# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study information

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|---|---|
| **Title** | Prospective Observational Study of Mobile App-Based Patient-Reported Outcomes in Advanced Breast Cancer |
| **Protocol number** | A5481074 |
| **Protocol version identifier** | Version 2.0 |
| **Date of last version of protocol** | 20 June 2017 |
| **EU Post Authorisation Study (PAS) register number** | Study Not Registered |
| **Active substance** | Palbociclib (L01XE33) |
| **Medicinal product** | Palbociclib (IBRANCE) |
| **Research question and objectives** | The primary objectives of this prospective non-interventional study (NIS) are to assess and describe patient-reported outcomes (PROs) in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving:<br>1) IBRANCE in combination with an aromatase inhibitor or fulvestrant as per product label (GROUP 1) or<br>2) Approved therapies for ABC/mBC other than IBRANCE (GROUP 2) |
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## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ABC | advanced breast cancer |
| AE | adverse event |
| AEM | adverse event monitoring |
| CES-D-10 | Center for Epidemiological Studies Depression Scale |
| eCRF | electronic case report form |
| CRF | case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EDC | electronic data capture |
| ER | estrogen receptor |
| ER+ | estrogen receptor positive |
| HER2 | human epidermal growth factor receptor 2 |
| HER2– | human epidermal growth factor receptor 2 negative |
| HR | hormone receptor |
| HR+ | hormone receptor positive |
| HRQOL | health-related quality of life |
| IRB | institutional review board |
| mBC | metastatic breast cancer |
| NIS | non-interventional study |
| PRO | patient-reported outcome |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SF-12 | 12-Item Short Form Health Survey |

## 2. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation | Address |
|---|---|---|---|
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## ABSTRACT

**Study Title:** Prospective Observational Study of Mobile App-Based Patient-Reported Outcomes in Advanced Breast Cancer

**Protocol Version and Date:** Version 1.0; 22 July 2016

**Primary Author:** Lynn McRoy, MD, FACS; Senior Director, Medical Affairs, Pfizer, Inc.

**Rationale and Background:** Palbociclib (IBRANCE) is a new oral agent developed by Pfizer for the treatment of advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer in postmenopausal women.

To date, there have been few studies evaluating the day-to-day effects of advanced breast cancer (ABC) or metastatic breast cancer (mBC) and its treatment on patients in a real-world setting, and information about the effects of treatment-induced neutropenia on patients' daily functioning outside the context of clinical trials is particularly lacking. To contribute new information about patients' day-to-day functioning, Pfizer has endeavored to develop a smartphone-based mobile application to collect patient-reported data on outcomes associated with the disease and its treatment in a real-world setting.

**Research question and objectives:** To assess patient-reported outcomes (PROs) in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving:

1. IBRANCE in combination with an aromatase inhibitor or fulvestrant as per product label (Group 1)

   or

2. Approved first-, second-, or third-line therapies for ABC/mBC other than IBRANCE (Group 2)

**Study design:** Prospective, non-interventional, multicenter study of patients initiating treatment for HR+, HER2– advanced or metastatic breast cancer in the United States (US).

**Population:** Between 300 and 450 women diagnosed with HR+, HER2– ABC or mBC will be enrolled into two independent patient groups for the purpose of describing the experiences of those on IBRANCE and those on other treatments for ABC or mBC:

**Group 1:** Patients initiating IBRANCE treatment

- Approximately 150 to 300 women with HR+/HER2– ABC/mBC who are initiating
  - IBRANCE + an aromatase inhibitor as initial endocrine-based therapy for ABC or mBC per label

    or

- IBRANCE + fulvestrant for patients with disease progression following endocrine therapy for ABC or mBC per label

**Group 2:** Patients with ABC/mBC initiating first-, second-, or third-line treatment with any regimen other than those containing IBRANCE

- Approximately 150 patients who are initiating treatment with any regimen other than those containing IBRANCE for ABC/mBC in first, second, or third lines of treatment

**Variables:** Detailed definitions of variables that will be collected or derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP).

**Data sources:** Study data will be collected via a baseline site questionnaire; PRO questions via mobile application at daily, weekly, and cycle-based intervals; and patient medical information from medical records into an eCRF at baseline and at the end of the follow-up period. There are no protocol-mandated tests, procedures, or clinic visits for this study. All data collection for this study will occur over a 12-month period (from the first patient's first visit to the last patient's end of follow-up assessment), assuming a 6-month enrollment period with a 6-month follow-up period. Group 1 may be given the option to continue with the study for an additional 6 months.

**Study size:** Between 300 and 450 women diagnosed with HR+/HER2– ABC or mBC will be enrolled across multiple centers in the US. Any woman who meets the eligibility criteria will be invited to participate in the study. Eligibility will be assessed prior to enrollment during a scheduled visit.

**Data analysis:** Analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). All variables will be summarized descriptively through tabular displays of mean, median, ranges, and standard deviations of continuous variables and frequency distributions of categorical variables. Exploratory analyses may be conducted to examine associations and/or other research questions (eg, time-to-first-neutropenia using Kaplan-Meier methods). No formal hypothesis testing or comparisons between treatment groups is planned. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP.

**Milestones:**

| Milestone | Planned date |
|---|---|
| Start of data collection | December 2016 |
| End of data collection | July 2018 |
| Registration in the EU PAS register | October 2016 |
| Database lock | September 2018 |
| Analyses complete | December 2018 |
| Final study report | January 2019 |
| Study report addendum if additional 6-month follow-up is selected | July 2019 |

## 3. AMENDMENTS AND UPDATES

| Amendment number | Date | Substantial or administrative amendment | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| 1 | 20 June 2017 | Substantial | 2, 3, 4, 5, 6, 7.1, 7.2.1, 7.2.3, 7.2.4, 7.5, 7.9, 8.1, 8.3, 9.1,9.2, 13 | Updated the Group 1 definition from "IBRANCE in combination with letrozole or fulvestrant as per product label" to read "IBRANCE in combination with an aromatase inhibitor or fulvestrant as per product label"<br><br>Consolidated Management and Reporting of AEs/ARs into one section<br><br>Removed references to "legally acceptable representatives"<br><br>Removed "concomitant medications" from data collection table.<br><br>Clarified that SAEs should be submitted to IRBs only as required or requested<br><br>Removed "postmenopausal" from inclusion criteria | Protocol amended to reflect the broadened indication of IBRANCE for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination an aromatase inhibitor as initial endocrine based therapy<br><br>The Management and Reporting of AEs/ARs sections were consolidated as only one reporting standard per protocol is permitted<br><br>The data collection table was updated to reflect the final approved data collection forms (eg, removed one data point not collected and included one that initially omitted<br><br>Additional changes in this amendment are language clarifications based on investigator inquiries |

## 4. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | December 2016 |
| End of data collection | July 2018 |
| Registration in the EU PAS register | October 2016 |
| Database lock | September 2018 |
| Analyses complete | December 2018 |
| Final study report | January 2019 |
| Study report addendum if additional 6-month follow-up is selected | July 2019 |

## 5. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer among women in the United States (US), with an estimated 246,660 new cases occurring in 2016 (Siegel et al., 2016).[1] Although the 5-year survival rates are high among patients diagnosed with earlier-stage breast cancer, only 22% of patients with advanced breast cancer survive for 5 years after their diagnosis (American Cancer Society, 2014).[2]

Palbociclib (IBRANCE) is a new oral agent developed by Pfizer for the treatment of advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer in postmenopausal women. In a phase 2 trial, PALOMA-1, women with advanced ER+/HER2– breast cancer treated with IBRANCE in combination with letrozole as initial endocrine treatment for their advanced disease had a doubling of progression-free survival (PFS) duration compared to patients receiving letrozole alone (median PFS: 20.2 months [95% CI 13.8-27.5] vs. 10.2 months [95% CI 5.7-12.6], respectively [hazard ratio 0.488, 95% CI 0.319-0.748, one-sided p = 0.0004]) (Finn et al., 2015). The most common grade 3 or 4 adverse event (AE) was neutropenia (54% in the IBRANCE plus letrozole arm vs 1% in the letrozole arm), but no case of febrile neutropenia or neutropenia-related infection was reported during the study. PALOMA-2 is a phase 3 randomized trial of palbociclib plus letrozole versus letrozole alone in 666 postmenopausal women with ER+/HER2– advanced breast cancer who had no prior systemic therapy for advanced disease. The median PFS was 24.8 months in the palbociclib plus letrozole arm compared with 14.5 months in the letrozole alone arm (hazard ratio 0.58 [95% CI 0.46-0.72], p < 0.000001). Neutropenia of any grade occurred in 79.5% of patients in the combination arm (grade 3 in 56.1%; grade 4 in none; febrile neutropenia in 2.5%) versus neutropenia of

any grade in 6.3% of those in the letrozole alone arm. Overall survival results from this study have not yet been reported (Finn et al., 2016). A phase 3 trial, PALOMA-3, assessing women with metastatic HR+/HER2– breast cancer who had progressed on or following endocrine therapy were treated with IBRANCE in combination with fulvestrant similarly found prolonged PFS among patients receiving the IBRANCE combination compared to the fulvestrant and placebo groups (median PFS: 9.5 months [95% CI 9.2-11.0] vs. 4.6 months [95% CI 3.5-5.6], respectively [hazard ratio 0.46, 95% CI 0.36-0.59, $p < 0.0001$]) (Cristofanilli et al., 2016).[5] The most common grade 3 or 4 AE was neutropenia (65% in the IBRANCE plus fulvestrant arm and 1% in the fulvestrant plus placebo arm), but febrile neutropenia was uncommon in both groups (3 patients vs 1 patient, respectively). On March 31, 2017, FDA approved a supplemental New Drug Application (sNDA) for IBRANCE based on the results from the confirmatory Phase 3 trial PALOMA-2. The FDA action converts the accelerated approval of IBRANCE to regular approval and broadens the range of anti-hormonal therapy that may be administered with IBRANCE. IBRANCE now is indicated in combination with an aromatase inhibitor, expanding on its earlier indication in combination with letrozole, as initial endocrine based therapy in postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (Pfizer, 2017).[6]

To date, there have been few studies evaluating the day-to-day effects of advanced breast cancer (ABC) or metastatic breast cancer (mBC) and its treatment on patients in a real-world setting, and information about the effects of treatment-induced neutropenia on patients' daily functioning outside the context of clinical trials is particularly lacking. To contribute new information about patients' day-to-day functioning, Pfizer has endeavored to develop a smartphone-based mobile application to collect patient-reported data on outcomes associated with the disease and its treatment in a real-world setting. Information will also be collected on a case report form to describe the occurrence of neutropenia among patients being treated with ABC or mBC in this study and to assess any association between neutropenia and patient-reported outcomes (PROs).

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

## 6. RESEARCH QUESTION AND OBJECTIVES

The primary objectives of this prospective non-interventional study (NIS) are to assess PROs in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving:

1. IBRANCE in combination with an aromatase inhibitor or fulvestrant as per product label (GROUP 1) or

2. Approved first, second or third line therapies for ABC/mBC other than IBRANCE (GROUP 2)

The study is not intended to compare outcomes between the two groups.

The following research objectives will be addressed separately for both groups 1 and 2.

- Characterize patients with HR+ HER2– ABC initiating treatment (eg, baseline patient demographics [eg, age, race] and clinical characteristics [eg, comorbidities, tumor stage, histology])
- Describe changes in patients' general health status as measured by monthly (cycle-based) administration of the 12-Item Short Form Health Survey (SF-12)
- Describe changes in patients' psychological distress as measured by monthly (cycle-based) administration of the Center for Epidemiological Studies Depression Scale (CES-D)
- Describe the extent to which locally advanced or metastatic breast cancer and its treatment are associated with changes in patients' lives in terms of symptoms, functioning and quality of life as measured by daily and weekly administration of targeted patient-reported questions
- For patients who are employed at baseline, quantify time lost from work in relation to locally advanced or metastatic breast cancer and its treatment
- Assess patient's satisfaction with treatment
- Describe dosing patterns (eg, reduction, interruptions, duration)

The following research objectives will be addressed for Group 1 only.

- Describe the incidence, severity, and duration of neutropenia; time to first neutropenia event
- Changes in IBRANCE dose and/or schedule
- Explore the association between patient-reported functioning and quality of life and neutropenia

## 7. RESEARCH METHODS

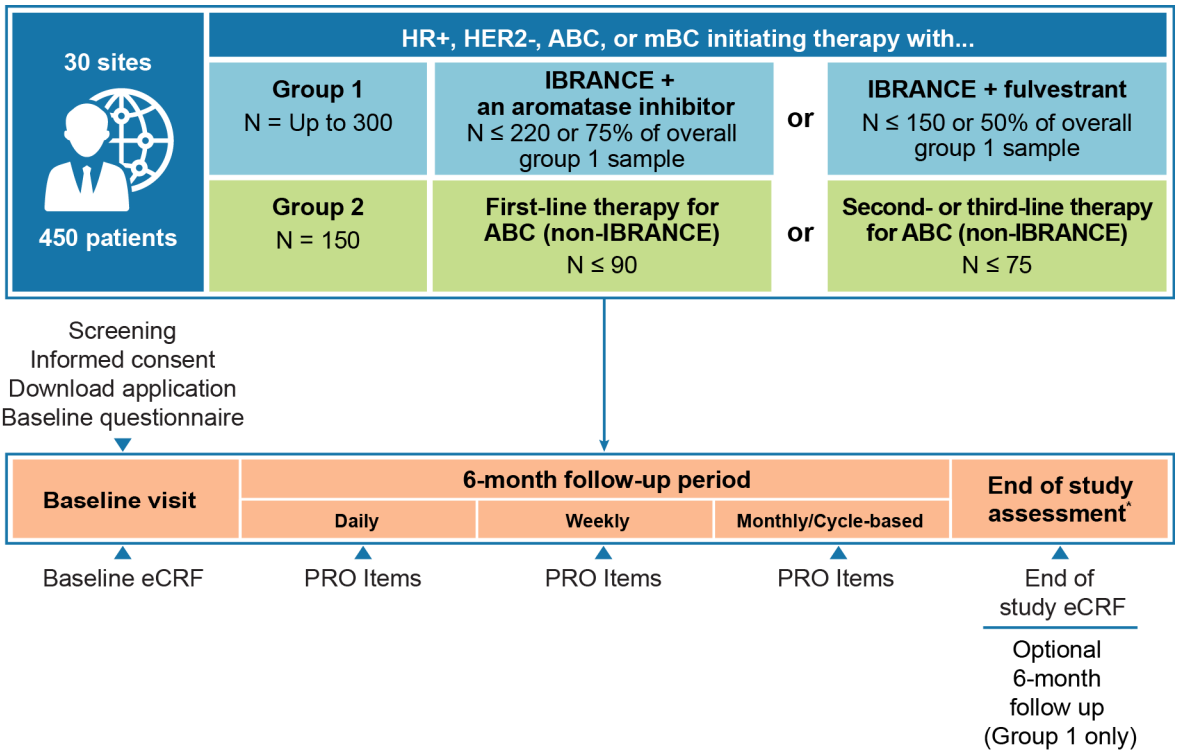
### 7.1. Study design

The study is a prospective, non-interventional, multicenter study of patients initiating treatment for HR+, HER2– advanced or metastatic breast cancer in the United States. Participating investigators will screen patients for eligibility, obtain informed consent, and enroll patients meeting the eligibility criteria. Investigators or trained site personnel will then complete a brief case report form (CRF) to capture demographic, medical history, and treatment information at enrollment. Interim changes in treatment and clinical outcomes will be recorded for a period of 6 months after enrollment (end-of-study assessment). Enrolled patients will be provided access to and trained on the use of a mobile application to complete

baseline, daily, weekly, and cycle-based assessments for a period of 6 months. If an additional follow-up of 6 months is selected, only cycle-based assessments and a subset of eCRFs will be completed during this period.

Figure 1 summarizes the overall study design.

**Figure 1. Study Design**




*ABC = advanced breast cancer; eCRF = electronic case report form; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; mBC = metastatic breast cancer; PRO = patient-reported outcome.*

*[*] Final monthly/cycle-based.*

## 7.2. Setting

Between 300 and 450 women diagnosed with HR+, HER2– ABC or mBC will be enrolled into this non-interventional prospective study across multiple centers in the US. All patients will be required to have had a diagnosis of mBC or locoregionally advanced breast cancer not amenable to resection or radiation therapy with curative intent at the time of study entry. Patients could have either a de novo diagnosis of advanced or mBC or recur from an earlier stage. Any woman who meets the eligibility criteria will be invited to participate in the study. Eligibility will be assessed prior to enrollment during a scheduled visit.

Participation in this study is not intended to change the routine treatment that patients receive as determined by their prescribing clinicians; all treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician. No additional visits to the clinic will be required for the purposes of the study.

### 7.2.1. Patient Population

Two independent patient groups will be included in this study for the purpose of describing the experiences of those on IBRANCE and those on other treatments for ABC or mBC:

**Group 1**: Patients initiating IBRANCE treatment

- Approximately 150 to 300 women with HR+/HER2– ABC/mBC who are initiating
    - IBRANCE + an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with ABC or mBC per label;

      or

    - IBRANCE + fulvestrant for patients with disease progression following endocrine therapy for ABC or mBC per label

**Group 2**: Patients with ABC/mBC initiating first, second or third line treatment with any regimen other than those containing IBRANCE

- Approximately 150 patients who are initiating treatment with any regimen other than those containing IBRANCE for ABC/mBC in first, second, or third lines of treatment

### 7.2.2. Study Duration

It is anticipated that all data collection for this study will occur over a 12-month period (from the first patient's first visit to the last patient's end of follow-up assessment), assuming a 6-month enrollment period with a 6-month follow-up period. The duration of data collection for an individual patient will be approximately 6 months, although this period may be truncated due to treatment switching, patient withdrawal from the study, or death. Specifically, follow-up for patients in Group 1 will end if they discontinue the IBRANCE combination initiated at the start of the study, and follow-up for patients in Group 2 will end if they begin a treatment regimen that includes IBRANCE.

Patients in Group 1 may be given the option to continue with the study for an additional 6 months, leading to a total study duration of 18 months.

### 7.2.3. Stratification

Patients enrolled into the study will be stratified based on two main characteristics as described in Table 1.

**Table 1. Sample Stratification**

| | Group 1 (N = 150-300) | Group 2 (N = 150) |
|---|---|---|
| **First therapy** | IBRANCE + an aromatase inhibitor:<br>Maximum of 220 patients or 75% of overall Group 1 sample | Maximum of 90 patients who are initiating their first systemic therapy in the ABC setting |
| **Second therapy** | IBRANCE + fulvestrant:<br>Maximum of 150 patients or 50% of overall Group 1 sample | Maximum of 75 patients who are initiating their second or third systemic therapy in the ABC setting |

ABC = advanced breast cancer.

### 7.2.4. Inclusion criteria

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

- Owns or has regular access to an Apple iPhone (version 5.0 or higher with latest software: iOS 9.0 or higher) or Android phone (eg, Nexus or Galaxy with latest software: version 4.4.2 or higher).
- Adult women (≥ 18 years of age) with diagnosis of adenocarcinoma of the breast with evidence of metastatic disease or locoregionally advanced disease not amenable to resection or radiation therapy with curative intent.
- Documented evidence of HR+ tumor based on the patient's most recent tumor biopsy.
- Documented evidence of an HER2– tumor based on the patient's most recent tumor biopsy. HER2– is determined as an immunohistochemistry score of 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2 or, for single probe assessment, a HER2 copy number < 4).
- Initiating first, second or third line treatment with one of the following therapies: IBRANCE and an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with advanced or metastatic disease as per label, or IBRANCE with fulvestrant if the patient has experienced disease progression following endocrine therapy as per label, or other approved therapy as the first treatment for advanced or metastatic breast cancer, or initiating other approved therapy as the second or third treatment for ABC or mBC.
- Evidence of a personally signed and dated informed consent form document indicating that the patient has been informed of all pertinent aspects of the study.
- Able to read and understand English
- Willing and able to complete collection of data via mobile app.

### 7.2.5. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Patient is initiating neoadjuvant systemic therapy.
- In the judgment of the investigator, the patient's life expectancy is fewer than 3 months at the time of diagnosis of ABC or mBC.
- The patient is participating in any interventional clinical trial that includes investigational or marketed products. Patients participating in other investigator initiated research or non-interventional studies can be included as long as their standard of care is not altered by the study.
- The patient is on active treatment for other malignancies other than ABC or mBC.

Patient eligibility should be reviewed, documented, and confirmed by an appropriately qualified member of the investigator's study team before patients are enrolled in the study.

## 7.3. Variables

As this is prospective, observational study, information collected in the data collection materials will be directly transferred into variables, namely patient medical information collected in the electronic case report form (eCRF) and PROs collected in the mobile application (see Table 2). In addition, the SF-12 and the CES-D-10 will be scored according to each instrument's scoring algorithm. Detailed definitions of additional variables that will be derived from the collected data for the statistical analysis will be included in the Statistical Analysis Plan (SAP) and/or in a separate analytic variable specification document.

## 7.4. Data sources

Data for this study will be obtained via the following sources:

- **Site Questionnaire:** At the time of site enrollment, basic site characteristics such as geographic location, size of practice, type of hospital, volume of patients with HR+, HER2– ABC or mBC seen will be collected via a brief site questionnaire.
- **Patient-Reported Questions via Mobile Application:** All patients will be asked to complete a baseline questionnaire, as well as series of questions at daily, weekly, and/or monthly/cycle-based intervals via a mobile application downloaded onto their smartphones. Two validated PRO instruments will be administered at baseline and monthly; the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D-10) (Björgvinsson et al., 2013; Irwin et al., 1999) and the 12-Item Short Form Health Survey (SF-12) (Ware et al., 1996; Jenkinson et al., 1997).[7-10] Appropriate agreements with the copyright owners will be in place for use in this study. All other items have been developed specifically for this study.

- **Patient medical information:** The investigator or authorized medical staff will record clinical and treatment data from patients' medical records into an eCRF at baseline and at the end of the 6-month follow-up period. Site staff may opt to enter data on an ongoing basis (eg, at the time labs are available) rather than wait until the end of the 6 month follow-up. Types of data to be obtained from patient medical records are described in Table 2.

### 7.5. Data Collection Schedule

This prospective, non-interventional study does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be enrolled into the study during a regularly scheduled office visit prior to initiating their treatment. There are no protocol-mandated tests and procedures for this study. It is the responsibility of the investigator to perform medically appropriate tests and procedures as necessary to ensure the safety and well-being of the patient per normal practice and standard of care.

The data collection schedule is presented in Table 2. All clinical data obtained for these assessments must be supported in the patients' source documentation. Patient will be provided with a window of time to complete assessments after which they will not be able to access those assessments. Specifically, daily assessments will close at midnight each day. Weekly assessments will remain open for up to 3 days (72 hours) and monthly/cycle based assessments will remain open for up to 7 days (168 hours).

## Table 2. Data collection schedule

| | Data Source | Enrollment | Daily | Weekly | Monthly/ Cycle-Based[a] | End of Study |
|---|---|---|---|---|---|---|
| **Site characteristics** | Site Staff | X | | | | |
| **Screening** | CRF | X | | | | |
| Diagnosis of ABC/mBC | | | | | | |
| Cancer subtype (HR+/HER2–) | | | | | | |
| Treatment being initiated | | | | | | |
| Line of therapy | | | | | | |
| **Informed consent** | ICF | X | | | | |
| **Baseline CRF** | Medical record/ CRF | | | | | |
| Disease and treatment history | | X | | | | |
| Comorbid conditions | | X | | | | |
| Performance status | | X | | | | |
| Site of metastases (if present) | | X | | | | |
| Treatment plan at enrollment | | X | | | | |
| **Patient-reported questions** | Patient | | | | | |
| Age | | X | | | | |
| Race/ethnicity | | X | | | | |
| Education | | X | | | | |
| Employment | | X | | | | |
| Insurance | | X | | | | |
| SF-12 | | X | | | X | |
| CES-D-10 | | X | | | X | |
| Mood (7-point scale) | | X | X | | | |
| Pain (0-to-10 NRS) | | X | X | | | |
| Fatigue (0-to-10 NRS) | | X | X | | | |
| Use of pain medication | | | X | | | |
| IBRANCE use[b] | | | X | | | |

## Table 2. Data collection schedule

| | Data Source | Enrollment | Daily | Weekly | Monthly/ Cycle-Based[a] | End of Study |
|---|---|---|---|---|---|---|
| Impact on mood or emotions | | | | X | | |
| Interference with family life | | | | X | | |
| Interference with social life or activities | | | | X | | |
| Physical activity | | | | X | | |
| Energy or stamina | | | | X | | |
| Productivity | | | | X | | |
| Missed work time (number of hours) | | | | X | | |
| Overall health rating | | | | X | | |
| Neutropenia Awareness | | | | X | | |
| Overall quality of life rating | | | | X | | |
| Overall satisfaction with treatment | | | | | X | |
| **CRF (capturing data for 6 months)[c]** | Medical record/ CRF | | | | | |
| Experience with adverse events including neutropenia (eg, type, grade)[d] | | | | | | |
| Disease progression | | | | | | |
| Reason for discontinuation (if applicable) | | | | | | |
| Treatment changes/switching (Group 2) | | | | | | |
| IBRANCE-related dose changes and interruptions[b] | | | | | | |

## Table 2. Data collection schedule

| | Data Source | Enrollment | Daily | Weekly | Monthly/ Cycle-Based[a] | End of Study |
|---|---|---|---|---|---|---|
| **End of Study CRF** | **Investigator** | | | | | |
| Study Completion or Early Discontinuation (and reason) | | | | | | X |

ABC = advanced breast cancer; CES-D-10 = 10-item short form of the Center for Epidemiologic Studies Depression Scale; CRF = case report form; HR+/HER- = hormone receptor-positive/human epidermal growth factor receptor 2-negative; ICF = informed consent form; mBC = metastatic breast cancer; NRS = numerical rating scale; PRO = patient-reported outcome; SF-12 = 12-Item Short Form Health Survey.

a. The optional 6-month extension will be composed of only Group 1 patients who have provided consent for the additional follow-up period.

b. Group 1 only.

c. Site personnel may input data into this CRF on an ongoing basis or complete at the end of follow-up.

d. Safety reporting will following applicable regulations and is detailed in Section 9.

### 7.6. Missing data

As this study collects data from patients on daily, weekly, and monthly/cycle-based schedules over 6 months (and the optional additional 6 months for Group 1 patients who consent to follow-up), it is anticipated that there will be missing data. For the two validated PRO instruments (CES-D-10 and the SF-12) scoring documentation provides guidance for handling of missing data:

- CES-D-10: A score is not to be calculated if more than 2 of the 10 items are missing
- SF-12: A score will be considered missing if any of the items are missing

If a patient has not entered data into the ePRO system (mobile application) for a period of 2 weeks, the site will be notified and asked to reach out to the patient. A patient will be discontinued if they have not entered for another consecutive 2 weeks (for total of 4 weeks of no data entered).

Detailed methods for handling missing data will be described in the statistical analysis plan.

### 7.7. Study size

The current enrollment target for this non-interventional prospective study is between 300 and 450 women across multiple centers in the US with a minimum of 150 to a maximum of 300 patients enrolled in Group 1 and 150 patients enrolled in Group 2. This is an observational study designed to provide descriptive summary information and is not designed for hypothesis testing. As such, no formal power calculation has been performed. The number of patients was chosen on a practical basis in conjunction with the ability to have reasonable precision around key estimates.

### 7.8. Data management

The EDC system that will be used to capture study data at the site (eCRFs) is the OpenClinica clinical database management system. The OpenClinica system is 21 Code of Federal Regulations Part 11 compliant. The system will be programmed by RTI-HS data managers and hosted by OpenClinica on secure servers located in the United States. The EDC system will be used to collect, monitor, and report clinical data as specified in the protocol. Investigators or authorized staff will enter clinical data directly into the OpenClinica system at enrollment, baseline, and end of study. All data collected via the eCRF will be reviewed by remote data managers for clarity and completeness. Missing or unclear data will be queried according to the data management plan. The database and data management plan, describing data systems used, data sources, data cleaning procedures, and data transfer procedures, will be generated according to approved specifications.

Patient-reported data will be captured using the mobile application designed, programmed, and hosted by InTouch Solutions. These data will be transferred to RTI Health Solutions for analysis as part of the study's primary objectives. Data transfers between RTI Health Solutions and InTouch Solutions will be managed using procedures described in a jointly

developed data transfer plan. All data transferred between InTouch Solutions and RTI Health Solutions will be identified only by a subject ID code. Data in both systems will be compared weekly to ensure that participant status is the same in both systems. RTI Health Solutions will combine the InTouch Solutions data and the OpenClinica eCRF data at the end of the study.

### 7.9. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). All variables will be summarized descriptively through tabular displays of mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables. Exploratory analyses may be conducted to examine associations and/or other research questions (eg, time-to-first-neutropenia using Kaplan-Meier methods).

No formal hypothesis testing or comparisons between treatment groups is planned.

### 7.10. Quality control

#### 7.10.1. Site training

Investigators and study coordinators will be trained with an initial WebEx training session on the protocol, study flow, EDC system (eCRF), mobile app (ePRO), documentation, site responsibilities and expectations, and any applicable study processes. Any new information relevant to the performance of this non-interventional study will be forwarded to the medical staff during the study.

No on-site monitoring visits are planned for this study. Remote data monitoring will be conducted during the life of the study to ensure linkage and integrity between the EDC and PRO systems and to identify missing or unclear data in the EDC system and issue queries. The remote study monitor and RTI-HS project manager will closely monitor the patient recruitment and data collection to ensure sampling/quota requirements are being met. RTI-HS will also provide oversight of activities, including screening patients, recruiting and obtaining consent from patients, and completing the eCRFs. RTI-HS will maintain regular communication with all sites and will assess progress and site performance and address any issues as they arise.

#### 7.10.2. Data transfers, recording and document retention

Data transfers between RTI-HS and InTouch Solutions will be described in a detailed Data Transfer Plan. The transfers made during the course of the study will be used to ensure that participants have the same status (eg, active, completed) in both data systems. At the end of the study, InTouch Solutions will transfer their complete data set to RTI Health Solutions, which will combine the data sets.

Archiving of study documents will be performed according to Pfizer standard operating procedures (SOPs).

### 7.10.3. Data quality assurance

All applicable SOPs and data-cleaning procedures will be followed with the aim of removing errors and inconsistencies in the data that would otherwise affect the analysis, reporting aims, or credibility of the final study report.

For the analysis, all programming written by one study analyst will be reviewed independently by a different analyst with oversight by a senior statistician.

All key study documents—such as the analysis plan, data collection forms, and study reports—will undergo quality-control review, senior scientific review, and editorial review.

The study database will be backed up each night. Access to the EDC system will be by username/password combination only and available only to authorized personnel.

## 7.11. Limitations of the research methods

The sample of participating sites is a convenience sample and is not guaranteed to be representative of all centers that treat patients with ABC/mBC across the US. Likewise, the patient selection and the diagnostic or monitoring procedures are those applied per the usual treatment paradigm of the treating physician and not dictated by the protocol. Heterogeneous patient populations could make the interpretation of the outcomes difficult.

As with all studies that require patients to self-report outcomes and behavior, completeness and accuracy of reporting can be a concern. Study participants wishing to be seen as responsible patients may over-report compliance. In addition, while patients will be asked to complete the daily questions at a consistent time of day, they will be able to access and complete the daily questions at any point during the 24-hour period.

The data collection methods have been designed to be appropriate and accessible to the study population. Nevertheless, some errors in recording information and some missing information can be anticipated, particularly given the frequency and length of PRO data collection (daily, weekly, and monthly items over a 6-month data collection period).

As this study will collect PRO data through the use of a mobile app, use and knowledge of mobile devices is required to participate, the study population may not be representative of the ABC population, which may include technology- or mobile device-naive patients.

In summary, the source data described in this protocol contain the inherent limitation of any current non-interventional, real-world study. These studies have the potential for missing, inaccurate, or incomplete data. These limitations can result in methodological challenges in attributing causality to outcomes. Hence, this study is intended for hypothesis generation as opposed to hypothesis confirmation.

### 7.12. Other aspects

Not applicable.

## 8. PROTECTION OF HUMAN SUBJECTS

### 8.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data. Data transferred between RTI Health Solutions and InTouch Solutions will be identifiable only by subject ID number.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study and any changes made during the course of the study must be prospectively approved by both the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

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 form.

### 8.2. Patient withdrawal

Patients may withdraw from the study 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, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a patient is switched from Group 1 (IBRANCE) to another line of therapy, the patient will be considered discontinued. If a patient in Group 2 (non-IBRANCE) is changed to another line of therapy, they may continue with the study unless they are started on IBRANCE at which point the patient will be considered discontinued.

### 8.3. Institutional Review Board/Independent Ethics Committee

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

The study protocol, the ICF, and the HIPAA authorization form must be approved by an appropriate IRB before the study is initiated at the site. Documentation of this approval must be provided to RTI Health Solutions before the site training visit is conducted. The IRB used must comply with current ICH GCPs.

The investigator's responsibilities regarding IRB are as follows:

- Obtain IRB approval for any protocol amendments and ICF revisions before implementing the changes
- Provide the IRB with information regarding serious adverse event (SAE) reports regardless of causality during the study as required or requested by their IRB
- Submit progress reports to the IRB, as required, during the conduct of the study; requesting re-review and approval of the study, as needed

### 8.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, the International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, , and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

## 9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

### 9.1. Management and Reporting of AEs/ARs

This section (Section 9.1) describes the management and reporting of AEs/ARs. This section applies to Group 1 (IBRANCE in combination with an aromatase inhibitor or fulvestrant as per product label) and Group 2 (approved therapies for ABC/mBC other than IBRANCE)

The table below summarizes the requirements for recording safety events on the eCRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and

(3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

**Table 3. Requirements for Recording and Reporting Safety Events**

| Safety event | Recorded on the eCRF | Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness |
|---|---|---|
| SAE | All | All |
| Non-serious AE | All | None |
| Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure | All (regardless of whether associated with an AE), **except occupational exposure** | All (regardless of whether associated with an AE) |

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety 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 events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse 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 or its designated representative.

**Reporting period**

For each patient, the safety event reporting period begins at the time of the patient's first dose of palbociclib or other oncologic medicinal products for HR+/ HER2- MBC or the time of the patient's informed consent if s/he is already exposed to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation or failed screening criteria, the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC, the SAE also must be reported to Pfizer Safety.

**Causality assessment**

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that palbociclib or other oncologic medicinal products for HR+/ HER2- MBC caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether palbociclib or other oncologic medicinal products for HR+/ HER2- MBC caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that palbociclib or other oncologic medicinal products for HR+/ HER2- MBC did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

## DEFINITIONS OF SAFETY EVENTS

### Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

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

**Serious adverse events**

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

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 outcomes listed in the definition above, 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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to 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, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly exam)
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol)

**Scenarios necessitating reporting to Pfizer Safety within 24 hours**

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) palbociclib or other oncologic medicinal products for HR+/ HER2- MBC, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC (maternal exposure).

   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).

2. A male has been exposed, either due to treatment or environmental exposure to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with palbociclib or other oncologic medicinal products for HR+/ HER2- MBC, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to palbociclib or other oncologic medicinal products for HR+/ HER2- MBC in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

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; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy

termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

Additional information about pregnancy outcomes that are reported 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 investigational product

Additional information regarding the exposure during pregnancy may be requested. 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 study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. 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 AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

### 9.2. Single reference safety document

The US Prescribing Information for IBRANCE (palbociclib) in combination with aromatase inhibitors or fulvestrant will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study. Should SAEs be reported on any non-Pfizer product used in the treatment of MBC, the SRSD for such a product will be the US manufacturer's USPI.

The SRSD should be used by the investigator for prescribing purposes and guidance.

## 10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are not part of any planned regulatory submission. The results may be submitted for abstracts and publications. The final CSR will be filed in Pfizer's Global Document Management System upon final study completion

## 11. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent 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 a Pfizer 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 NI study protocol that the investigator becomes aware of.

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## 13. LIST OF TABLES



## 14. LIST OF FIGURES



## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

# Document Approval Record

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