TREATMENT PATTERNS AND CLINICAL OUTCOMES AMONG PATIENTS RECEIVING PALBOCICLIB COMBINATIONS FOR HR+/HER2- ADVANCED/METASTATIC BREAST CANCER IN REAL WORLD SETTINGS

[redacted]

STUDY INFORMATION

Title	**Treatment Patterns and Clinical Outcomes Among Patients Receiving Palbociclib Combinations For Hr+/Her2- Advanced/Metastatic Breast Cancer in Real World Settings**
Protocol number	A5481090
Protocol version identifier	Version 2.0
Date of last version of protocol	25 Nov 2019
Active substance	L01XE33 Palbociclib
Medicinal product	Ibrance (palbociclib)
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 in line with locally licensed indications in real world settings across multiple countries. **Primary objectives** • To describe demographics and clinical characteristics of patients who have received palbociclib combination treatment in line with locally approved indications. • To describe 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, 3, 6, 12, 18 months);
	  • Objective response rate (ORR) - depending on availability of follow-up data;
	  • Proportion of patients alive after 1 and 2 year post palbociclib combination initiation (sample size permitting) - depending on availability of follow-up data.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC/MBC	advanced/metastatic breast cancer
AE	adverse events
AEM	adverse events monitoring
CDK	cyclin-dependent kinase
DFI	disease free interval
ECOG	eastern cooperative oncology group
eCRF	electronic case report forms
EMA	European Medicines Agency
EU	European Union
FTP	file transfer protocol
FTP	file transfer protocol
GPP	good pharmacoepidemiology practices
HER2-	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
IEC	Independent Ethics Committee
IRB	International Review Board
ISPE	International Society for Pharmacoepidemiology
LHRH	luteinizing hormone-releasing hormone
NIS	non interventional study
ORR	objective response rate
PFS	progression free survival
PHI	protected health information
SAP	statistical analysis plan
CCI	[redacted]
UK	United Kingdom
US	United States

[redacted]

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

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

Rationale and background: Breast cancer is a major cause of cancer-related death in females worldwide. Hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the most commonly diagnosed subtype accounting for around 73% of all diagnosed breast cancers. Palbociclib is a first in class CDK4/6 inhibitor that has been approved for use in HR+/HER- advanced/metastatic breast cancer (ABC/MBC) patients in a number of indications on the basis of efficacy demonstrated in three pivotal clinical trials; PALOMA-1 and PALOMA-2 (initial endocrine-based therapy) and PALOMA-3 (after progression following endocrine therapy). As a result of the recent approvals there is a need to understand the real world usage and clinical outcomes of patients receiving palbociclib in order to inform future treatment decisions. This study has been previously conducted in the US and Argentina with an additional 'interim' chart review conducted in Germany whereby no long term clinical outcomes were collected.

Research question and objectives: The primary objectives of this study are to describe the patient demographics, clinical characteristics, treatment patterns, and clinical outcomes of adult female patients who have received palbociclib combination treatments in line with locally licensed indications in real world settings across multiple countries.

Study design: This retrospective physician based medical record review will collect data from medical records of patients, who have received palbociclib combination in line with locally approved indications in 13 countries globally (data collection in four countries, US, Argentina and "interim" German data in 2018 and Canada and Germany "core" data in 2019 have already been conducted). In countries where palbociclib has been on the market for a sufficient period of time and therefore sufficient follow-up data are available, a one-time review of patient's medical records will be conducted. The study composed of two data collection phases, a core medical record review and an interim medical record review. The core study will be conducted across all markets whereby all variables collected, including sections relating to clinical outcomes (progression free rates, survival rates, best response etc.). The interim study will collect all data except the clinical outcomes due to lack of follow up time (ie, time since palbociclib approval was not long enough ago in some markets for sufficient follow up time to collect clinical outcomes data). The interim study was conducted in Germany in 2018 and is not planned for additional markets.

Population: Data will be collected from France, Italy, UK, Switzerland, Belgium, Spain, Netherlands, Portugal and Japan, with approximately 15-60 oncologists or gynecologists recruited per country. To be eligible to participate physicians must have treated or be treating a minimum of 2 or more (dependent on country) HR+/HER2- ABC/MBC patients who meet the eligibility criteria for this study. Each physician will complete between 3-14 electronic case report forms (eCRFs). Previously, data has been collected in the US

(65 oncologists providing 652 eCRFs), Argentina (41/162), Canada (33/259) and Germany core (35/251). In addition, an interim data collection was completed in Germany (whereby clinical outcomes were not collected due to lack of follow up data) with 42 physicians providing 257 eCRFs. Including previous data collection in the US, Argentina, Germany and Canada, it is expected that approximately 476-486 physicians will be recruited, this will enable data to be collected for approximately 3131 patients overall.

Recruited physicians must go back in their records to the specific index date and select the next n number of eligible patient records from patients who have been treated with a palbocicib combination. 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 female, aged 18 or over, have been diagnosed with HR+/HER2- ABC/MBC and must have received palbociclib combination in line with locally approved indications. For the core study, patients must have initiated palbociclib with fulvestrant a minimum of three months, or palbociclib with letrozole/aromatase inhibitor a minimum of six 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 (core medical record review only) and time since deceased (no. of days) if applicable.

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

Study size: For the core study up to approximately 476-486 physicians will be recruited, this will enable data to be collected for approximately 3131 patients. Approximately 30- 40 physicians will be recruited collecting 240-250 eCRFs each in Italy, France, Spain, and the UK. For Belgium and Netherlands, 15 physicians will be recruited collecting 150 and 60 eCRFs per country respectively. Approximately 20 physicians will be recruited in Switzerland collecting 100 eCRFs and 50 physicians recruited in Japan to complete approximately 150 eCRFs. Approximately 20 physicians will be recruited in Portugal collecting 100 eCRFs. For the US study 652 eCRFs were collected from 65 physicians, whilst in Argentina 162 eCRFs were collected from 41 physicians. For the German interim review 42 physicians were recruited with 257 eCRFs completed and for the German core study 35 physicias were recruited completing 251 eCRFs. In Canada, 33 physicians completed 259 eCRFs.

Data analysis: All analyses will be descriptive in nature. Categorical variables will be described using the number of observations, number and percent (%) in each category, and number of missing observations. Numeric variables will be described using the number of observations, mean and standard deviation, and minimum, maximum, median, interquartile range, and number of missing observations. Time to event will be described using a Kaplan-Meier chart or the median.

[redacted]

Milestones: The medical record review data collection began in April 2017 and should be completed by 2019, however this will depend upon anticipated market approval dates and the required follow-up time for outcomes evidence. The US and Argentina data collection were completed in Q1 2018 with results and subsequent dissemination of data carried out throughout 2018. The German interim medical record review data collection was completed in October 2017. The US and Argentina core report were completed in February 2018. The Germany core and Canada data was completed in June 2019 with the results due for delivery by the end of 2019. Following completion of the core study in all additional markets, the final study report will be written and completed by Q2 2021.

4. AMENDMENTS AND UPDATES

Amendment Number	Date	Substantial or Administrative Amendment	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V1.0	May 06, 2019	Administrative		1. Addition of additional markets in which the research is being conducted in. 2. New Pfizer HEOR project lead. 3. Text amends referring to previous record reviews in the US, Argentina and Germany. 4. Added in clarifying text as requested following Pfizer review to include information on additional markets, indications and more in depth information on methodology. 5. Added references to guidelines on Protection of Human Subjects and AE reporting. Update safety language per the latest SOP.	
v2.0	25 November 2019			6. Increased sample sizes in Germany, Canada, UK, Italy, France, Japan, Belgium. 7. Inclusion of Spain,– sample sizes and indications. 8. Inclusion of countries Netherlands and Portugal.	

5. MILESTONES

Milestone	Planned date
Start of core data collection (US and Argentina data collection completed by January 2018)	April 2017
Start of German interim data collection	September 2017
End of German interim data collection	October 2017
Study Report: US and Argentina report	February 2018
Start of data collection – Canada, Germany (core))	June 2019
Start of data collection – Belgium, Italy, UK, Switzerland, Japan	Q4 2019
Start of data collection – France, Spain, Netherlands, Portugal	Q1 2020
Study Report – All Countries (US, Argentina, Canada, France, Germany, Italy, UK, Switzerland, Belgium, Spain, Netherlands, Portugal and Japan)	Q2 2021

6. RATIONALE AND BACKGROUND

Breast cancer is the most common diagnosed cancer and the most common cause of cancer-related death in females worldwide. There were 1.67 million new cases of breast cancer diagnosed globally in 2012, which equated to 12% of all diagnosed cancers. Out of these new cases 522,000 females died of the disease, which represented 15% of female deaths from cancer in 2012.[1] There is a huge worldwide variation in breast cancer survival rates, ranging from 80% or more in North America, Sweden and Japan to 60% in middle-income countries and as low as 40% in low-income countries.[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 females with stage 0/I breast cancer is near to 100%, compared to that of Stage II and III, which are 93% and 72% respectively. Females 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 in order 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). Overall HR status is the most important biomarker for breast cancer classification, as around 75% of all breast cancer tumors are HR positive (HR+). Tumors that are HR+ grow in response to increased levels of the hormones estrogen and progesterone. HR+ breast tumors are the most favorable, as they respond well to hormone therapies. In contrast HR- breast tumors do not respond well to hormone therapies. These tumors are known to be the most aggressive cancers, in regards to tumor size, grade, stage and patient outcome. HER2 positive (HER2+) breast tumors represent around 15% of all breast tumors. These tumors tend to be more aggressive and faster growing than HER2 negative (HER2-) tumors. HR+/HER2- breast cancer is the most common subtype diagnosed in the US. This subtype accounted for around 73% of diagnosed breast cancer cases in 2010. Around 15-20% of breast tumors do not contain HR or HER2; these are known as triple negative breast cancers.[5]

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-1 trial, the FDA 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. 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.[6] 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.[7] The label has since been expanded to include any aromatase inhibitor in this indication.[8]

[redacted]

In October 2016, palbociclib was granted approval to be used in combination with fulvestrant. 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 10.8 months in those receiving fulvestrant in combination with palbociclib vs. 4.8 months in patients receiving fulvestrant with placebo.[8]

As a result of the recent approval of palbociclib, 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- advanced/metastactic breast cancer (ABC/MBC) will provide valuable insight to help inform treatment decisions.

7. 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 in line with locally licensed indications in real world settings across multiple countries:

Canada/Argentina:

- Palbociclib in combination with letrozole as early endocrine therapy to treat advanced/metastatic HR+/HER2- post-menopausal breast cancer (CAN: May 2016, ARG: December 2015).

- Palbociclib in combination with fulvestrant for the treatment of females with HR+/HER2- ABC/MBC with disease progression following endocrine therapy (CAN: May 2017, ARG: August 2016). In pre- or perimenopausal females, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Across the EU, Switzerland, US and Japan:

- Palbociclib in combination with aromatase inhibitor as initial endocrine based therapy for the treatment of females with HR+/HER2- locally ABC/MBC (EMA: November 2016, Switz: October 2017, US: Feb 2015, updated Mar 2017).

- Palbociclib in combination with fulvestrant for the treatment of females with HR+/HER2- ABC/MBC who have received prior endocrine therapy (EMA: November 2016 Switz: March 2017). In pre- or perimenopausal females, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

[redacted]

- Palbociclib in combination with fulvestrant for the treatment of females with HR+/HER2- ABC/MBC with disease progression following endocrine therapy (US: Feb 2016).

- In patients with inoperable or recurrent breast cancer, approved in combination for 1L => Palbociclib + Letrozole, Approved in combination for 2nd line => Palbociclib + Fulvestrant (Japan).

Primary Objectives

- To describe the demographic and clinical characteristics of patients who have received palbociclib combination treatments in line with locally approved indications.

- To describe 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 multiple intervals (eg, 3, 6, 12, 18 months);

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

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

CCI [redacted]

8. RESEARCH METHODS

8.1. Study Design

This study will be conducted as a retrospective physician based medical record review of patients who have received palbociclib combination in line with locally approved indications. In some countries data may be collected from patients receiving palbociclib combinations before the local reimbursement date, however patients must still be receiving palbociclib combinations in line with the approved indication. The study will comprise of a medical record review conducted in the **US, Canada, Argentina, Italy, UK, France, Germany, Belgium, Switzerland, Spain, Netherlands, Portugal and Japan**. The study design is outlined in Figure 1. The study has been previously conducted in the US, Argentina, Canada with an additional 'interim' record review conducted in Germany (with a minimum of 3 month follow up) whereby no long term clinical outcomes were collected. The core German study is now completed with clinical outcome data.

Data collection will be online via electronic data capture using electronic case report form (eCRF). Eligible physicians will be invited to complete an eCRF for up to between 3-14 patients that meet the study criteria. Each eCRF will take a minimum of 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 + letrozole was available Feb 1, 2015 in the US and the physician initiated a patient on palbociclib+ letrozole the next day, the index date will be April 2, 2015). The index date will differ for the specific indications/combination partners if approved on different dates.

Study materials (ie, the CRF) will be subject to pilot testing with physicians followed by interviews to discuss the length, feasibility, ease of understanding and use, and the relevance to the objectives.

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.

8.1.1. Core Medical Record Review

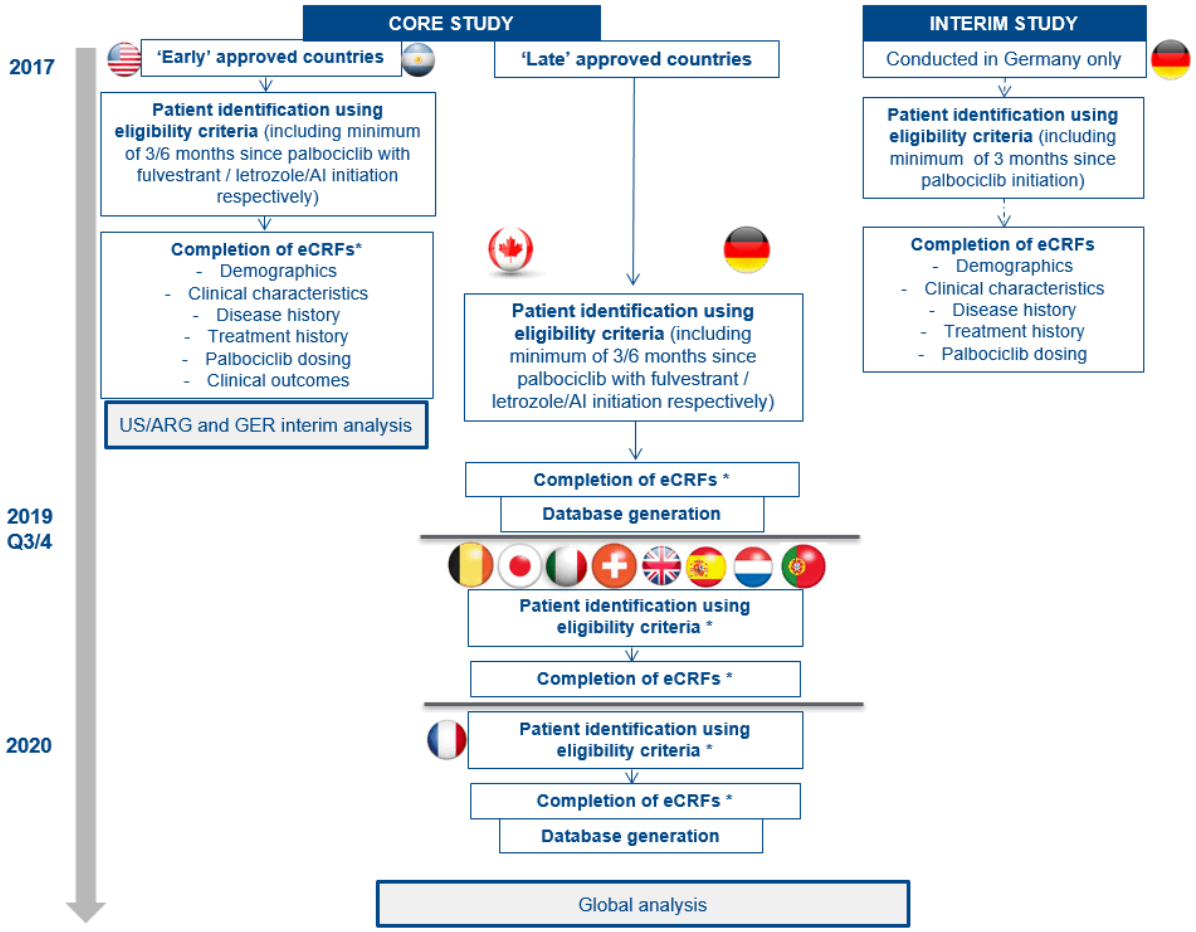
The core medical record review will capture data from approximately 3131 patients on demographics, clinical characteristics, disease history, treatment history, palbociclib dosing, clinical outcomes and post-palbociclib combination therapy treatment data. The study will be descriptive in nature therefore no control or comparator groups will be included.

The core medical record review has already been conducted in the US and Argentina in 2017 and for Germany (core) and Canada in Q3 2019. Palbociclib has only been recently approved for use in the EU, therefore, additional European data collection in Belgium, Italy and the UK for the core medical record review will commence in Q4 2019 and for Spain, Netherlands, Portugal and France in Q1 2020. Similarly, data collection for Switzerland and Japan will commence Q4 2019, depending on the date of approval of palbociclib in each individual country. In some countries data may be collected from patients receiving palbociclib combinations before the local reimbursement date, however patients must still be receiving palbociclib combinations in line with the approved indication. In France patients must have initiated palbociclib combinations post- 01 Jan 2018 to avoid capturing any patient data for those receiving palbociclib combinations via an early access program.

8.1.2. German Interim Medical Record Review

A German interim medical record review was conducted in Germany in October 2017. This interim medical record review allowed for the collection of a number of baseline characteristics data. This study had the same methodology as the core study and an almost identical eCRF, capturing demographics, clinical characteristics, disease history, treatment history and palbociclib dosing for patients receiving palbociclib combination treatment in line with the approved indications. However, appropriate sections from the CRF relating to clinical outcomes associated with palbociclib combination were omitted from the interim eCRF (ie, ORR, CRF, progression free rates and survival rates). A further full core medical review will be conducted in Germany in April 2019 in line with the methodology outline in Section 8.1.1.

Figure 1. Study Design Depicting the Proposed Time Frame for the Medical Record Reviews



8.2. Setting

Upon study completion, data will be collected from 13 countries with approximately 15-60 physicians (oncologists/gynecologists)[1] recruited per country. Each physician will complete between 3-14 eCRFs (country and sample size dependent). 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.

[1] Breast surgeons/general surgeons/gastro-surgeons may also be included as relevant treaters in Japan.

To be eligible, physicians must have treated or be treating two 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. Physicians are recruited by local fieldwork agencies in each market. The recruitment process occurs either via custom lists or a panel approach via telephone or email. In keeping with compliance, physicians must have previously stated their willingness to be contacted to participate in such research. Once physicians have been recruited, they must go back to a specific index date, defined in 8.1, and select the next n 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. Physicians will confirm patient eligibility.

Patient records must meet the following criteria to be eligible for the medical record reviews. They must be female, aged 18 or older and they must have been diagnosed with HR+/HER2- ABC/MBC. Patients must have received palbociclib combination in line with country/locally approved indications. For the core record review, palbociclib and letrozole/aromatase inhibitor must have been initiated a minimum of 6 months prior to date of medical record review, and palbociclib and fulvestrant must have been initiated a minimum of 3 months prior to date of medical record review. This will permit the capture of meaningful clinical outcomes data. For the German interim record review, palbociclib was required to have been initiated a minimum of 3 months prior to data collection regardless of partner therapy.

A full list of the eligibility criteria can be found in 8.2.1.

In order to ensure that sufficient data is captured for each indication, indication quotas will be enforced. This will be determined on a country by country basis.

8.2.1. Inclusion Criteria

Physician inclusion criteria

- Oncologist or gynecologist.[2]
- Responsible for treating a minimum of ≥2-6 (depending on country) ABC/MBC patients who meet the eligibility criteria.
- Agrees to participate in the study and complete the eCRFs within the data collection period.

[2] Relevent treaters on a country level will be included.

Patient inclusion criteria:

- Female.
- ≥18 years old.
- HR+/HER2- breast cancer diagnosis with confirmed metastatic or advanced disease.
- Received palbociclib plus letrozole/aromatase inhibitor or palbociclib plus fulvestrant in line with the licenced indication(s).
- No prior or current enrolment in an interventional clinical trial for ABC/MBC.
- Minimum of three months of follow up data since palbociclib with fulvestrant initiation, or minimum of six months of follow up data since palbociclib with letrozole/aromatase inhibitor initiation (core medical record review).
- Minimum of three months of follow up data since palbociclib initiation (German interim medical record review only).
- Inoperable or recurrent breast cancer (Japan only).

8.2.2. Exclusion Criteria

Physician exclusion criteria:

- Qualified less than 2 years ago or more than 35 years ago.
- Particpated in observational research for ABC/MBC in the last 3 months.
- Have not prescribed either palbociclib plus fulvestrant or palbociclib plus aromatase inhibitor in line with the licenced indication(s).

[redacted]

8.3. 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	Patient status (alive/deceased), time since deceased (no. of days), time since initial BC diagnosis, time since ABC/MBC 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, time from diagnosis palbociclib initiation.
Comorbid conditions	Baseline	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/neoadjuvant 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, changes in dose, interruptions, cycle delays and discontinuations. Where possible reasons for change in treatment. Line of treatment.
Clinical outcomes (**Core medical record review only**)	Outcomes	Patient records	Proportion progression free, ORR, CCI, PFS, 1-yr and 2-yr survival in all patients and within specific subgroups.

8.4. Data Sources

The data source for both core and interim medical record reviews will be patient medical records.

8.5. Study Size

Table 2. Sample Size for Core Medical Record Review

Country	Approximate† Number of Physicians	Number of eCRFs
US (complete)	65	652
Argentina (complete)	41	162
Canada (complete)	33	259
UK	30-40	250
France	40	250
Germany interim (compelte)	42	257
Germany core (complete)	35	251
Italy	30	240
Belgium	15	150
Spain	40	250
Switzerland	20	100
Japan	50	150
Netherlands	15	60
Portugal	20	100
Total (approximate):	**476-486**	**3131**
†Actual no. physicians stated where data collection complete in US, AR, CAN, DE		

The sample size above should be considered flexible, with scope to increase the sample size if feasible. This will be assessed on a country by country basis.

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.

8.6. Data Management

Physician reported data from the eCRF will be transferred to a single electronic database. All data will be de-identified and anonymized. Incomplete data may be excluded from analysis following discussion with Pfizer.

De-identified raw data files will be transferred to Pfizer by a secure file transfer protocol (FTP) site.

Analyses will be conducted in STATA statistical software version 14.1 (StataCorp, 2016. Stata statistical software: Release 14. College Station, TX, StataCorp LP).

8.7. 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 analysed 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 and Standard deviation;
  - Minimum, Maximum, Median and 1st and 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 take into account those patients for which the event has not as yet occurred;
  - 1-yr and 2-yr rates, median or some more appropriate percentiles if the median time is not reached in the sample.

The analyses will be conducted (using the methods above) in a number of phases, as already detailed in the study design section.

1. Non EU countries – all variables (as shown in Section 8.3) will be described.

[redacted]

2. EU countries – selected variables (all shown in Section 8.3 excluding clinical outcomes) will be described.

3. EU countries - all variables will be described.

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.

Subgroup Analysis

Exploratory stratifications will be conducted to explore differences between line of therapy, demographics, treatments, clinical characteristics, baseline co-morbidities or 'responders' and 'non-responders' to treatment, however these will be only descriptive in nature. Responders and non-responders will be defined according to the best recorded response to palbociclib treatment.

Sample size permitting, additional stratifications may include:

- Insurance type.
- Eastern Cooperative Oncology Group (ECOG) Performance status.
- Age.
- Menopausal status.
- De novo vs. recurrent disease.
- Bone only disease.
- Visceral vs. non-visceral metastases.
    - By primary site, eg, liver, lung.
- Burden of metastases (eg, visceral involvement, multiple liver lesions, bilateral vs single lung involvement, presence of pleural effusion).
- Duration of disease free interval (DFI).
- Specific comorbidities.
- Comorbidity index.
- Prior endocrine treatment.

- Treatment sequence.

8.8. Quality Control

To maximize data quality the following 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.
- There will be no monitoring visits or source data verification in this study.

8.9. 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 a number of 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 in line with locally approved indications. We will not collect data from patients from non-participating physicians, thus introducing a potential selection bias. To minimize this multiple physicians will be recruited in each country 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 criteria will be included and stressed to each participating physician. This will be further defined in the eCRFs, but will take into account the date of palbociclib approval for each indication. Patients who received palbociclib prior to approval or off-label are not 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.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. 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.

This study will involve secondary data collection which will include human review of unstructured data. No protected health information (PHI) will be collected and all data will be de-identified. The research poses a minimal risk to patients, will not affect the rights or welfare of the patient and the study would not be feasible should informed consent be required. As a result, informed consent will not be sought for this study.

9.2. Patient Withdrawal

Not applicable.

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

The study will be submitted to a centralized independent IRB board in Europe for methodological review. In addition, a Western 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.

9.4. 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) (https://www.pharmacoepi.org/resources/guidelines_08027.cfm). Compliant with the regulatory details outlines in the external guidance document CT24-WI_GL02-RF04 1.0.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

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 (AEs) 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 eCRF 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:

- *"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.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A global report will be provided on completion of the entire study with additional country specific reports provided in PowerPoint format as and when data collection is included in each market. These reports will incorporate methodology, sample, tables of results and summaries. All documents used throughout the study will be contained within the report as appendices.

In addition to the two study reports, the following slide decks will be produced.

- Country specific slide decks on completion of each market.
- Final reports and publications per market requirement.
- A global slide deck when the entire study is completed.

Additional country specific slide decks will be developed as needed. 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.

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 which 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.

12. REFERENCES

1. Global cancer statistics | Centers for diseases control and prevention [Internet]. [cited 2016 Sep 23]. Available from : http://www.cdc.gov/cancer/international/statistics.htm.

2. Coleman MP et al. (2008). Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol, 9, 730–56.

3. Breast cancer statistics | World Cancer Research Fund International [Internet]. [cited 2016 Sep 23]. Available from: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics.

4. Breast cancer survival rates, by stage | American cancer society [Internet]. [Cited 2016 Nov 30]. Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage.

5. Dai X, Xiang L, Bai Z. Cancer Hallmarks, Biomarkers and Breast Cancer Molecular Subtypes. Journal of cancer. 2016; 7(10):1281-1294.

6. McCain M. First-in-Class CDK4/6 Inhibitor Palbociclib Could Usher in a New Wave of Combination Therapies for HR+, HER2− Breast Cancer. PharmTher.2015 Aug;40(8):511-20.

7. FinnR, Martin M, Rugo H, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925-1936.

8. Full Prescribing Information, IBRANCE [Internet]. Food and Drug Administration; 2017 [cited 2017 Apr 6]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207103s004lbl.pdf.

13. LIST OF TABLES AND FIGURES