. If the RDE proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the RDE may result in a RP2D dose lower than the RDE. A RP2D for PF-06873600 as a single agent, in combination with letrozole, and in combination with fulvestrant are planned to be individually determined based on the respective RDE/MTD and other considerations including available pharmacokinetic, pharmacodynamic, and clinical benefit data.

3.2. Part 2 PF-06873600 Combination Dose Expansion

Part 2 dose expansion is an open-label, multi-center, non-randomized study to assess the preliminary anti-tumor activity and the safety and tolerability of PF-06873600. PF-06873600 will be administered at the RDE in 28 days cycles in combination with endocrine therapy in two separate dose expansion arms. Patients may be treated with IR or MR formulations depending on emerging data from Part 1 and availability.

The single agent PF-06873600 RDE from Part 1A will be used to initiate the Part 2 dose expansion arm studies, which may be de-escalated, depending on emerging data if indicated. Additionally, the PF-06873600 RDE in combination with letrozole and PF-06873600 RDE in combination with fulvestrant from Part 1B will be used to initiate the Part 2 respective combination dose expansion arm studies, which may be de-escalated, depending on emerging data if indicated.

3.2.1. Part 2/Arm A- PF-06873600 in Combination with Fulvestrant in HR-Positive HER2-Negative Locally Advanced or mBC (Second- or Third-Line Setting)

PF-06873600 will be evaluated in combination with fulvestrnnt at the RDE in HR-positive HER2-negative advanced or mBC in patients who have received prior combined CDK4/6 inhibitor and a nonsteroidal aromatase inhibitor, and up to 1 prior line of chemotherapy. This expansion coho1t will emoll approximately 40 patients.

3.2.2. Part 2/Arm B - PF-06873600 in Combination with Letrozole in HR-Positive HER2-Negative Locally Advanced or mBC (nai've to CDK4/6 inhibitors).

PF-06873600 will be evaluated in combination with letrozole at the RDE in HR-positive HER2-negative advanced or mBC in patients, with suppo1tive available preliminaiy PF-06873600 clinical data. Patients who have not received any prior treatment with a CDK4/6 inhibitor in the advanced or metastatic setting (prior adjuvant therapy with AI is permitted) will be emolled. This expansion coho1t will emoll approximately 30 patients.

3.2.3. Part 2/Arm C- PF-06873600 in Combination with Fulvestrant in HR-Positive HER2-Negative Locally Advanced or mBC (nai've to CDK4/6 inhibitors)

PF-06873600 will be evaluated in combination with fulvestrant at the RDE in HR-positive HER2-negative advanced or mBC in patients who have not previously received treatment with a CDK4/6 inhibitor in the advanced or metastatic setting. Paiticipants who have prior treatment with CDK4/6 inhibitors, fulvestrant, everolimus, and any agents with MOA that inhibits PI3k-mTOR pathway ai·e excluded. This expansion coho1t will emoll approximately 30 patients.

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4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are emolled. The following eligibility criteria are designed to select patients for whom pa1ticipation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a paiticular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for emollment in the study:

1. Pait 1:

   - Patients with HR-positive HER2-negative advanced or metastatic breast cancer (third or fomth line setting) (histologically or cytologically proven).

- Documentation of ER-positive and/or progesterone receptor-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless non-measurable disease where most recent documentation will be provided) utilizing an assay consistent with local standards.

- Documentation of HER2-negative tumor: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

- Received one prior line of combined CDK4/6 inhibitor and endocrine therapy.

- Received 1 or 2 prior lines of cytotoxic chemotherapy in the advanced or metastatic setting.

- Measurable disease or non-measurable disease per RECIST 1.1 (with the exception of Part 1B where measurable disease per RECIST 1.1 is required).

- Patients in the biomarker cohort must have a lesion amenable to biopsy.

Part 1A and 1C only:

- **TNBC: Patients with locally recurrent/advanced or metastatic TNBC** who have received up to 2 prior lines of chemotherapy in the advanced or metastatic setting.

  - Documentation of ER-negative and/or progesterone receptor-negative tumor (<1% positive stained cells) based on local testing on most recent tumor biopsy (described above).

  - Documentation of HER2-negative tumor based: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative *by in situ* hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

- **Ovarian cancer: Patients with advanced platinum resistant epithelial ovarian cancer (EOC)/fallopian tube cancer/primary peritoneal cancer (PPC)** (histologically or cytologically proven) who have received up to 3 prior lines of therapy (NOTE: each line of therapy that includes platinum [as a single agent or in combination] will be considered a unique treatment line).

Part 2:

Arm A:

Patients with HR-positive HER2-negative locally advanced or ≥mBC (second or third line setting) (histologically or cytologically proven).

- Documentation of ER-positive and/or progesterone receptor-positive tumor (≥1% positive stained cells) and HER2-negative tumor (described above).
- Received one prior line of combined CDK4/6 inhibitor and a nonsteroidal aromatase inhibitor with disease progression either on or after treatment.
- More than one prior line of cytotoxic chemotherapy in the advanced or metastatic setting is allowed after discussion with sponsor.
- More than one line of prior endocrine therapy in the advanced setting may be permitted after discussion with the sponsor.
- Have measurable disease per RECIST 1.1. Participants with only non-measurable disease may be enrolled if a compelling clinical rationale is provided by the investigator and approved by the sponsor.

Arm B:

Patients with HR-positive HER2-negative locally advanced or mBC who are naïve to CDK4/6 inhibitors (histologically or cytologically proven).

- Documentation of ER-positive and/or progesterone receptor-positive tumor (≥1% positive stained cells) and HER2-negative tumor (described above).
- Have not received a CDK4/6 inhibitor as treatment as adjuvant therapy or as treatment in the advanced or metastatic setting.
- Have not received an aromatase inhibitor in the advanced or metastatic setting (prior adjuvant therapy with AI is permitted).
- One prior line of cytotoxic chemotherapy in the advanced or metastatic setting is allowed if the patient is CDK 4/6 inhibitor naïve.
- Have measurable disease per RECIST 1.1. Participants with only non-measurable disease may be enrolled if a compelling clinical rationale is provided by the investigator and approved by the sponsor.

Arm C:

Patients with HR-positive HER2-negative locally advanced or mBC who are naïve to CDK4/6 inhibitors (histologically or cytologically proven).

- Documentation of ER-positive and/or progesterone receptor-positive tumor (≥1% positive stained cells) and HER2-negative tumor (described above).
- Have not received a CDK4/6 inhibitor as treatment as adjuvant therapy or as treatment in the advanced or metastatic setting. One prior line of cytotoxic chemotherapy in the advanced or metastatic setting is allowed if the patient is CDK 4/6 inhibitor naïve.
- Have measurable disease per RECIST 1.1. Participants with only non-measurable disease may be enrolled if a compelling clinical rationale is provided by the investigator and approved by the sponsor.
- Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or peri-menopausal, or
- Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or peri-menopausal.

2. All patients must be refractory to or intolerant of existing therapies known to provide clinical benefit for their condition (Part 1 only).
3. Female patients age ≥18 years (all Parts) or male patients ≥18 years (Part 1A and Part 1C) and/or ≥20 years in Japan.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
5. Adequate Bone Marrow Function, including:
    a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
6. Hemoglobin ≥9 g/dL.
7. Adequate Renal Function, defined as:
    a. Estimated creatinine clearance ≥60 mL/min for Part 1 and ≥50 mL/min for Part 2 as calculated using the method standard for the institution. In equivocal

cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

8. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;

   b. Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;

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

9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment.

10. For Part 2 only, measurable disease as defined by RECIST 1.1 is required.

11. Serum pregnancy test (for females of childbearing potential) negative at screening.

    Female patients of nonchildbearing potential must meet at least 1 of the following criteria and will not require a serum pregnancy test at screening:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months not due to prior chemotherapy, endocrine therapy or other pharmacologic cause and with no alternative pathological or physiological cause; postmenopausal status may be confirmed with a serum follicle-stimulating hormone (FSH) level. When there is a high FSH level, it should be confirmed that there is no other medical cause.

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy.

    - Have medically confirmed ovarian failure.

    - Female patients who do not meet the above criteria (including female patients with tubal ligations) are considered to be of childbearing potential. Female patients with HR-positive HER2-negative advanced or mBC considered to be of child bearing potential must then undergo medically-induced menopause by treatment with luteinizing hormone-releasing hormone (LHRH) agonist goserelin, the gonadotropin releasing hormone (GnRH) agonist leuprolide (Lupron Depot®), or equivalent agents to induce chemical menopause (See Section 4.3).

12. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Known active uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, Cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization and have no evidence of progression at time of study enrollment.

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

3. Patients with an indwelling catheter that has an external component such as those used for drainage of effusion(s) or central venous catheter that is externally exposed (eg, peripherally inserted central catheter (PICC) line). Indwelling catheters that are fully internalized (eg, PORT-A-CATH®) are permitted.

4. Any other active malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.

5. Major surgery within 4 weeks prior to study entry.

6. Radiation therapy within 4 weeks prior to study entry.

7. Last anti-cancer treatment within 2 weeks (or 5 half-lives, whichever is shorter, unless the last immediate anti-cancer treatment contained an antibody based agent(s) (approved or investigational), then the interval of 4 weeks or 5 half-lives (whichever is shorter)) is required prior to receiving the investigational product.

8. Participation in other studies involving investigational drug(s) within 4 weeks (or 5 half-lives, whichever is shorter) prior to study entry.

9. Previous high-dose chemotherapy requiring stem cell rescue.

10. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) - related illness. In equivocal cases, with positive serology, those patients with a negative viral load are potentially eligible provided the other entry criteria are met. This protocol excludes patients with active infections, as noted above. While SARS-CoV2 testing is not

mandated for entry into this protocol, testing should follow local clinical practice standards. If a patient has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV2, he/she is excluded. See Appendix 6 for more information around SARS-CoV2.

11. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism; deep venous thrombosis (DVT); arterial occlusive disease; ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE Grade ≥2, atrial fibrillation of any grade that is uncontrolled, or QTcF interval >470 msec at screening.

12. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

13. Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or goserelin (if applicable).

14. Known or suspected hypersensitivity to active ingredient/excipients of PF-06873600, letrozole, fulvestrant and goserelin (or equivalent agent to induce chemical menopause).

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

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

17. Pregnant female patients; breastfeeding female patients, female patients of childbearing potential and fertile male patients (Part 1A and Part 1C only) who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

18. Active inflammatory gastrointestinal (GI) disease, known diverticular disease or previous gastric resection or lap-band surgery. Impairment of gastro-intestinal

function or GI disease that may significantly alter the absorption of PF-06873600, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1. Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed.

19. Current use of drugs as shown in Appendix 5, which have a risk for QTc prolongation.

20. Current use or anticipated need for food or drugs that are known strong CYP3A4/5 inhibitors, including their administration within 5 half-lives of the CYP3A4/5 inhibitor, prior to first dose of investigational product. Current or anticipated use of moderate CYP3A4/5 inhibitors (including their administration within 5 half-lives of the CYP3A4/5 inhibitor, prior to first dose of investigational product) should be avoided if possible, and any use will need to be reviewed and approved by the Sponsor (See Section 5.7).

21. Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers, including their administration within 5 half-lives of the CYP3A4/5 inducer, prior to the first dose of investigational product (See Section 5.7).

4.3. Lifestyle Requirements

In this study, female patients who are of childbearing potential, and fertile male patients as applicable to the study will receive PF-06873600 as a single agent or in combination with endocrine therapy, which currently has unknown teratogenicity/fetotoxicity so must be considered as suspected. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of PF-06873600. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient (and her partner(s)) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal as approved by local

regulatory authority), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label). All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of PF-06873600.

4.3.1. Potential for Photosensitivity

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet B (UVB) light sources such as tanning beds, tanning booths and sunlamps. Patients may wish to limit exposure to the sun and should be encouraged to apply sunscreen/sunblock daily.

4.4. Sponsor's Qualified Medical Personnel

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

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are PF-06873600, letrozole, and fulvestrant.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax or e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a patient identification number and supply this number to the site. The patient identification number will be used on all study-related documentation at the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level for that patient (and Arm in Part 2) and;
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.2. Patient Compliance

Fulvestrant will be administered by the appropriately designated study staff at the investigational site. PF-06873600 tablets and letrozole will be distributed to the patient by the appropriately designated study staff at the investigational site.

Patients will be required to return all unused study treatment at the beginning of each cycle. The number of tablets returned by the patient will be counted, documented, and recorded.

A patient diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed PF-06873600 doses. Patients will be required to return all bottles of PF-06873600 every cycle. The number of PF-06873600 tablets remaining will be documented and recorded at each clinic visit or Day 1 of each cycle. The patient diary may also be used to support this part of the accountability process. The information above, regarding diary completion,

requirement to return all bottles and accountability documentation will also be performed on patients receiving letrozole (where applicable).

Letrozole and fulvestrant will be administered in accordance with the package insert (or equivalent). All PF-06873600, letrozole, and fulvestrant administration will be documented on the corresponding investigational product administration CRF.

5.3. Investigational Product Supplies

PF-06873600, letrozole, and fulvestrant will be supplied by Pfizer. Study centers will receive PF-06873600 as well as letrozole and fulvestrant if needed, prior to enrollment of the first patient.

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. PF-06873600

PF-06873600 will be provided as tablets for oral administration. The 5 mg, and 25 mg immediate release tablets and the 10 mg and 40 mg MR tablets will be supplied in separate bottles and labeled according to local regulatory requirements. PF-06873600 immediate release tablets are supplied in 68-count bottles, modified release tablets are supplied in 62-count bottles.

5.3.1.2. Letrozole

Letrozole will be supplied by Pfizer. Letrozole is available as 2.5 mg tablets in a 30-count bottle or a 28 count blister pack. Detailed information about letrozole can be found in the approved package insert.

5.3.1.3. Fulvestrant

Fulvestrant (Faslodex®) will be supplied by Pfizer. Fulvestrant is available as two 5-mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to the barrel.

Refer to the local package insert fulvestrant (Faslodex®) for instructions and steps necessary for drug preparation and administration. Drug preparation and administration will be performed at the site by a physician, registered nurse, or other qualified health care provider.

5.3.2. Preparation and Dispensing

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

The study treatment should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense the investigational product in the bottles provided, in

quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site at the next study visit.

Dose adjustments or discontinuations should be managed according to the Section 5.4.3 below. However, per the investigator's discretion, other dose adjustments may be discussed with the Sponsor.

Any unused product or waste material should be disposed of in accordance with local requirements.

5.4. Administration

5.4.1. PF-06873600

Patients will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

PF-06873600 will initially be administered orally BID on a continuous basis. If supported by emerging data, the QD continuous regimen or alternative intermittent dosing regimen may be considered. A cycle is defined as 28 days, regardless of missed doses or dose delays.

The dosing intervals are as follows:

- For the QD dosing regimen, the single dose should be administered in 24 ±4 hour intervals (ie, no less than 20 hours and no more than 28 hours apart);
- For the BID dosing regimen, the doses should be administered in 12 ±4 hour intervals (ie, no less than 8 hours and no more than 16 hours apart);

PF-06873600 will be administered orally on an empty stomach without adjustment for body size at every cycle. Patients 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 patient misses a dose or day of treatment, she or he must be instructed not to "make it up" (unless it was less than 4 hours since their planned dosing time) and to resume subsequent doses the next scheduled time as prescribed. In addition, if a patient vomits any time after taking a dose; she or he must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. Lastly, if a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-06873600.

Letrozole

Letrozole will be administered orally once daily continuously together with PF-06873600. Refer to the package insert for additional administration instructions.

No dose adjustment for letrozole is permitted but dosing interruptions are allowed. Treatment interruption for letrozole-related toxicities will be performed as per the investigator's best medical judgment.

Fulvestrant

Fulvestrant 500 mg will be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock. Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider. Refer to the local product label for Faslodex® for detailed administration instructions.

No dose adjustment for fulvestrant is permitted. A single fulvestrant injection can be skipped in case of a fulvestrant-related toxicity or dosing can be delayed. Treatment delay for fulvestrant-related toxicities will be performed as per the investigator's best medical judgment, but by no more than 7 days. If a delay of longer than 7 days is required then the dose should be skipped. In the event of a toxicity requiring dosing delay of PF-06873600, fulvestrant can also be delayed by a maximum of 7 days. Fulvestrant should not be administered if the platelet count is <50,000/mm^3.

5.4.2. Food Requirements

5.4.2.1. Food Requirements

Oral PF-06873600 will be administered with at least 8 ounces (240 mL) of water on an empty stomach. No food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose throughout the study for BID dosing. No food or liquids other than water will be consumed for 2 hours before and 2 hours following each dose throughout the study for QD dosing. These fasting requirements may be removed (via a letter to the investigators) if the data from the food-effect study indicate that there is no meaningful effect of food on the bioavailability of PF-06873600.

5.4.3. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;

- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.3.1. Dosing Interruptions

Patients experiencing the following adverse events should have their treatment interrupted:

- DLT in Cycle 1 (DLT observation period of 28 days [see Section 3.1.6]);

- AEs meeting DLT criteria after the DLT observation period.

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

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient may need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting 4 weeks treatment resumption will be decided in consultation with the sponsor.

5.4.3.2. Dose Interruption of Patients with Presumed or Active COVID-19/SARs-CoV2 Infection

Ongoing patients who have active (confirmed [positive by regulatory authority-approved test] or presumed [test pending/clinical suspicion]) SARS-CoV2 infection, should follow the treatment guidelines:

- For symptomatic patients with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms. This delay is intended to allow resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the patient should be afebrile for 72 hours and SARS-CoV2-related symptoms should have recovered to Grade ≤1 for a minimum of 72 hours. The sponsor should be informed when restarting treatment.

- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

5.4.3.3. Dose Delays

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

- ANC ≥1,000/mm^3;
- Platelets count ≥50,000/mm^3;
- Hemoglobin ≥8.0 g/DL;
- Nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the patient).

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

If these conditions are met within 2 weeks of treatment interruption or cycle delay, PF-06873600 may be resumed. Refer to the Dose Reductions section for adverse events requiring dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed up to a maximum of 4 weeks. If patients require discontinuation of PF-06873600 for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless it is for reasons other than treatment -related toxicity or the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor's medical monitor.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when PF-06873600 is restarted will be counted as Day 1 of the next cycle but tumor assessment will be maintained relative to Cycle 1 Day 1.

5.4.3.4. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06873600 dose may need to be reduced when treatment is resumed.

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

Dose reduction of PF-06873600 by 1 and, if needed, 2 dose levels, or intermediate dose levels, will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor.

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

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved at the discretion of the investigator. No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. However, patients experiencing recurrent and intolerable toxicity that does not meet the criteria for DLT (ie, recurrent transient high grade neutropenia or diarrhea) or are Grade 2 may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Dose reductions during the DLT observation period are not permitted unless the patient experiences a DLT. However, at the discretion of the investigator or sponsor based on emerging safety data, patients may be asked to reduce their dose within the DLT window.

Recommended dose reductions for Part 1 and Part 2 are described in Table 3.

Table 3. Dose Modifications for PF-06873600-Related Toxicity

Toxicity	Grade 1	Grade 2*	Grade 3**	Grade 4
Nonhematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.***
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. Reduce the dose by 1 level if recurrent or prolonged Grade 3 hematologic toxicity ***	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment. Reduce the dose to 15 mg BID if Grade 4 neutropenia***

*For recurrent and intolerable toxicity that does not meet DLT criteria or Grade 2, see language above.
**Nausea, vomiting, or diarrhea must persist at Grade 3 despite optimal supportive care to require dose modification. Thrombocytopenia must be Grade 3 with Grade ≥2 bleeding to require dose modification.
For QTcF ≥501 msec, refer to Section 7.1.5.
***Cycle will not be extended to cover for the missing doses.
Note: Patients with confirmed Hy's Law, must be discontinued.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including marketed products, are stored in a secured area with

controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. PF-06873600 should be stored as described on the label and as outlined in the IP manual and patient dosing diaries.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label (for each combination drug letrozole/fulvestrant).

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All bottles of study drug, including any unused tablets, must be returned to the investigator by the patient at designated study visits and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

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

For all bottles returned to the investigator by the patient, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

5.7. Concomitant Treatment(s)

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

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

Because inhibition of CYP3A4/5 isoenzymes may increase PF-06873600 exposure leading to potential increases in toxicities, the use of known strong CYP3A4/5 inhibitors is not permitted within 5 half-lives of the respective CYP3A4/5 inhibitor(s), prior to the first dose of PF-06873600.

Strong CYP3A4/5 inhibitors may include grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan.

Use of moderate CYP3A4/5 inhibitors should be avoided if possible, and any use needs to be reviewed and approved by the sponsor. Moderate CYP3A4 inhibitors may include erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, and cimetidine.

Because induction of CYP3A4/5 isoenzymes may decrease PF-06873600 exposure leading to potential decrease in efficacy, the use strong CYP3A4/5 inducers is not permitted within

5 half-lives of the respective CYP3A4/5 inducer(s), prior to the first dose of PF-06873600. Strong CYP3A4/5 inducers may include phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort. In addition, the use of moderate CYP3A4/5 inducers warrants caution. Moderate CYP3A4/5 inducers may include bosentan, efavirenz, etravirine, modafinil, and nafcillin (www.druginteractioninfo.org).[26]

Concomitant use of PF-06873600 and a CYP3A4/5 substrate may increase the exposure of the CYP3A4/5 substrate. Therefore, caution is warranted for the coadministration of PF-06873600 with CYP3A4/5 substrates with a narrow therapeutic indices. CYP3A4/5 substrates of a narrow therapeutic indices, may include astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, (alfentanil and fentanyl, excluding transdermal patch), or ergot alkaloids (ergotamine, dihydroergotamine) (www.druginteractioninfo.org).[26]

Concomitant use of PF-06873600 and a substrate of the MATE1 or MATE2K renal transporters may increase the exposure of the MATE1 or MATE2K substrate. Therefore, caution is warranted for the coadministration of PF-06873600 with MATE1 or MATE2K substrates. MATE1 or MATE2K substrates may include metformin, cimetidine, procainamide, cephalexin, acyclovir, gancyclovir, fexofenadine (www.druginteractioninfo.org).[26]

5.7.1. Other Anti-tumor or Experimental Drugs

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select herbal supplements (including those listed in Section 5.7) is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06873600 with radiotherapy, PF-06873600 treatment should be interrupted during palliative radiotherapy, stopping 3 days or 5 half-lives (whichever is longer) before and resuming treatment after recovery to baseline.

5.7.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to available American Society of Clinical Oncology (ASCO) guidelines.

Female patients currently being treated with a gonadotropin-releasing hormone agonist (GnRH agonist) prior to study enrollment may continue treatment while on study treatment as long as the GnRH agonist treatment has been well tolerated for at least 3 months prior to study entry.

5.7.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted prior to Cycle 1, Day 1 (C1D1), but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines. For Japan only: since the indication and dosage of G-CSF compounds approved in Japan may differ from ASCO guidelines, refer to Japanese package insert and local clinical guideline.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia (Note: erythropoietin is not approved for anemia caused by chemotherapy in all local regions, nor is it currently approved in Japan).

5.7.4. Diarrhea Management

Diarrhea is a possible adverse event based on the preclinical toxicology data. As there is no prior clinical experience with PF-06873600, the exact nature of treatment related diarrhea in humans is unknown. In general, management of cancer treatment-induced diarrhea have been described (Benson et al, 2004).[28] Initial management for mild to moderate diarrhea may include dietary modifications (eliminating lactose and other high-osmolar dietary supplements), loperamide or diphenoxylate/atropine, along with oral antibiotics if persistent with concern for infection. Management of higher severity or more complicated diarrhea may also include consideration of intravenous fluids for hydration, electrolyte replacement, octreotide, stool workup along with hospitalization for observation and treatment if indicated in the investigator's medical judgment.

5.7.5. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted prior to C1D1. Anti-diarrheal and anti-emetic therapies may be used to treat treatment emergent diarrhea, nausea and vomiting as early as during Cycle 1. The choice of the drug 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 Treatment(s) section.

5.7.6. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) section.

5.7.7. Corticosteroids

Chronic systemic corticosteroid use for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.7.8. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06873600 required to minimize the risk

of impaired wound healing and bleeding has not been determined. Stopping PF-06873600 is recommended at least stopping 3 days or 5 half-lives (whichever is longer) prior to surgery. Postoperatively, the decision to reinitiate PF-06873600 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.9. Permitted Medications

- **H_2-Receptor Antagonists (H_2RAs)** for symptomatic treatment of gastrointestinal disorder (including, but not limited to famotidine, ranitidine, nizatidine, cimetidine).

- **Local antacids** for symptomatic treatment of gastrointestinal disorder (eg, aluminum/calcium hydroxide, aluminum/calcium carbonate, bismuth subsalicylate).

- **Acid reducing agents (including proton pump inhibitors (PPIs))** can be used for symptomatic treatment of gastrointestinal disorder.

5.8. Luteinizing Hormone Releasing Hormone (LHRH) Agonist

Pre/peri-menopausal women with HR-positive HER2-negative advanced or mBC can be enrolled if amenable to be treated with the LHRH agonist. Treatment with a LHRH agonist (eg, goserelin, leuprolide acetate or equivalent agents) should be used according to the prescribing information for all women who are pre- or peri-menopausal at study entry to induce chemical menopause throughout the study.

Patients not currently receiving an LHRH agonist prior to study entry must have commenced treatment with LHRH agonist at least 1 week prior to C1D1 for the monthly administration form and at least 3 weeks prior to C1D1 for patients receiving the LHRH on an every 3 month schedule.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the Schedule of Activities and ASSESSMENTS sections.

6.2. Study Period

For the treatment period procedures, see the Schedule of Activities and ASSESSMENTS sections.

6.3. Follow-up

For follow-up procedures see the Schedule of Activities and ASSESSMENTS sections.

6.4. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment 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 patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient 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.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section) or behavioral reasons, or the inability of the patient to comply with the protocol -required schedule of study visits or procedures at a given investigator site.

In rare instances, it may be necessary for a patient to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive 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;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death;

A patient may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If the investigator feels that the patient is still deriving benefit from the therapy, may elect to continue therapy at the same dose or 1 dose lower in consultation with the sponsor until the benefit no longer exists.

7. ASSESSMENTS

The collection of the efficacy, safety, PK, biopsy and biomarker data per protocol will be completed as of the primary completion date (PCD). Participants who continue on study beyond PCD will follow local standard of care for safety procedures and the disease assessment. SAE reporting to Pfizer Safety will continue per protocol until end of trial. AEs reporting in eCRF will continue to be collected per local regulatory requirements. Refer to Section 13.2 and Appendix 8 for the details.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

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

See Appendix 6 for alternative measures during public emergencies including the COVID-19 pandemic.

7.1. Safety Assessment

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

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving PF-06873600 (1 negative pregnancy test at screening and 1 at the baseline visit immediately before PF-06873600 administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the patient may receive PF-06873600. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at Day 1 of every other Cycle and at the end of the study to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local

regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product and from the study.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Safety laboratory assessment to be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories.

Table 4. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Other:
Hemoglobin	ALT*	PT or INR*	Urine dipstick for urine protein: If positive collect 24-hour and microscopic (Reflex Testing)	Pregnancy test: for female patients of childbearing potential, serum (screening) or urine
Platelets	AST*	PTT or aPTT		
WBC	Alk Phos*			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	
Absolute Eosinophils	Chloride			Hepatitis B testing**
Absolute Basophils	Total calcium			Hepatitis C virus Antibodies***
	Total bilirubin*			Human immunodeficiency virus (HIV)
	BUN or Urea			
	Creatinine*			
	Uric Acid			
	Glucose (nonfasted)			
	Albumin			
	Phosphorus or Phosphate			
	Amylase			
	Lipase			

Table 4. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Other:
	Carbon Dioxide or Bicarbonate			

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

** Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) to be conducted by local laboratory where required by local regulations or if warranted by patient history.

*** Hepatitis C virus antibodies (HCVAb) to be conducted by local laboratory where required by local regulations or if warranted by patient history.

7.1.4. Vital Signs and Physical Examination

Patients will have a full physical examination to include an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, as acceptable according to local regulation. Blood pressure and heart rate should be recorded after approximately 5 minutes rest. An abbreviated physical exam is an assessment for emergent toxicities or changes from prior visits and a symptom directed exam conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.

7.1.5. (12-Lead) Electrocardiogram

Standard electrocardiogram (ECG): 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs (except single ECG at screening and End of Treatment) will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged ≥501 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.

If manual reading verifies a QTcF of ≥501 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 501 msec. If QTcF interval reverts to less than 501 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring.

If reversible causes are treated and the QTcF intervals remains ≥501 msec, the investigational product will be held until the QTcF interval decreases to less than 501 msec. Patients will then restart the investigational product at the next lowest dose level.

If the QTcF interval has still not decreased to less than 501 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.2. Pharmacokinetics Assessments

Additional details regarding the collection, processing, storage and shipping of the PK plasma samples will be offered, prior to study start, in a manual developed by the sponsor-identified central laboratory.

7.2.1. Plasma for PK analysis of PF-06873600

Blood samples (3 mL) to provide a minimum of 1 mL plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as outlined in the Schedule of Activities. The PK sampling schedule may be modified based on emerging PK data, but the total number of PK samples will remain the same.

On days when patients have clinical visits where require pre-dose PK sampling assessments are to be obtained, the morning dose of PF-06873600 should be held (NOT taken) prior to the study visit. On those days, the PF-06873600 morning dose can be taken after the study procedures that are required prior to the morning dose have been performed (ie, the pre-dose PK sampling is obtained).

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

Where noted in the Schedule of Activities, blood samples for PF-06873600 concentrations will be collected at approximately the same time as other assessments such as PD samples, ECGs (first ECG then PK collection) and bone marrow aspirate collections etc, wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF.

If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

PK samples will be assayed for PF-06873600 using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

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

As pa1t of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal explorato1y purposes. These data will not be included in the Clinical Study Report (CSR).

CCI

[redacted]

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[redacted]

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone x-rays for patients with known or suspected bone metastases. Use of contrast in imaging is at the investigator's discretion. In the case of known allergy or hypersensitivity to contrnst agent, non-contrast CT of the chest and MRI of the abdomen may be considered.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, dming ti·eatment as specified in the Schedule of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from ti·eatment (if not done in the previous 8 weeks).

Assessment of response will be made using RECIST version **1.1** (see Appendix 4).

All patients' files and radiologic images must be available for somce verification and for potential peer review.

7.5. Tumor Markers

Blood tumor markers will be analyzed according to the Schedule of Activities. For patients that are emolled with HR-positive HER2-negative and TNBC, CA 15-3 and CEA will be assessed. For patients with ovarian cancer, CA 125 will be assessed.

CCI

[redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for repo1iing safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Fo1m to Pfizer Safety. These requirements are delineated for 3 types of events: **(1)** SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

8.1.1. Additional Details On Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

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

Part 2 Only: During the long-term follow-up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

If a patient 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.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;

- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. 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 patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

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

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients 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:

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further

testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract), total bile acids, and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy (EDP)

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of

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

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

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

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

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

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

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in

accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

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

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

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

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

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

In the event of medication dosing error, the sponsor should be notified immediately.

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Analysis Sets

1. Safety analysis set.

   The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

2. Full analysis set.

   The full analysis set includes all enrolled patients.

3. Per-protocol analysis set (evaluable for MTD).

   The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during the first cycle. Patients with major treatment deviations during the first cycle of treatment are not evaluable for the MTD assessment and will be replaced as needed to permit the MTD estimation. Major treatment deviations include the failure to satisfy major entry criteria (eg, confirmation of the target disease; signed informed consent) or use of other anticancer treatments during the active treatment period and disease follow-up phases other than as defined/allowed in this protocol. Major treatment deviations will also include:

   - Administration of less than 75% of the planned number of doses of PF-06873600 (provided that the reduction in doses is not due to toxicity attributable to PF-06873600).

   - Administration of more than 110% of the planned number of doses of PF-06873600.

4. Modified Intent-to-Treat (mITT) Population.

   - The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of investigational product with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population

will be used for analyses and to support conference presentations when the study is still ongoing.

5. PK analysis sets.

   The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest. The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

6. Biomarker analysis set(s).

   - The PD/Biomarker analysis population is defined as all enrolled patients with PD/Biomarkers evaluated at pre-and/post dose.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity.

The traditional mTPI design (Ji et al., 2010)[29] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. The proposed modified TPI method for this protocol includes stopping rules and dose escalation/finding criteria, which prevents the target DLT rate to reach ≥33% for determining the MTD. This proposed mTPI method is more conservative than the traditional TPI method. Being a rule-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation and de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table (See Section 3.1.5). Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement. Recently, a Phase 1 study based on the mTPI design has been published (Fanale, 2011).[30]

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e_1), the over-dosing interval (pT+e_2, 1), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. Based on the safety profile of PF-06873600 as a single-agent in study (C3661001), e_1 is selected as

0.05 and e_2 is selected as 0.05. Therefore, the target interval for the DLT rate is (0.225, 0.325).

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose-escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to remaining at the current dose (S). Given a dosing interval and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al. (2010)[29] have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision). The decision rules to "dose escalate" (E), "no change in dose" (S), "dose de escalate" (D) or "dose de escalate, unacceptable toxicity" (U) are described in Section 3.1.5 (see Table 1).

9.2.2. Statistical Method for Estimating the MTD

This study contains dose escalation and/or de-escalation with single agent in Part 1 followed by a single agent and combination dose expansion (Part 2). The MTD determination will be assessed independently for each dosing regimen evaluated in Part 1A and 1C and dose de-escalation Part 1B based on the mTPI method described in Section 9.2.1. The overall study design is depicted in Figure 8.

Parts 1A and 1C will estimate the MTD/RDE in sequential dose escalation cohorts in:

- HR-positive HER2-negative advanced or mBC patients with prior CDK4/6 inhibitor and endocrine therapy in the advanced or metastatic setting, or
- Locally recurrent/advanced or metastatic TNBC, or
- Advanced platinum resistant epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer.

During Part 1 dose finding, all available safety information from safety and biomarker cohorts in Part 1A and 1C will be used to determine the respective MTD/RDE. Because these additional patients in biomarker cohorts will receive a dose lower than the concurrent dose escalation safety cohort or will be enrolled at a dose following the DLT evaluation period in the first 2-4 dose escalation safety cohort patients enrolled, their potential DLT observations may not be strictly used in the mTPI method for the ongoing dose finding in Part 1A and 1C. However, the safety profile from these additional patients in biomarker cohorts will be used to establish the respective MTD or RDE in Part 1A and Part 1C, if applicable.

Part 1B will include PF-06873600 in combination with letrozole and in combination with fulvestrant. The starting dose for this combination will start with PF-06873600 at MTD/RDE for the single agent (established in Part 1A or Part 1C) and the prescribed dose for letrozole and fulvestrant, respectively. The PF-06873600 dose may be decreased if determined to be intolerable in a dose de-escalation manner based on mTPI. The MTD/RDE for this combination regimen, if selected, will be based on 6 to 12 patients.

For data analysis purpose, data from all patients receiving the MTD/RDE in Part 1B and Part 2 expansion cohort will be combined under the same treatment regimen and same tumor type.

Part 2 will evaluate the PF-06873600 dose selected (MTD/RDE) from Part 1 as a single agent (from Part 1A or Part 1C) and in combination with endocrine therapy (from Part 1B).

The dose finding process in Part 1 using mTPI is designed to establish the MTD defined as the highest dose that yields a target of approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) of (22.5%, 32.5%). The 27.5% target was chosen based on safety considerations and is considered appropriate based on simulations performed on other Pfizer Phase 1 study protocols (ie, B7831001, PF-06671008) and expert input. The prior distribution of DLT is set as a beta (0.5,0.5) and the threshold probability for early termination and dose exclusion is set to 0.95 as suggested in the original mTPI method (Ji et al., 2010).[29] A modification of the mTPI could be applied for dose levels that are tested in more than 6 patients: a decision to increase the dose could be made only if the observed DLT rate is <22.5% (2 DLT out of 10 Patients) and a decision to test more patients at a dose only if the DLT rate is below 32.5%. In addition, doses with an incidence of DLT, eg, 4 out of 10, or apparently higher than 32.5% cannot be selected as MTD, even though it might be allowed by the mTPI method.

Cohorts of patients could receive doses already tested but a dose that is associated with decision to “Dose de-escalate, unacceptable toxicity” cannot be revisited and no more patients should be treated at this dose or higher doses for the remainder of the trial.

The maximum sample size for Part 1 would be approximately N=75 for the dose escalation/finding safety cohorts and N=6 to 12 for the biomarker cohorts but actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization.

The study will continue accruing until one of the three stopping conditions below is triggered.

The algorithm will stop if any of the following criteria is met:

1. The maximum sample size has been achieved;

2. MTD has been identified with sufficient accuracy: 6 to 12 patients have been accumulated on a dose that is currently estimated to be the MTD/RDE; or

3. All doses explored appear to be overly toxic and the MTD cannot be detennined.

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the trne Probability (DLT) is fairly low. This could result in the estimated posterior DLT rate to exceed the targeted 27.5% ve1y early in the trial.

The following table shows the probability of escalating to the next dose level for a range of underlying trne DLT rates. For example, for a coho1t size of n=3 and for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients with DLTs.

Probability of Escalating Dose

True underlying DLT rate	10%	20%	30%	40%	*50%*	60%	70%	80%	90%
Probability of escalating dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

9.3. Sample Size Determination

9.3.1. Part 1

In Pait IA, Pait lB, and Part IC patients will paiticipate in a dose escalation/finding phase aimed at estimating the MTD. The sample size for this component of the study will vaiy depending on the number of DLTs observed.

Approximately 75 patients ai·e expected to be enrolled in the dose escalation/finding safety coho1ts and an additional 6-12 patients are expected in the biomarker cohorts in Paits IA and IC. The actual number of patients enrolled will depend on the tolerability of PF-06873600 and the number of dose levels required to identify the MTD/RDE. Pait IA, Pait 1C and each independent combination coho1t in Pait lB (PF-06873600 in combination with letrozole and PF-06873600 in combination with fulvestrant) can be stopped and MID declai·ed with approximately 6 to 12 patients. As for the number of patients treated at each dose, it is expected to be at 1 to 4 patients for the doses actually studied. However, since vai·iable coho1t size is allowed, the actual number of patients treated at each dose (including MTD) will vaiy from 1 to 12.

9.3.2. Part 2

Pait 2, the expansion aims will be conducted to assess efficacy as well as safety and tolerability of PF-06873600 in single agent and combination therapy. The sample sizes for Pait 2 are dete1mined based on published historical data as benchmai·k data, I-sided type 1 eITor rate of a, =0.1 with 80% power or higher. Approximately 100 patients ai·e expected to be enrolled in Pait 2. Enrolhnent of paiticipants into a iven coho1t ma be discontinued if minimal or no anti-tumor activi , is obse1ved. CCI

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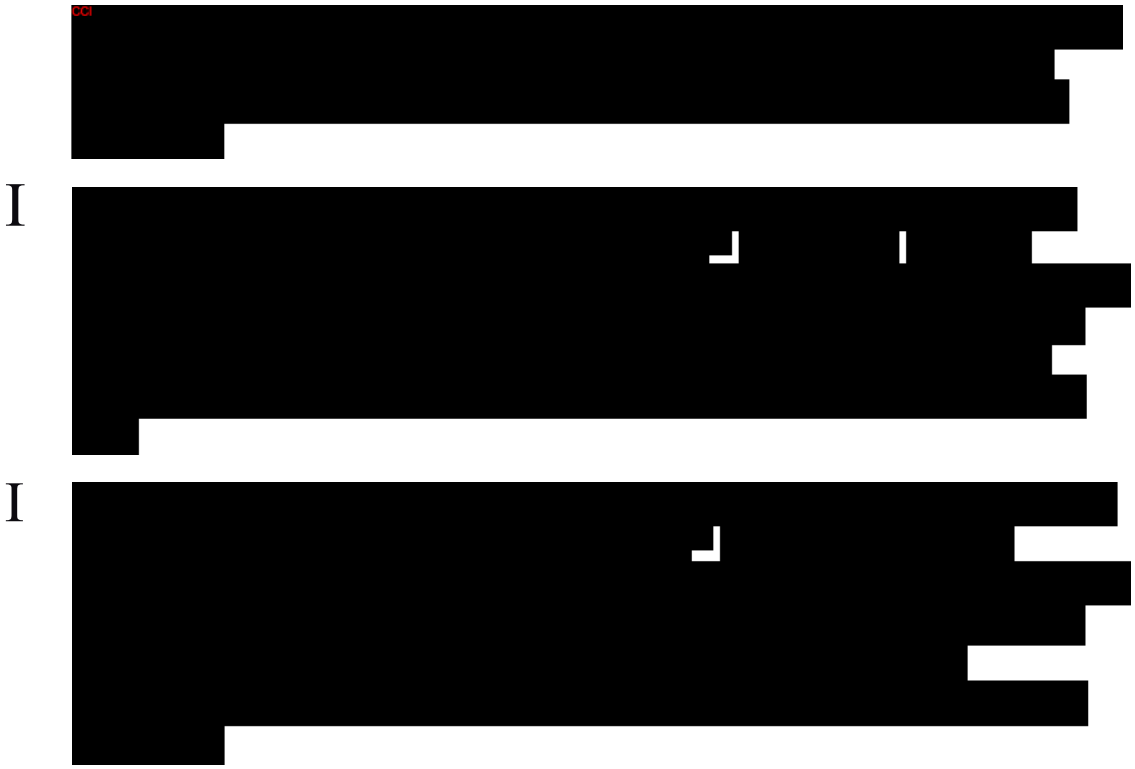

9.4. Efficacy Analysis

In this First In Patient study anti-tumor activity is a primaiy objective for Pait 2 of the study. Tumor response will be presented in the fo1m of patient data listings that include, but are not limited to, tumor type, staiting dose, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), time to progression (TTP), and duration of response (DoR) will be sUilllnai·ized and presented if data pe1mits.

The definition of each response catego1y is provided in Appendix 4 (RECIST 1.1).

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Single-Dose and Steady-State PF-06873600 Pharmacokinetic Analysis

Plasma concentrations of PF-06873600 will be smnmai·ized descriptively (n, mean, standai·d deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day, and nominal time.

Plasma concentration-time data within a dose interval after the morning dose on Cycle 1, Day 1 (for patients of Part 1A and 1B), Cycle 1, Day 15 (for all patients, with exception of the MR formulation selection cohort) or for patients of the MR formulation selection cohort, plasma concentration-time data after Day -7 and Day -4, respectively, will be analysed for individual patients using noncompartmental methods. The noncompartmental analysis will estimate PK parameters including the following:

1. Cycle 1 Day 1 (and also Lead-in Day -7 and Day -4 for patients of the MR formulation selection cohort within Part 1C): the maximal concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve from time 0 to the last sampling time point within the dose interval (AUC_{last}), and if data permit, area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), apparent oral plasma clearance (CL/F), apparent volume of distribution (Vz/F);

2. Cycle 1 Day 15: steady state C_{max} ($C_{max,ss}$), T_{max}, AUC within one dose interval ($AUC_{\tau,ss}$), minimum plasma concentration ($C_{min,ss}$), oral CL (CLss/F), and if data permit, apparent volume of distribution (V_{ss}/F), $t_{1/2}$, and accumulation ratio (R_{ac}).

The single-dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

Dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

9.5.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Population PK assessment may be conducted with plasma PF-06873600 concentrations from all patients using the nonlinear mixed effect modeling. The population PK model may be further combined with data on biomarkers and relevant efficacy and safety endpoints for population PK/PD analysis.

The population PK and PK/PD analysis, if performed, will be reported in a Population Modeling and Analysis Report (PMAR), separate from the clinical study report of this study.

9.5.2.1. Pharmacokinetic/Pharmacodynamic Correlation

The relationship between PF-06873600 exposure and PD endpoint(s), such as p-Rb, and TK activity will be explored if data permit.

CCI [redacted]

9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

9.6.1. Analysis of the Primary Endpoint for Part 1

DLT is the prima1y endpoint of the Pali 1 component of the study. The occmTence ofDLTs observed in the dose levels to be evaluated is used to estimate the MTD as described in the STUDY DESIGN section. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Primary Endpoints for Safety for Part 1 and 2

Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionaiy for Regulato1y Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.6.3. Electrocardiogram

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

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, heart rate, RR and PR interval, QRS, QTcF (and other correction factors, eg, QTcB as appropriate). Individual QT (all evaluated corrections) intervals will be listed. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment, dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.7. Data Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review by a safety review team, comprised of the investigators and the sponsor, will be applied in order to review individual and summary data collected in the safety and clinical databases. These data would also include all treated participants.

Discussions between the investigators and the sponsor regarding safety will occur in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further patient enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

13.2. Primary Completion Date

The Primary Completion Date (PCD) is the date of the last study visit where data is collected for the primary analysis of study outcome(s) also as stated in Section 13.1. The PCD will take place on or around 5 April 2023. The final CSR will include data collected up to PCD. At the time of PCD the applicable participants will either 1) complete the transition to PfizerCares (expanded access) program, where such program is available, or 2) continue on study under Amendment 9 in the countries where expanded access program is not available.

The end of trial will take place when last patient discontinues study treatment or on October 31 2024, whichever occurs first. The study procedures after PCD are detailed in Appendix 8. The supplemental CSR will include safety data collected after PCD until the end of study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06873600 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 72 hours. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (CSR synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. 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.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
ACRIN	American College of Radiology Imaging Network
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BID	twice daily
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
CCND1	Cyclin D1
CCI [redacted]	[redacted]
CCNE2	Cyclin E2
C1D1	Cycle 1, Day 1
C2D1	Cycle 2, Day 1
CDK	Cyclin-dependent kinase
CEA	Carcinoembryonic antigen
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
C_{eff}	efficacious concentration
CL	clearance
CLp	plasma clearance
CLp/F	oral plasma clearance
C_{max}	maximal concentration
C_{min}	minimal concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response

Abbreviation	Term
CRF	case report form
CRM	Continual Reassessment Method
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLI	Donor Lymphocyte Infusion
DLs	dose levels
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	Duration of Response
DU	dispensable unit
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
eg,	for example
EFS	event-Free Survival
ELISA	enzyme-linked immunosorbent assay
EOC	epithelial ovarian cancer
ER	estrogen receptor
ER+BC	estrogen receptor positive breast cancer
ET	endocrine therapy
Etc	‘and other things’ or ‘and so forth’
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FIP	first in patient
FSH	follicle-stimulating hormone
Gap 1	G1
Gap 2	G2
GCS-F	Granulocyte-colony stimulating factors

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone agonist
GVHD	graft versus host disease
H2RAs	H2 receptor agonists or H2 blockers
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HbcAb	hepatitis B core antibody
HCVAb	hepatitis C virus antibodies
HCV	hepatitis C virus
HER	human epidermal growth factor receptor
Hgb	hemoglobin
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hormone receptor
HRCT	High-resolution computed tomography
IB	Investigator's brochure
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	identification
ie	that is
IHC	immunohistochemistry
IIP	Idiopathic interstitial pneumonitis
ILD	interstitial lung disease
IND	investigational new drug application
INR	international normalized ratio
IP manual	Investigational Product manual
IR	immediate release
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWR	interactive Web-based response
J-LIC	Japan Lead-in-Cohort
JSH	Japan Society of Hepatology
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KL-6	clinical biomarker assessment for ILD
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LSLV	last subject last visit

Abbreviation	Term
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
mITT	modified intent-to-treat
mTPI	modified toxicity probability interval
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MOA	Mechanism of action
MR	modified release
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N	number
N/A	not applicable
NCI	National Cancer Institute
NE	non evaluable
NGS	next generation sequencing
NOS	not otherwise specified
OBD	optimal biological dose
OR	Objective Response or Overall Response
ORR	overall response rate
OS	overall survival
pT	target probability
PACL	Protocol Administrative Change Letter
PAD	pharmacologically active dose
PCD	primary completion date
PD	pharmacodynamics
PET	positron emission tomography
PFS	Progression-Free Survival
PFS	prefilled syringe
PI	principal investigator
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic
P-gp	p-glycoprotein 1
PGx	pharmacogenomics
PMDA	Pharmaceuticals and Medical Devices Agency
PO	by mouth
PPC	primary peritoneal cancer
PPIs	proton pump inhibitors
PR	partial response
p-Rb	phospho-Rb
PS	performance status
PT	prothrombin time

Abbreviation	Term
PTT	partial thromboplastin time
QD	every day
QT	time between the start of the Q wave and the end of the T wave
RAC	accumulation ratio
Rb	retinoblastoma
RD	Response/Remission Duration
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
CCI	[redacted]
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous
SCHH	Sandwich Cultured Human Hepatocytes
SD	single dose, stable disease
SOP	standard operating procedure
$Sp0_2$	oxygen saturation
SRSD	single reference safety document
SS	steady-state
STD10	severely toxic dose in 10% of animals
$T_{1/2}$	terminal elimination half-life
TBili	total bilirubin
TBR	tumor background ratio
TCGA	The Cancer Genome Atlas Network
TDI	time-dependent inhibition
TGI	tumor growth inhibition
TID	three times a day
TK	thymidine kinase
Tmax	time to maximal concentration
TNBC	triple negative breast cancer
TPI	toxicity probability interval
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States package insert
UVB	ultraviolet B
Vd/F	apparent volume of distribution
Vss	volume of distribution at steady state

Abbreviation	Term
Vz/F	apparent volume of distribution
WBC	white blood cell

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

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

- With 2 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate and consider current dose as intolerable.
- With 3 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate;
  - 3 DLTs -> de-escalate and consider current dose as intolerable.
- With 4 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1-2 DLTs -> remain at the same dose;
  - 3-4 DLTs -> de-escalate and consider current dose as intolerable.
- With 5 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1-2 DLTs -> remain at the same dose;
  - 3 DLTs -> de-escalate;
  - 4-5 DLTs -> de-escalate and consider current dose as intolerable.
- With 6 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2 DLTs -> remain at the same dose;
  - 3 DLTs -> de-escalate;

    - 4-6 DLTs -> de-escalate and consider current dose as intolerable.
- With 7 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-3 DLTs -> remain at the same dose;
    - 4 DLTs -> de-escalate;
    - 5-7 DLTs -> de-escalate and consider current dose as intolerable.
- With 8 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-3 DLTs -> remain at the same dose;
    - 4 DLTs -> de-escalate;
    - 5-8 DLTs -> de-escalate and consider current dose as intolerable.
- With 9 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-4 DLTs -> remain at the same dose;
    - 5-9 DLTs -> de-escalate and consider current dose as intolerable.
- With 10 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-4 DLTs -> remain at the same dose;
    - 5 DLTs -> de-escalate;
    - 6-10 DLTs -> de-escalate and consider current dose as intolerable.
- With 11 patients treated at current dose level:
    - 0-1 DLT -> escalate;
    - 2-5 DLTs -> remain at the same dose;
    - 6-11 DLTs -> de-escalate and consider current dose as intolerable.

- With 12 patients treated at current dose level:
    - 0-2 DLTs -> escalate;
    - 3-5 DLTs -> remain at the same dose;
    - 6 DLTs -> de-escalate;
    - 7-12 DLTs -> de-escalate and consider current dose as intolerable.

Appendix 3. ECOG Performance Status*

Grade	ECOG
0	Fully active, able to cany on all pre-disease perfonnance without restriction.
1	Resti·icted in physically sti·enuous activity but ambulato1y and able to cany out work of a light or sedentaiy nature, eg, light house work, office work.
2	Ambulato1y and capable of all self-care but unable to cany out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot cany on any self-care. Totally confined to bed or chair.
5	Dead.

*As published in Am J Clin Oncol 5:649-655, 1982.

Appendix 4. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

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

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

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

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

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

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to randomization and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be non-evaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as CR, Non-CR/Non-PD, PD, Non-evaluable (NE). Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses might be non-evaluable.

Target Disease

1. Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

2. Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

3. Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

4. Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

5. Non-evaluable (NE): Progression has not been documented, and

    - One or more target measurable lesions have not been assessed; or

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

    - One or more target lesions were excised or irradiated.

Non-target disease

1. CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be ‘normal’ in size (<10 mm short axis).

2. Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

3. PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

4. NE: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 5. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE or Missing	No	PR
PR	Non-CR/Non-PD, NE or Missing	No	PR
SD	Non-CR/Non-PD, NE or Missing	No	Stable

Table 5. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
NE or Missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 6. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Best Overall Response

The best overall response (BOR) is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories.

- **Complete response (CR)**: At least one objective status of CR documented before progression.
- **Partial response (PR)**: At least one objective status of PR documented before progression.
- **Stable disease (SD)**: At least one objective status of stable documented at least 6 weeks after randomization date and before progression but not qualifying as CR, PR.
- **Progressive Disease (PD)**: Objective status of progression within 16 weeks of randomization, not qualifying as CR, PR or SD.

- **Non-evaluable (NE)**: Progression not documented within 16 weeks after randomization and no other response category applies.

Appendix 5. List of High Risk Medications for QTc Prolongation

Antiarrhythmics: Amiodarone; Disopyramide; Dofetilide; Ibutilide; Procainamide; Quinidine; Sotalol.	Miscellaneous: Arsenic; Cisapride; Droperidol; Thioridazine; Pentamidine.

Adapted from: **Regions Guidelines for Managing Medications and QTc prolongation**. Source: https://cpnp.org/sites/default/files/shared/2013/QTc_Prolongation_Med_Managment_Guideline.doc.

Appendix 6. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

These planned changes are being implemented immediately in response to the COVID-19 pandemic and are planned for the duration of the COVID-19 pandemic. This applies to patients who are quarantined or wish to not attend scheduled visits or perform study procedures or tests on site due to safety concerns and/or local government health or health institute suggestions and/or guidelines issued in an effort to limit exposure of vulnerable populations to the virus.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per exclusion criterion # 10: "Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness. In equivocal cases, with positive serology, those patients with a negative viral load are potentially eligible provided the other entry criteria are met.

Telehealth Visits

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

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study patients at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the patient and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses using the protocol required dosing diary.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.1.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Section 4.3 and the Laboratory Testing section of this appendix regarding pregnancy tests.
- Review of physical symptoms in place of mandated physical exams.

Study patient must be reminded to promptly notify site staff about any change in their health status.

Alternative Facilities for Safety Assessments

If the study participant is unable to visit the study site, protocol specified safety laboratory tests and/or tumor assessments may alternatively be performed at an alternative local laboratory or facility, where allowable by law or local guidance.

Laboratory Testing

If a study patient is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. At the discretion of the treating physician home blood draws may be permitted. All safety laboratory tests outlined in this protocol can be done at a local laboratory.

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

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

Any results that are considered clinically significant must be reported in a timely manner and as directed in the protocol.

Imaging and Efficacy Assessments

If the patient is unable to visit the study site for planned or unplanned imaging assessments the patient may visit an alternative facility to have these assessments performed. Qualified study site personnel must order, receive, and review results and any abnormalities, including progression of disease must be reported to the Pfizer clinical team in a timely manner and as directed in the protocol.

Electrocardiograms

If the patient is unable to visit the study site for ECGs, the patient may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

Study Intervention

If the safety of a trial patient is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that patient from study intervention must be considered.

PF-06873600 and letrozole may be shipped by courier to study patient if permitted by local regulations and in accordance with storage and transportation requirements for the PF-06873600 and letrozole. Pfizer does not permit the shipment of PF-06873600 and letrozole by mail. The tracking record of shipments and the chain of custody of PF-06873600 and letrozole must be kept in the patient's source documents/medical records.

Pfizer's standard clinical stability studies for small molecule clinical drug products support the temporary lift for the use of temperature monitors if the total duration of ground transportation only from initiation, defined as movement outside of clinical site control, ie, picked up by courier to receipt at final destination is <36 hours. Air transport is not permitted.

Your investigational site must document the shipment process followed (including courier tracking details) and obtain study patient's verbal consent to accept delivery of the study drug at home. Consent is to be documented in the patient medical record.

- Study sites should follow up with the patient once the investigational product is received by the patient to review when to start using the new bottles, the dosing instructions, and completion of the dosing diary/logs.

- Dosing diary/logs should be shipped with the investigational product.

- Upon delivery of study drug, the patient (or caregiver) must communicate the below information back to the site:

    - Description of the state of the package (any physical damage);

- Contents.
  - Number of bottles and lot numbers.
  - Dosing diary/logs.
- Patients should be instructed not to re-use or dispose of any bottles dispensed at a previous visit.
- All bottles and dosing diary/logs must be returned to the study site at the next on-site visit.

The following is recommended for the administration of PF-06873600 for patient who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic patient with active SARS-CoV2 infection, PF-06873600, letrozole and fulvestrant should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the patient should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in this protocol for any concomitant medication administered for treatment of SARS-CoV2 infection.

Home Health Visits

A home health care service maybe utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the patient's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (at the discretion of the treating physician and in consultation with the SPONSOR): scheduled visits per the Schedule of Activities (eg, evaluation of physical symptoms in place of protocol mandated physical examinations, review of adverse events or serious adverse events, dosing compliance, contraception check, and concomitant medication checks, etc.).

Adverse Events and Serious Adverse Events

Study treatment should continue unless the investigator/treating physician is concerned about the safety of the patient, in which case temporary or permanent discontinuation may be required.

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

Patient Data Monitoring and Protocol Deviations

Every effort should be made to ensure that required protocol tests and procedures are completed as described with the protocol. However, the circumstances around the ongoing COVID-19 pandemic may make it unfeasible to perform some of the tests and procedures. In these cases, the investigator must take all of the necessary steps to ensure the safety and wellbeing of the study participant. When a required protocol test or procedure cannot be performed, the investigator will promptly document the reason for the missed test or procedure and any corrective and preventive actions they have taken to ensure that required processes will be adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

Patient data monitoring will continue without interruption. Remote data monitoring will be permitted, wherever possible. The CRA will continue monitoring data in an ongoing manner via remote access following all institutional processes, if applicable.

Any other deviations to the protocol, except for these approved modifications, must be documented as protocol deviations, and if related to the pandemic, the reason should clearly state “COVID-19”. These are not immediately required to be reported to health authorities or IRB/ECs unless requested locally.

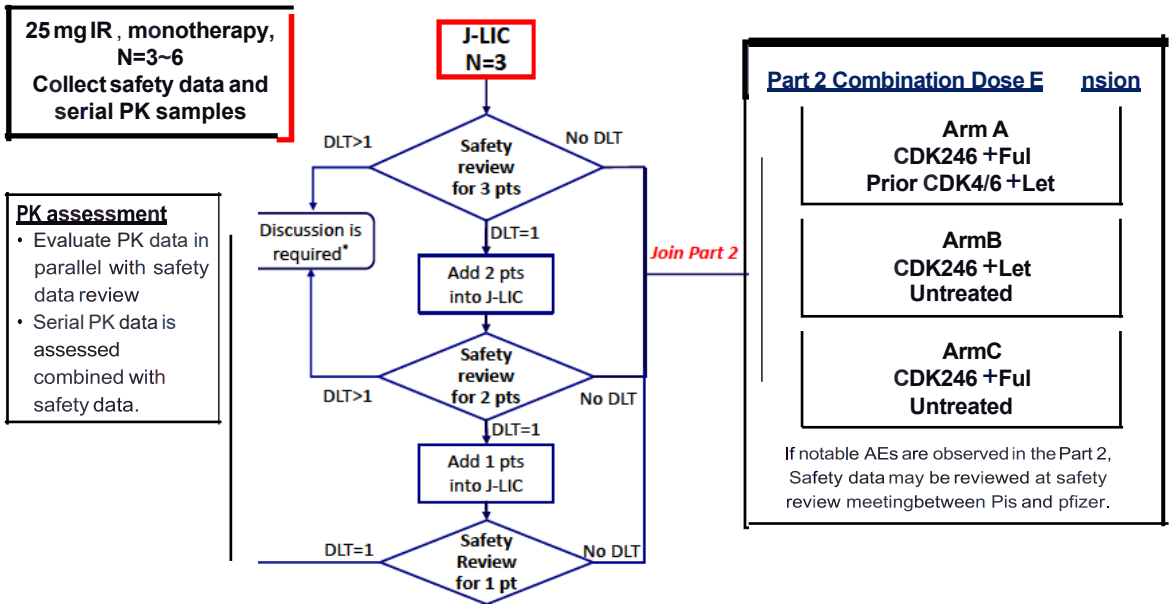
Appendix 7. Country-Specific Requirements

Appendix 7.1. Japan Specific Requirements

Japan Participation: Japan Lead-in Cohort

The Japan lead-in coho1i (J-LIC) will be conducted at sites in Japan and added as a sub-coho1i to this study. The primaiy and secondai ob·ectives ai·e to assess the safe ty, tolerabili and PK of PF-06873600. CCI [redacted] See Section 2 for more infonnation about the endpoints of this study. For paiiicipants emolled into the J-LIC, PF-06873600 will be administered orally BID on a continuous basis as a single agent. At least 3 patients, and if necessaiy up to 6 patients, will be emolled in this coho1i overall.

Figure 10. Japanese Lead-in Cohort Schema



*Dose de-escalation or discontinuation of patient enrollment would be considered

The dose of J-LIC will be the RDE of monotherapy (ie, 25 mg IR) that was detennined to be tolerable based on mTPI in a non-Japanese population in Pa1i IA. At this RDE, no DLTs were repo1ied. While dose escalation and de-escalation decision will not be selected for J-LIC, DLT evaluation will follow the mTPI using a beta (0.5,0.5) as a prior DLT distribution on the RDE for Japanese patients; therefore, evaluation results on the RDE co1Tesponding to DLT outcomes in J-LIC ai·e the saine as for non-Japanese patients in Table 1. The sample size for J-LIC will be 3-6 patients. If no patients in the first 3 patients experienced DLT in Cycle 1, this dose level will be declai·ed tolerable for Japanese patients (Actions to be taken in Table 1 will be "E"). If one patient experienced DLT in the first 3 patients (Actions to be taken in Table 1 will be "S"), 2-3 additional patients will be treated with the saine dose. If the additional patients do not experience DLTs in Cycle 1, this dose

level will be declared tolerable for Japanese patients (Actions to be taken in Table 1 will be "S"). If 1 DLT is observed in the additional patient group (ie, 2 of 5 patients), 1 additional patient (total 6 patients) will be enrolled. Japan participation in Part 2 will be determined based on the safety data review meeting comprised of the investigator and the sponsor, in order to ensure the safety of Japanese patients. If DLT is observed in ≥2 of 3 patients or ≥3 of 6 patients, dose de-escalation, or discontinuation of patient enrollment will be considered.

Patients not evaluable for assessment of DLT (eg, consent withdrawal in Cycle 1) will be replaced, and the safety information obtained from all patients who received at least 1 dose will be used for tolerability assessment.

When a dose level of J-LIC is deemed safe following a DLT observation period of 28 days and based on discussion by the safety review team (comprised of the Investigators and the Sponsor), Japanese participants will be able to join in Part 2 of the main study.

Japanese participants will be evaluated according to the current eligibility criteria will undergo the same study procedures and DLT evaluation period and will be evaluated using the same discontinuation criteria as participants in the dose escalation cohort of Part 1 of the main study, unless otherwise specified. The followings are only applicable in J-LIC.

1. DLT Definition:

In addition to Section 3.1.6 DLT Definition, the following toxicities will be classified as DLTs if they occur in patients in the J-LIC.

- Grade 4 anemia.
- Grade 3 anemia requiring transfusions or steroids.
- Grade 3 thrombocytopenia requiring transfusions.
- Inability to complete at least 75% of the first cycle doses of PF-06873600 due to investigational product related toxicity.
- Clinically important or persistent toxicities (eg, toxicities responsible for >3 weeks dose delay) that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor. All DLTs need to represent a clinically significant shift from baseline.

2. Eligibility criteria:

In J-LIC, the inclusion criteria #1 and #2 (Section 4.1) will be replaced with "Patients with a histological or cytological diagnosis of locally advanced or metastatic solid tumor that is resistant to standard therapy or for which no standard therapy is available." mBC and solid tumors with known CCNE amplification will be encouraged to enroll. The specific type of

solid tumor with CCNE amplification considered after consultation between the investigator and the sponsor as necessary.

2.1. Rationale for including additional solid tumors in Japan:

The target participants for J-LIC follow the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan.[1] Given the potential mechanism of action for the study drug, participants with mBC and other solid tumor with known to CCNE amplification will be encouraged to enroll.

CCNE amplification has been observed in several cancers[2,3,4] and may be a predictive factor for chemotherapy resistance[5] and a powerful driver in tumor growth.[6] No effective anti-tumor treatments exist for participants with these cancers currently. Preclinical models testing PF-06873600 in ER+ BC, triple negative breast cancer, and ovarian cancers have all shown evidence of anti-tumor activity. Further, translation of these in vitro findings to in vivo models has been successful in triple negative breast, ovarian and head and neck cancers (See Section 1.2.3). Additionally, preclinical studies testing CDK2 inhibitors showed anti-tumor activity in several sarcomas, a tumor with evidence of CCNE1 amplification/increased expression.[6]

These data support the hypothesis that PF-06873600 may provide clinical benefit for patients with CCNE amplification (irrespective of the solid tumor type) that is resistant to standard therapy or for which no standard therapy is available.

3. Exclusion Criteria:

The underlined parts were added into the exclusion criteria for patients considered for the J-LIC.

#14. Known or suspected hypersensitivity or severe allergy to active ingredient/excipients of PF 06873600, letrozole, fulvestrant and/or goserelin (or equivalent agent to induce chemical menopause).

#17. Pregnant female patients; breastfeeding female patients (including participants who intend to interrupt breastfeeding), female patients of childbearing potential and fertile male patients (Part 1A and Part 1C only) who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of investigational product.

#22. Current or history of idiopathic interstitial pneumonias (IIPs), drug-induced pneumonitis or radiation pneumonitis. In some cases, imaging findings with scarring may be observed in asymptomatic patients resulting from prior treatments. These cases (eg, if the scarring is identified at baseline and not considered clinically significant and/or active disease) may be eligible to enroll at the discretion of the PI, following a discussion and agreement with the sponsor. This criteria is only applicable in Japan.

4. Lifestyle Requirements:

Lifestyle Requirements follow Section 4.3, methods of contraception which as indicated with an asterisk have not been approved in Japan.

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted*, injected*, implanted*, transdermal* as locally approved), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

        - Oral;
        - Intravaginal*;
        - Transdermal*;
        - Injectable*.

    b. Progestogen only hormone contraception associated with inhibition of ovulation:

        - Oral*;
        - Injectable*.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female* condom used WITH a separate spermicide product* (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label). All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose of PF-06873600.

5. Hepatitis B Viral monitoring:

Participants with positive HBsAb or positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks. Participants with HBsAb positive who have been vaccinated with HBV are exempted from the testing of HB viral load.

A participant who is tested viral load positive for HBV at any time during the study will interrupt administration of PF-06873600, and should consider starting nucleoside antagonist immediately in parallel with consultation with hepatologist in accordance with the Japan Society of Hepatology (JSH) Guidelines for the management of Hepatitis B Virus infection.[7]

6. Hospitalization during the DLT assessment period:

The study investigator determines the necessity of hospitalization and its duration each participants with the circumstance of participants. Although hospitalization is not mandatory required, it may necessary to permit evaluation of the safety of participants in the event of the need for an emergency response. Hospitalization should be considered if participants' safety is difficult to ensure.[1]

7. Condition to be met for discharge (in cases of hospitalization):

- When a participant is discharged from the hospital during the DLT evaluation period, the following conditions (tests, medical examinations, etc.) should be performed on the day of the scheduled discharge by the investigators, and the appropriateness of discharge should be determined. The tests/medical examinations which are needed to confirm the participant's status will be conducted per clinical practice at the study site as appropriate.

- There are no current clinically significant adverse or side effects or medical reasons that require monitoring in a hospital setting.

- If a clinically significant adverse or side effect has occurred or continues to be present, the investigator will determine that the event is manageable by appropriate treatment or prophylaxis in an out-of- hospital setting. The investigator will ensure the adverse event are followed up according to the protocol requirement.

- Overall physical condition is stable and acceptable.

- In case of emergency, the participant may return to the clinical study site or other medical institution. If a participant goes to a medical institution other than the clinical study site, the clinical study site will ask that the participant contacts the study site, study investigator and doctor at the medical institution who will communicate to discuss appropriate treatments. A study site keeps the framework for emergency situations that is available even during nights and holidays, and the sponsor will ensure that the selected study site will thoroughly follow all participants according to study procedures.

CCI [redacted]

[redacted]

[redacted]

9. Granulocyte-colony stimulating factors

Primary prophylactic use of granulocyte-colony stimulating factors are not pennitted during the DLT observation period, but they may be used for ti·eatment emergent neuu-openia per Japanese package inse1i and local clinical guideline. If GCS-F is used prophylactically in Cycle 1 (28 days), the patient will not be DLT evaluable.

10. Interstitial lung disease (ILD) and pneumonitis

10.1. Screening for IIPs, drug-induced pneumonitis or radiation pneumonitis, and ILD/pneumonitis monitoring for early detection

1. SpO2and auscultation of the chest will be monitored at screening and study visits following the Schedule of Activities in Japan only.

2. Clinical biomarker KL-6 will be assessed eve1y cycle Day 1 in Japan only.

3. Evaluate ILD/pneumonitis by CT/MRI for tumor assessments following the SCHEDULE OF ACTIVITIES (Paii 1, Part 2 and J-LIC). In addition, high-resolution(HR) CT of the chest will be perfo1med as necessaiy for patients with suspected ILD/pneumonitis in Japan only.

4. Advise patients to immediately repo1i cough, dyspnea, fever, and/or any new or worsening respirato1y symptoms.

5. Conducts a detailed interview and cai·eful examination for signs and symptoms of ILD/pneumonitis (eg, cough, dyspnea, fever, hypoxemia). Evaluate patients with suspected ILD/pneumonitis with Chest X-ray and Chest HRCT, if deemed necessa1y per PI clinical judgement.

10.2. Dose interruption and discontinuation of PF-06873600 related ILD/pneumonitis

If::::Grade •1 pneumonitis is observed after PF-06873600 adminisu-ation, dosing must be intenupted immediately and initiation of co1iicosteroid ti·eatment should be considered. The

dosing of PF-06873600 must be discontinued if the ILD or pneumonitis is related to PF-06873600.

* CTCAE version 4.03.

11. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving PF-06873600. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and before the patient may receive PF-06873600. Pregnancy tests will also be repeated at Day 1 of every other Cycle and at the end of the study to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product and from the study.

[1] The Guidelines for clinical Evaluation Methods of Anti-Cancer Drugs in Japan, 31 Mar 2021, available from https://www.mhlw.go.jp/hourei/doc/tsuchi/T210401I0060.pdf. Accessed 15 May 2021.

[2] Gorski JW, Ueland FR, Kolesar JM. CCNE1 amplification as a predictive biomarker of chemotherapy resistance in epithelial ovarian cancer. Diagnostics. 2020; 10(5), 279.

[3] Kim B, Shin, HC, Heo YJ, et al. CCNE1 amplification is associated with liver metastasis in gastric carcinoma. Pathology - Research and Practice. 2019; 215(8), 152434.

[4] Skalicky DA, Kench JG, Segara D, et al. Cyclin E expression and outcome in pancreatic ductal adenocarcinoma. Cancer Epidemiology and Prevention Biomarkers. 2006; 15(10), 1941-1947.

[5] Gorski JW, Ueland FR, Kolesar JM. CCNE1 amplification as a predictive biomarker of chemotherapy resistance in epithelial ovarian cancer. Diagnostics. 2020; 10(5), 279.

[6] Kohlmeyer JL, Gordon DJ, Tanas MR, et al. CDKs in sarcoma: Mediators of disease and emerging therapeutic targets. International journal of molecular sciences. 2020; 21(8), 3018.

[7] JSH Guidelines for the Management of Hepatitis B Virus Infection, May 2021, version 3.4, https://www.jsh.or.jp/lib/files/medical/guidelines/jsh_guidlines/B_v3.4.pdf., Accessed May 15, 2021.

Appendix 8. Study Procedures After Primary Completion Date (PCD) Until End of Trial

The Sponsor made a business decision to terminate the Phase 1 clinical study C3661001 on 07 September 2022. The PCD is defined as the date of the last study visit where data is collected for the primary analysis of study outcome(s) and will occur around 5 April 2023. The participants who continue to derive clinical benefit and wish to continue study treatment, will have access to the investigational product 1) through PfizerCares (expanded access) program, where it is available, or 2) under Amendment 9 in the countries where expanded access is not available due to regulatory requirements.

The end of trial will occur when the last patient discontinues study treatment or on 31 October 2024, whichever occurs first. The participants are allowed to be followed for 28 days (up to 35 days) after last dose of study treatment or until the consent is withdrawn, whichever occurs first.

Upon approval of Amendment 9, for the patients who continue on study:

- Study drug (PF-06873600 and fulvestrant) administration will continue per protocol as described in Section 5.4 end of trial.

- Efficacy assessment will continue per local standard of care and institutional guidelines. No reporting of efficacy data to the sponsor is required.

- Safety assessment will continue per the local standard of care, institutional guidelines, and PI judgement based on the available safety profile of the study drug.
  SAE reporting will continue per Pfizer guidance as in Section 8. AE reporting after PCD and until end of study is required per Japan and EU regulations, therefore AEs collected by the investigators will continue to be reported to the Sponsor.