Study Information

Title	Treatment Patterns and Clinical Outcomes Among Indian Patients Receiving Palbociclib Combinations for HR+/HER2- Advanced/Metastatic Breast Cancer in Real World Settings
Protocol number	A5481145
Protocol version identifier	Version 1.0
Date	19/10/2020
Active substance	L01XE33 Palbociclib
Medicinal product	Palbace (palbociclib)
Development phase	This is a retrospective, non-interventional study (NIS)
Population of interest	Adult female patients with HR+/HER2- advanced/metastatic breast cancer
Research question and objectives	To describe patient demographics, clinical characteristics, treatment patterns and clinical outcomes of adult female patients who have received palbociclib combination treatments for hormone receptor positive/ human epidermal growth factor 2 negative (HR+/HER2-) advanced/metastatic breast cancer in real world settings in India. **Primary objectives** • To describe demographics and clinical characteristics of patients who have received

	palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy.
	
	• To summarize adjuvant therapies received for the treatment of early or locally advanced breast cancer (Stages 0-IIIa).
	
	• To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use.
	
	• To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice.
	
	• To describe supportive therapies received by patients while receiving palbociclib combination treatments.
	
	• To determine in overall population and defined subgroups, clinical outcomes including (but not limited to):
	
	  • Proportion of patients who are progression free at specific intervals (eg, 6, 12, 18 months).
	
	  • Objective response rate (ORR) – depending on availability of follow-up data.
	
	  • Proportion of patients alive after 1 and 2 years post palbociclib combination initiation - depending on availability of follow-up data (sample size permitting).
	
	 

Country	India
Author	PPD MBBS MD Pharmacology PPD PPD MD, Radiation Oncology, PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC/MBC	advanced/metastatic breast cancer
AE	adverse events
AEM	adverse events monitoring
CDK	cyclin-dependent kinase
CDSCO	Central Drugs Standard Control Organization
DFI	disease free interval
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ER	estrogen receptor
GPP	Guidelines for Good Pharmacoepidemiology practices
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
HR+/HER2-	Hormone receptor positive / human epidermal growth factor 2 negative
IEC	independent ethics committee
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
LHRH	Leutinizing Hormone Releasing Hormone
NI	non-interventional
NIS	non-interventional study
ORR	objective response rate

OS	overall survival
PALOMA	Palbociclib: Ongoing Trials in the Management of Breast Cancer
PFS	progression free survival
PHI	protected health information
SAP	statistical analysis plan
SAS	Statistical software suite developed by SAS Institute for advanced analytics
CCI [redacted]	
USFDA	United States Food and Drug Administration
YRR	your reporting responsibility

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD MD, PPD PPD	PPD	PPD	PPD
PPD MBBS MD, Pharmacology	PPD	PPD	PPD

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4. ABSTRACT

Title: Treatment Patterns and Clinical Outcomes Among Indian Patients Receiving Palbociclib Combinations for HR+/HER2- Advanced/Metastatic Breast Cancer in Real World Settings.

Rationale and background: Breast cancer is a leading cause of cancer-related death in females worldwide. An approximately 75% of all breast cancer are diagnosed to be HR positive (HR+) which grow in response to increased levels of the hormones estrogen and progesterone. Palbociclib is a first in class CDK4/6 inhibitor that has been approved for use in HR+/HER2- advanced/metastatic breast cancer (ABC/MBC) patients. The approval of palbociclib combination treatment was based on the results of the 3 globally conducted PALOMA (Palbociclib: Ongoing Trials in the Management of Breast Cancer) trials. In India palbociclib, in combination with letrozole, was approved in the month of August 2016. It has been more than 2 years since palbociclib has been used in India for the treatment of HR+/HER2- advanced/metastatic breast cancer (ABC/MBC) patients. However there is

scarce information regarding how and when palbociclib combination is prescribed in routine clinical practice, and the outcomes associated with palbociclib use. Therefore, real world data on the characteristics, treatment patterns and clinical outcomes among patients receiving palbociclib combinations to treat HR+/HER- ABC/MBC will provide valuable insight to help inform treatment decisions.

Research question and objectives: The primary objective of this real world study is to describe the patient demographics, clinical characteristics, treatment patterns, and clinical outcomes of adult female patients who have received palbociclib combination treatments for HR+/HER2- ABC/MBC in real world settings in India.

Study design: This retrospective physician based medical record review will collect data from medical records of patients, who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy. Data will be collected retrospectively at a single point in time from patient medical records.

Population: Data will be collected from the Indian routine clinical practice settings. Approximately 10 oncologists will be included. To be eligible to participate, physicians must have treated, or be treating 10 or more HR+/HER2- ABC/MBC patients with palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy. Each physician will complete at least 10-15 electronic case report forms (eCRFs). Included physicians must go back in their records to the specific index date and select the next number of eligible patients for which they will complete eCRFs. The 'index date' will be defined as 60 days after the physician first prescribed palbociclib + partner therapy following the availability of specific indication in the market. To be eligible, patients must be females, aged 18 or over, have been diagnosed with HR+/HER2- ABC/MBC and must have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) as initial endocrine therapy in postmenopausal MBC patients or with fulvestrant in patients who have progressed on prior endocrine therapy. For the study, patients must have initiated palbociclib with fulvestrant a minimum of 3 months, or palbociclib with aromatase inhibitor a minimum of 6 months prior to data collection.

Variables: The variables assessed in this study will be patient demographics at the time of data collection, clinical characteristics, comorbid conditions, early and advanced breast cancer treatment history, palbociclib treatment patterns including dose changes, clinical outcomes and date of death if applicable.

Data sources*:* Patient medical records will be used as the data source for the study.

Study size: Approximately 10 physicians will be recruited across the India; this will enable data to be collected for approximately 150 patients.

Data analysis: All analyses will be descriptive in nature. Categorical variables will be described using the number of observations and number and percent (%) in each category.

Numeric variables will be described using the number of observations, mean and standard deviation, and minimum, maximum, median and interquartile range. Time to event will be described using a Kaplan-Meier chart for the median.

***Milestones*:** Data collection will begin in November 2020 and should be completed by January 2021. Following completion of the study, the final report will be written and completed by February 2021.

5. AMENDMENTS AND UPDATES

NONE

6. MILESTONES

Milestone	Planned date
Start of data collection	November 2020
End of data collection	January 2021
Study Report	February 2021
Manuscript/Conference abstract	April 2021

7. RATIONALE AND BACKGROUND

Breast cancer is the leading cause of cancer-related death in females worldwide. An approximately 1.7 million new cases of breast cancer were diagnosed in 2012, contributing to 12% of all newly diagnosed cancers worldwide.[1] According to estimates of Globocan 2012, India, United States and China collectively accounts for almost one third of the global breast cancer burden. The reported increase in the rate of incidence and mortality due to breast cancer in India was 11.54% and 13.82%, respectively during 2008-2012.[1] Among Indian females also breast cancer has been ranked the number 1 cancer with age adjusted rate as high as 25.8 per 100,000 women and mortality rate of 12.7 per 100,000 women. The age adjusted incidence rate of carcinoma of the breast was found as high as 41 per 100,000 women for Delhi, followed by Chennai (37.9), Bangalore (34.4) and Thiruvananthapuram (33.7) district.[2] Breast cancer survival rates have increased over the last 50 years, as relative survival increased from 75.2% in 1975 to 90.6% in 2008.[3] The 5-year survival rate for women with stage 0/I breast cancer is near to 100%, compared to that of stage II and III, which are 93% and 72% respectively. Women who are diagnosed with metastatic or stage IV breast cancer have a much lower 5-year survival rate of 22%.[4]

An increased understanding of breast cancer has enabled enhanced profiling of different disease subtypes. Subtype classification is essential to decide on the appropriate treatment regime. Breast tumors are grouped according to the expression of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2). An approximately 75% of all breast cancer tumors are diagnosed to be HR positive (HR+) which grow in response to increased levels of the hormones estrogen and progesterone. HER2 positive (HER2+) breast tumors grows more aggressively than HER2 negative (HER2-) tumors and represent around 15% of all breast tumors.[5] The standardized incidence rates of HR+/HER2- breast cancer was 75.21 per 100,000 women in 2012 across the world which accounted for 67.3% of all subtypes.[6]

Over the past few decades, hormonal therapies such as letrozole and fulvestrant have emerged as the preferred treatment for HR+ breast cancers. Following the success of the phase II PALOMA (Palbociclib: Ongoing Trials in the Management of Breast Cancer)-1 trial, the United States Food and Drug Administration (USFDA) granted accelerated approval of the CDK4/CDK6 inhibitor palbociclib that causes cell cycle arrest to be used in combination with letrozole to treat advanced/metastatic HR+/HER2- post-menopausal breast cancer, making it the first CDK 4/6 inhibitor approved in breast cancer. The PALOMA-1 trial demonstrated median progression-free survival of 20.2 months for post-menopausal patients with advanced/metastatic HR+/HER- breast cancer receiving letrozole in combination with palbociclib vs. 10.2 months in patients receiving letrozole and placebo.[7] The follow up phase III PALOMA-2 trial demonstrated median progression free survival of 24.8 months for post-menopausal patients with advanced/metastatic HR+/HER- breast cancer receiving letrozole in combination with palbociclib vs. 14.5 months in patients receiving letrozole and placebo.[8]

In October 2016, palbociclib was granted approval to be used in combination with fulvestrant by the USFDA. This was following the success of the Phase III PALOMA-3 trial, conducted in patients with advanced/metastatic HR+/HER- breast cancer that had relapsed or progressed during endocrine therapy. The PALOMA-3 trial demonstrated a median progression-free survival of 9.5 months in those receiving fulvestrant in combination with palbociclib vs. 5.6 months in patients receiving fulvestrant with placebo.[9]

Palbociclib in combination with letrozole was approved in August 2016 by the Central Drugs Standard Control Organization (CDSCO) for the treatment of postmenopausal women with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer as initial endocrine- based therapy for their metastatic disease. Palbociclib was also granted approval to be used in combination with fulvestrant in December 2017 by the CDSCO for the treatment of HR+/HER2- advanced or metastatic breast cancer in women with disease progression following endocrine therapy.

Palbociclib has been approved in India for over 3 years, based on the results of 3 multinational PALOMA trials, but significant data on the clinical utility of palbociclib combination in routine clinical practice and outcomes associated with palbociclib use are not available. Therefore, real world data on the characteristics, treatment patterns and clinical outcomes among patients receiving palbociclib combinations to treat HR+/HER- ABC/MBC will provide valuable insight to help inform treatment decisions.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this real-world study is to describe patient demographics, clinical characteristics, treatment patterns and clinical outcomes of adult female patients who have received palbociclib combination treatments for HR+/HER2- ABC/MBC in real world settings in India:

- Palbociclib in combination with aromatase inhibitor (as prescribed by the Physician) for the treatment of postmenopausal women with HR+/HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

- Palbociclib for the treatment of hormone receptor HR+/HER2- advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy.

Primary objectives

- To describe the demographics and clinical characteristics of patients who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy.

- To summarize adjuvant therapies received for the treatment of early or locally advanced breast cancer (Stages 0-IIIa).

- To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use.

- To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice.

- To describe supportive therapies received by patients while receiving palbociclib combination treatments.

- To determine in overall population and defined subgroups, clinical outcomes including (but not limited to):

    - Proportion of patients who are progression free at specific intervals (eg, 6, 12, 18 months).

    - Objective response rate (ORR) - depending on availability of follow-up data.

    - Proportion of alive patients 1 and 2 years post palbociclib combination initiation - depending on availability of follow-up data (sample size permitting).

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9. RESEARCH METHODS

9.1 Study Design

This is a post marketing, retrospective, non-interventional study (NIS). The study will be conducted as a retrospective medical record review of patients who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy. It will comprise of an initial screening and eligibility assessment of patients followed by data collection from eligible patient records.

Data collection will be conducted using a predesigned electronic case report form (eCRF). Eligible physicians will be invited to complete the eCRF of patients that meet the study criteria. Each eCRF will take around 25 minutes to complete. Patient eligibility will be confirmed by treating physicians. In order to allow for a sufficiently long observational window, treating physicians will be asked to go back to a specific point in time, the index date, and sequentially select the medical records of the next 'n' patients who meet the inclusion criteria. The 'index date' will be defined as 60 days after the physician first prescribed palbociclib + partner therapy following the availability of specific indication in the market (eg, if palbociclib + aromatase inhibitor was available on 25 October 2016 in India and the physician initiated a patient on palbociclib with aromatase inhibitor the next day, the index date will be 26 December 2016). The index date will differ for the specific indications/combination partners if approved on different dates.

The proportion of patients treated in accordance with the first line versus second or later line setting for metastatic disease will be approximately 7:3, as has been observed in the real world practice.

The advantage to a retrospective medical record review approach over a database analysis is that of being designed specifically to collect data that fulfils the study objectives. Thus, it readily collects and informs on all key drug related clinical outcome measures of critical importance to this study, in a consistent manner, across countries. The resulting data set enables direct comparisons across markets, delivering in turn greater confidence in the reliability of conclusions drawn from the research. An additional advantage of this approach lies in the ability to obtain information that only the treating physician may be aware of, such as the reasons for treatment switches or discontinuations or more perceptive questions that rely on the physicians' professional opinion.

9.2 Setting

Data will be collected from approximately 10 physicians recruited across India. Each physician will complete at least 10-15 eCRFs. Data will be collected retrospectively at a single point in time from patient medical records.

Initial screening questions/recruitment criteria will ensure the relevant physicians are selected and all other non-qualifying physicians will be excluded. In addition, during physician recruitment a representative geographical split and private/public practice split will be sought where possible to ensure a representative sample.

To be eligible, physicians must have treated or be treating 10 or more HR+/HER2- ABC/MBC patients who meet the eligibility criteria for the study. This will ensure that recruited physicians will be able to complete the minimum number of eCRFs required to participate in the study. Once physicians have been recruited, they must go back to a specific index date, defined in Section 9.1 and select the next number of eligible patient records from patients who have been treated with a palbociclib combination. The consecutive approach to recruitment will be stressed to each participating physician to limit selection bias.

Each participating physician and patient must meet the following criteria to be eligible for the medical record reviews.

9.2.1 Inclusion Criteria

Physician inclusion criteria

- Oncologist.
- Responsible for treating ≥ 10ABC/MBC patients who meet the eligibility criteria.
- Agrees to participate in the study and complete the eCRFs within the data collection period.

Patient inclusion criteria

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

- ≥18 years old females.
- HR+/HER2- breast cancer diagnosis with confirmed metastatic or advanced disease.
- Received palbociclib with aromatase inhibitor (as prescribed by the Physician) as initial endocrine therapy in postmenopausal MBC patients or with fulvestrant in patients who have progressed on prior endocrine therapy

- Patients on LHRH agonists for ovarian function suppression in pre- or perimenopausal stage only if prescribed palbociclib with fulvestrant.
- No prior or current enrolment in an interventional clinical trial for ABC/MBC.
- Minimum of 3 months of follow up data since palbociclib with fulvestrant initiation, or minimum of 6 months of follow up data since palbociclib with aromatase inhibitor initiation.

9.2.2 **Exclusion criteria**

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

- Cancers other than breast cancer
- Male breast cancer
- Indications other than mentioned in the protocol
- Visceral crisis

Overall, physicians will capture data from approximately 150 patients on demographics, clinical characteristics, disease history, treatment history, palbociclib dosing, clinical outcomes and post-palbociclib combination therapy treatment data. The study will be descriptive in nature therefore no control or comparator groups will be included.

9.3 Variables

Table 1. List of Study Variables

Variable	Role	Data Source(s)	Operational Definition
Patient demographics	Baseline Sub-group identifier	Patient records	Age, ethnicity, weight, height, biomarker status, family history of breast cancer.
Clinical characteristics	Baseline Sub-group identifier	Patient records	Time since diagnosis, staging, node status, menopause status. ECOG/Karnofsky functional status, diagnosis for which palbociclib combination was prescribed, sites of metastases, de novo vs. recurrent disease.
Comorbid conditions	Baseline Sub-group identifier	Patient records	Comorbid conditions.
Early treatment history	Baseline Sub-group identifier	Patient records	Adjuvant treatments received since breast cancer diagnosis, time since end of adjuvant treatment, surgery/radiotherapy received.
Advanced treatment history	Baseline Sub-group identifier	Patient records	Treatments and supportive therapies received since metastatic/advanced HR+/HER2- diagnosis, duration of treatments, reasons for regimen changes.
Palbociclib combination treatment	Exposure Sub-group identifier	Patient records	Starting dose, duration of treatment, line of treatment, changes in dose, interruptions, cycle delays and discontinuations; where possible reasons for change in treatment.
Clinical outcomes	Outcomes	Patient records	Proportion progression free, ORR, TTP, PFS, patient death, 1-year and 2-year survival in all patients and within specific subgroups.

9.4 Data Sources

Medical records collected through routine clinical care will be used as the data source for the study.

9.5 Study Size

The study will recruit approximately 10 physicians from the routine clinical practices in India who will capture data from a total of approximately 150 patients.

Table 2. Sample Size for Medical Record Review

City	Approximate Number of Physicians	Number of Patient Records
Mumbai	1	20
Pune	1	10
Delhi	2	40
Bangalore	2	20
Kolkata	1	10
Vellore	1	10
Jaipur	1	20
Chennai	1	20
Total (approximate):	**10**	**150**

The sample size above (city, physician number per city, number of patient records and total samples) should be considered flexible, with scope to increase based on availability of medical records with each participating physician/site.

The objectives do not state any hypotheses and therefore, do not require any statistical testing. All the analyses will be descriptive and so sample size calculations are not required.

9.6 Data Management

Physician reported data from the eCRF will be transferred to a single electronic data capture (EDC) tool. All data will be de-identified and anonymized. Incomplete data may be excluded from analysis following discussion with Pfizer. Any data related queries/ ambiguities will be resolved in consultation with physician.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. Patient confidentiality will be strictly maintained.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

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.

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

9.6.2. 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, e.g., CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records

should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., 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.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless IQVIA and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years 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.

9.7 Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (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.

All analyses are to be descriptive and so all methods to be used will reflect this descriptive nature. The specific method that will be used depends on type of variable being analyzed and those methods are:

- Categorical variables – will be described using:
    - Number of observations (n);
    - Number and percent (%) within each category;
    - Number of missing observations.
- Numeric variables – will be described using:
    - Number of observations (n);
    - Mean & Standard deviation;
    - Minimum, Maximum, Median and 1st & 3rd Quartiles;
    - Number of missing observations.

- Time to event – will be described using:
    - A Kaplan-Meier chart that will visually estimate the distribution of times to some events, eg, progression, and will consider those patients for which the event has not yet occurred;
    - 1-year and 2-year rates, median or some more appropriate percentiles if the median time is not reached in the sample.

Missing data will be excluded on a case by case basis and will not be imputed. This will mean that each table will not necessarily be based on the same number of patients.

All statistical analyses will be conducted with general purpose statistical software (SAS) version 9.0 or higher


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9.8 Quality Control

To improve data quality the following actions will be undertaken:

- Provision of standardized instructions on study design, methodology and procedures.
    - Physicians will be contacted via email or telephone and an overview of the study will be provided (detailing study objectives, patient inclusion criteria, correct completion of eCRF and interview and any other logistical aspects of the study).
    - Follow-up with the physicians to ensure queries are resolved quickly.
- The electronic materials will be tested thoroughly to ensure that all questions appear correctly on screen, allow easy interpretation/completion and that all routing and logic checks are working correctly. As such, there should be no missing data (given the online nature of the study, the physician will have to complete a question before he/she is able to move on the next) however, 'don't know or unknown' will be valid responses.
- To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF. All corrections will be visible from the systems audit trail.
- No regular monitoring or source data verification is planned in this study. However, in case of decreasing compliance (ie, of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

9.9 Limitations of the Research Methods

A key limitation of a study of this nature is the reliance on accurate, complete eCRFs; which is dependent on the correct completion of the study materials and the availability of a detailed, complete patient records. We have outlined several important quality control steps to be taken as part of the study procedures to minimize the impact of this. Notably, to reduce the administrative burden on all physicians, the materials will be as short and user-friendly as possible.

The representativeness of the sample is limited to the consulting population for participation, who has been previously prescribed palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy. We will not collect data from patients from non-participating physicians, thus introducing a potential selection bias. To minimize the risk of bias, multiple physicians will be recruited from a diverse geographical spread and mixed private/public practice where possible. To eliminate any patient identification bias during data collection a systematic patient selection criterion will be included and stressed to each participating physician. This will be further defined in the

eCRFs, but will consider the date of palbociclib approval for each indication. Patients who received palbociclib prior to approval or any other indication other than mentioned in the protocol will not be represented in this study.

Due to the observational design of the study, treatments received by patients may be subject to a channeling bias and thus must be interpreted with caution.

9.10 Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. 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 the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

Hence, the study will be submitted to institutional review board (IRB) of respective participating sites for methodological review or an independent ethics committee (IEC) for sites with no IRB. In addition, an IRB exemption will be sought on the basis that the study will collect only secondary data, no protected health information (PHI) will be collected and all data will be de-identified.

10.4 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 (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the chart record form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form;

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your reporting responsibility (YRR) Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A comprehensive study report will be written on completion of study. The reports will incorporate methodology, sample, analyses, tables of results and summaries. All documents used throughout the study will be contained within the report as appendices. Results of this study may be submitted to conferences and journals for publication. As per Pfizer's requirements, the project will only be considered complete upon delivery of the full study report and close of all study publications.

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

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable