TREATMENT PATTERNS AND CLINICAL OUTCOMES AMONG PATIENTS IN LATIN AMERICA RECEIVING FIRST LINE PALBOCICLIB COMBINATIONS FOR HORMONE RECEPTOR POSITIVE/ HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEGATIVE (HR+/HER2-) ADVANCED/METASTATIC BREAST CANCER IN REAL WORLD SETTINGS

Study Information

Title	Treatment Patterns and Clinical Outcomes Among Patients in Latin America Receiving First Line Palbociclib Combinations For hormone receptor positive/ human epidermal growth factor receptor 2 negative (HR+/HER2-) Advanced/Metastatic Breast Cancer in Real World Settings.
Protocol number	A5481125
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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 as first line therapy, regardless of combination partner and labelled use in real world settings across Latin America. <u>Primary objectives</u> To describe demographics and clinical characteristics of patients who have received palbociclib combination treatment as a first line therapy, regardless of combination partner and labelled use. 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, and delays associated with palbociclib use in clinical practice.

	To detail supportive therapies received by patients while receiving palbociclib combination treatment. To determine in overall population and defined subgroups, clinical outcomes including. Proportion of patients who are progression free at specific intervals (eg, 6, 12, 18 months). Objective response rate (ORR). Proportion of patients alive after 1- and 2-year post palbociclib combination initiation (sample size permitting). <u>Exploratory objectives</u> To evaluate time to progression (TTP)/Progression Free Survival (PFS) associated with palbociclib combination treatments – depending on availability of follow-up data.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced Breast Cancer
AE	Adverse Events
AEM	Adverse Event Monitoring
AI	Aromatase Inhibitor
CDK	Cyclin Dependent Kinase
eCRF	Electronic Case Report Form
FDA	Food Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HER2-	Human Epidermal Growth Factor Receptor 2 Negative
HR+	Hormone receptor positive
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRIS	Ibrance Real World Insights
ISPE	International Society for Pharmacoepidemiology
MBC	Metastatic Breast Cancer
NIS	Non-Interventional Study
ORR	Objective Response Rate
PFS	Progression Free Survival
PHI	Personal Health Information
Q1	First Quarter
SAP	Statistical Analysis Plan
TTP	Time to Progression
US	United States
WIRB	Western Institutional Review Board

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Title: Treatment Patterns and Clinical Outcomes among Patients in Latin America Receiving First Line Palbociclib Combinations for hormone receptor positive/ human epidermal growth factor receptor 2 negative (HR+/HER2-) Advanced/Metastatic Breast Cancer in Real World Settings.

Rationale and background: Breast cancer is a major cause of mortality 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 74% 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 several 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 at first line in order to inform future treatment decisions. The Global IRIS study has been previously conducted in the US, Canada, Germany, Belgium, UK, Italy, Spain, Switzerland, Netherlands, Japan, France, Portugal and a previous Latin American wave in Chile, Argentina, Peru, Mexico, Costa Rica, and Panama. Here we aim to replicate the IRIS study in Latin America however only focusing on palbociclib as first line therapy, regardless of combination partner or indication.

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 in the first line setting to treat HR+ /HER2- ABC/ MBC. All use of palbociclib in the first line setting will be captured regardless of combination partner and labelled use.

Study design: This retrospective physician based medical record review will collect data from medical records of patients, who have received palbociclib combination therapy as first line treatment for ABC/MBC, across 7 countries in Latin America. Data collection in 6 countries has already been conducted: Chile, Argentina, Peru, Mexico, Costa Rica, and Panama. 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.

Population: Data will be collected from Colombia with approximately 30-40 oncologists or gynecologists recruited. To be eligible to participate physicians must have treated or be treating 4 or more HR+/HER2- ABC/MBC patients with palbociclib combination therapy in the first line setting. Each physician will complete up to 8 electronic case report forms (eCRFs). Previously data has been collected in Chile (1 oncologist providing 8 eCRFs, Argentina (41/469), Peru (5/30), Mexico (15/99) and Costa Rica (6/35) and Panama (1/6).

Recruited physicians must go back in their records to the specific index date and select the next 'n' 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 female, aged 18 or over, have been diagnosed with HR+/HER2- ABC/ MBC and must have received palbociclib combination as a first line therapy. They also must have a minimum of six months follow up data since palbociclib + aromatase inhibitor initiation and three months follow up data for palbociclib + fulvestrant initiation.

It is expected that approximately 30-40 physicians will be recruited in Colombia to complete 200 eCRFs, combined and with previous data collection in Chile, Argentina, Peru, Mexico, Costa Rica and Panama, it is expected that approximately 99-109 physicians will be recruited in total, this will enable data to be collected for approximately 790-890 patients overall across Latin America.

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 time since deceased (no. of days) if applicable.

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

Study size: Approximately 30-40 physicians will be recruited in Colombia collecting data for approximately 200 patients. In Argentina, Mexico, Costa Rica, Panama, Peru and Chile, 69 physicians were recruited overall, which enabled data to be collected for 647 patients. This sample is in addition to that previously collected in Argentina in wave 1 Global IRIS (162 patient records were collected from 41 physicians, protocol no. A5481090). In Mexico, 15 physicians were recruited collecting 99 eCRFs. Five physicians in Peru collected 30 eCRFs. A total of 7 physicians were recruited across Costa Rica and Panama with a sum of 41 CRFs. In Chile 1 physician was recruited collecting a total of 8 eCRFs.

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 or the median.

Milestones: The medical record review data collection began in June 2019 and was completed by September 2019 for Argentina, Mexico, Costa Rica, Panama, Peru and Chile. Medical record review collection for Colombia is due to begin August 2020 and should be completed by October 2020; however this will depend upon market approval dates and the required follow-up time for outcomes evidence. Following completion of data collection in all markets, the final study report will be written and completed by December 2020.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	16 April 2019	Administrative		1. Added references to guidelines on Protection of Human Subjects and AE reporting. 2. Update to text in the MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS section to align with Pfizer SOPs.	Alignment with the Global IRIS protocol.
2.0	13 August 2020	Substantial	*4, 5, 6, 7, 8, 9, 10, 11, 12*	1. Addition of Colombia.	To expand the scope of data collection and include a wider geographic region within Latin America.

5. MILESTONES

Milestone	Planned date	Actual date completed
Start of data collection (Costa Rica and Panama, Chile, Peru, Mexico and Argentina)	Q1/Q2 2019	01 June 2019
End of data collection	Q2/Q3 2019	30 September 2019
Study Report – All Countries (Costa Rica and Panama, Chile, Peru, Mexico and Argentina)	Q3 2019	01 November 2019
Start of Colombia data collection	August 2020	
End of Colombia data collection	October 2020	
Final study report – all markets	December 2020	

6. RATIONALE AND BACKGROUND

Breast cancer is the most common diagnosed cancer and the most common cause of cancer-related death in females worldwide; Latin America is no exception. There were 1.67 million new cases of breast cancer diagnosed globally in 2012, which equated to 12% of all diagnosed cancers.[1] Out of these new cases 522,000 women died of the disease, which represented 15% of female deaths from cancer in 2012.[1] In Latin America, an estimated 114,900 women are diagnosed with breast cancer every year and 37,000 die of the disease in the region.[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] Even though mortality rates from breast cancer have been in decline during recent years, the mortality rate is higher in Argentina (17.56 per 100 000 women in 2012) than in most other Latin American countries, as well as some other European and North American countries.[1,3,4]

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%.[5]

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. 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 breast cancer subtype in Argentina, affecting 70% of patients.[6] Around 15-20% of breast tumors do not contain HR or HER2; these are known as triple negative breast cancers.[7]

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.[8] 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.[9] The label has since been expanded to include any aromatase inhibitor in this indication.[10]

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.[10]

The Global IRIS (Ibrance Real World Insights) study was the first multi-country retrospective chart review of women treated with palbociclib-based regimens according to approved indications in real-world clinical practice, aiming to describe their demographic and clinical characteristics, treatment patterns, and to assess clinical outcomes.[11] The Global IRIS study has already been conducted in North American and European markets, and was completed in February 2020, and a first wave of Latin American data was completed in September 2019.Previously data were also collected in Argentina as part of the IRIS Global study, for palbociclib + aromatase inhibitor and palbociclib + fulvestrant received as per the labelled indication across all lines of therapy, not solely restricted to first line treatment.[12-15] There remains a need to understand the wider use of palbociclib across further Latin American markets, in addition to understanding the complete picture of first line use, regardless of label.

There is currently scarce information, and limited follow up data, regarding palbociclib use in routine clinical practice at the first line, and associated outcomes, as a result of the recent approval of palbociclib in Latin America. Therefore, real world data on the characteristics, treatment patterns and clinical outcomes among patients receiving palbociclib combinations to treat HR+/HER- ABC/ MBC at first line, regardless of combination partner or labelled use, 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 as first line therapy, regardless of combination partner and labelled use:

Argentina:

- Palbociclib in combination with letrozole as early endocrine therapy to treat advanced/metastatic HR+/HER2- post-menopausal breast cancer (ARG:14th December 2015);

- Palbociclib in combination with fulvestrant for the treatment of women with HR+/HER2- ABC/MBC with disease progression following endocrine therapy (ARG: 16th August 2016).

Chile:

- Palbociclib in combination with letrozole as initial endocrine-based therapy for the treatment of postmenopausal women with HR+/HER2- locally ABC/MBC (June 2015);

- Palbociclib in combination with fulvestrant for the treatment of woman with HR+/HER2- ABC/MBC with disease progression following endocrine therapy (June 2015).

Colombia:

- Palbociclib in combination with letrozole as initial endocrine therapy to treat advanced/metastatic HR+/HER2- ABC/MBC in post-menopausal women (November 2018);

- Palbociclib in combination with fulvestrant for the treatment of women with HR+/HER2- ABC/MBC with disease progression following prior endocrine therapy (November 2018).

Costa Rica:

- Palbociclib in combination with aromatase inhibitor for the treatment of women with HR+/HER2- locally ABC/MBC (August 2016);

- Palbociclib in combination with fulvestrant for the treatment of woman with HR+/HER2- ABC/MBC who have received prior endocrine therapy (August 2016).

Panama:

- Palbociclib in combination with aromatase inhibitor as initial endocrine based therapy in postmenopausal women with HR+/HER2- locally ABC/MBC (July 2017);

- Palbociclib in combination with fulvestrant for the treatment of women with HR+/HER2- ABC/MBC with disease progression following endocrine therapy (July 2017).

Perú:

- Palbociclib in combination with aromatase inhibitor as initial treatment with endocrine basis for post-menopausal women with HR+/HER2- locally ABC/MBC (May 2016);

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

Mexico:

- Palbociclib in combination with letrozole as initial endocrine therapy in postmenopausal women with HR+/HER2- locally ABC/MBC (June 2016);

- Palbociclib in combination with fulvestrant for the treatment of woman with HR+/HER2- ABC/MBC who have received prior treatment (June 2016).

7.1. Primary Objectives

- To describe the demographic and clinical characteristics of patients who have received palbociclib combination treatments as first line treatment, regardless of combination partner and labelled use.

- 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 clinical outcomes including (but not limited to).

    - Proportion of patients who are progression free at multiple intervals (eg, 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 - depending on availability of follow-up data.

7.2. Exploratory Objectives

- To evaluate time to progression (TTP)/Progression Free Survival (PFS) associated with palbociclib combination treatments – depending on availability of follow-up data.

8. RESEARCH METHODS

8.1. Study Design

This study will be conducted as a retrospective medical record review of patients who have received palbociclib combination treatments as first line treatment regardless of combination partner and labelled use. Upon completion, the study will comprise of a medical record review conducted in Argentina, Chile, Peru, Mexico, Colombia and a combined sample in Costa Rica and Panama. Data collect for Argentina, Chile, Peru, Mexico, Panama and Costa Rica were completed in September 2019, data collection for Colombia is due in August 2020. The study design is outlined in Figure 1. The study design is similar to the IRIS Global study previously conducted (protocol no. A5481090).[10,11]

Data collection will be online via electronic data capture using electronic case report form (eCRF). In Colombia eligible physicians will be invited to complete an eCRF for between 6-8 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 + letrozole was available Dec 14, 2015 in Argentina and the physician initiated a patient on palbociclib+ letrozole the next day, the index date will be Feb 12, 2015). The index date will differ for the specific indications/combination partners if approved on different dates. Approval dates can be found in Section 6.

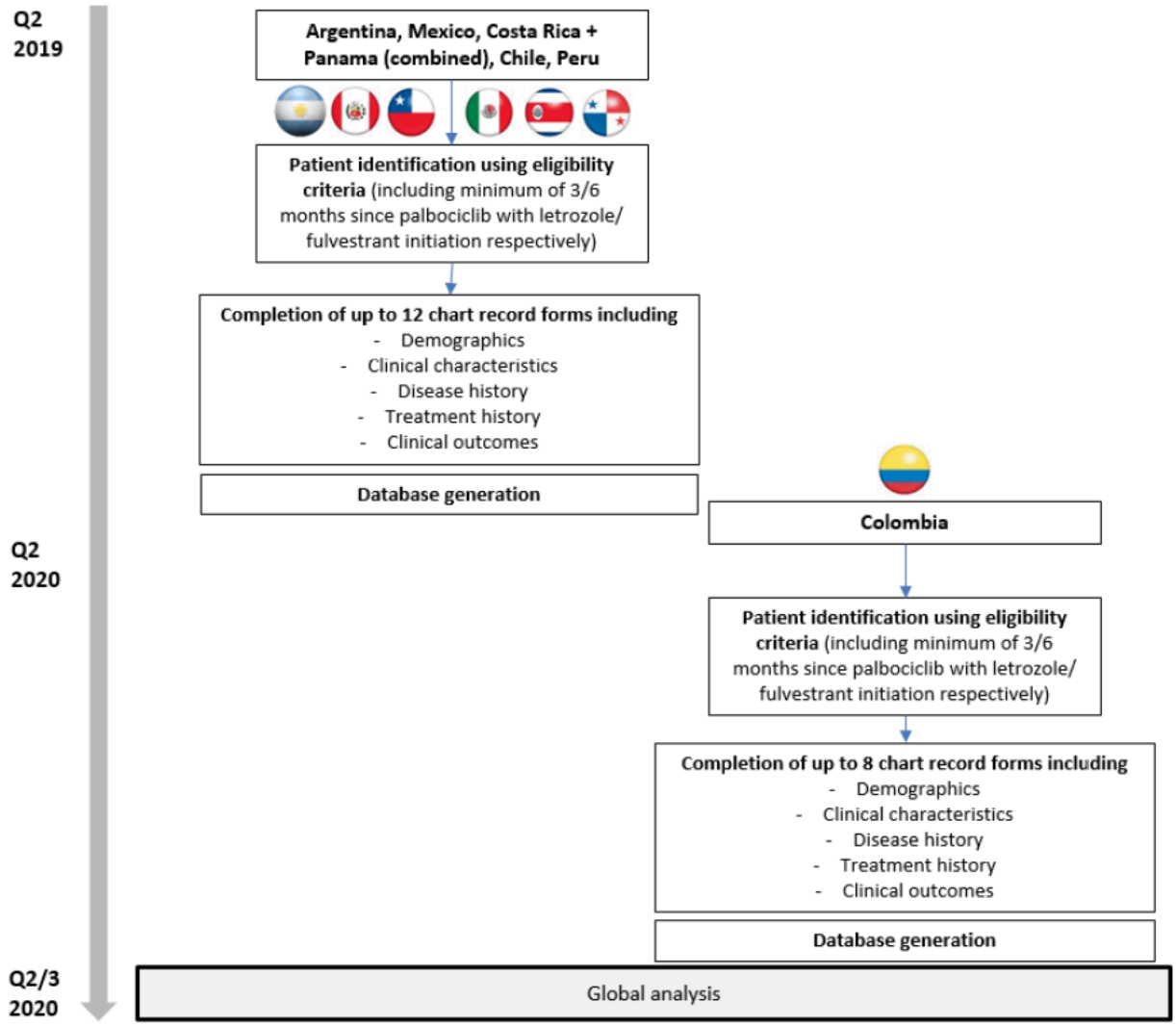
The advantage to a retrospective medical record review approach over a database analysis is that of being designed specifically to collect data that fulfils the study objectives. Thus, it readily collects and informs on all key drug related clinical outcome measures of critical importance to this study, 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 physician's professional opinion.

8.1.1. Medical Record Review

Upon study completion the medical record review will capture data from approximately 790-890 patients on demographics, clinical characteristics, disease history, treatment history, palbociclib dosing, clinical outcomes and post-palbociclib combination therapy treatment data (n=647 already achieved, approximately n=200 expected). The study will be descriptive in nature therefore no control or comparator groups will be included.

Data collection in Argentina, Chile, Costa Rica and Panama, Peru and Mexico has already been conducted between July – September 2019. Data collection in Colombia is planned in August 2020.

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 7 countries. Approximately 30-40 physicians will be recruited in Colombia. Data will be collected retrospectively at a single point in time from patient medical records. To date, 6 physicians in Costa Rica, 1 in Panama, 1 in Chile, 15 in Mexico, 41 in Argentina and 5 in Peru completed eCRFs.

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

To be eligible, physicians must have treated or be treating four 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 7.1, 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, over 18 years of age and they must have been diagnosed with HR+/HER2- ABC/MBC. Patients must have received palbociclib as a first line therapy. For the chart review, palbociclib and letrozole/aromatase inhibitor must have been initiated a minimum of 6 months prior to date of medical chart review, and palbociclib and fulvestrant must have been initiated a minimum of 3 months prior to date of medical chart review. This will permit the capture of meaningful clinical outcomes data.

A full list of the eligibility criteria can be found in Section 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.
- Responsible for treating ≥4-10 (depending on country) ABC/MBC patients who meet the eligibility criteria.
- Agrees to participate in the study and complete the CRFs within the data collection period.

Patient inclusion criteria:

- ≥18 years old.
- HR+/HER2- breast cancer diagnosis with confirmed metastatic or advanced disease.
- Received palbociclib as a first line therapy.
- 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.

8.2.2. Exclusion Criteria

Physician exclusion criteria:

- Qualified less than 2 years ago or more than 35 years ago.
- Participated in observational research for ABC/MBC in the last 3 months.
- Have not prescribed either palbociclib plus fulvestrant or palbociclib plus aromatase inhibitor as first line therapy.

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	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	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.

Variable	Role	Data Source(s)	Operational Definition
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.
Clinical outcomes	Outcomes	Patient records	Proportion progression free, ORR, TTP, PFS, 1-yr and 2-yr survival in all patients and within specific subgroups.

8.4. Data Sources

The data source the medical record reviews will be patient records.

8.5. Study Size

Table 2. Sample Size for Medical Record Review

Country	Approximate Number of Physicians*	Number of Patient Records
Argentina (complete*)	41	469
Mexico (complete*)	15	99
Chile (complete*)	1	8
Costa Rica + Panama (complete*)	7	41
Peru (complete*)	5	30
Colombia	30-40	200
Total (approximate):	**99-109**	**790-890**
*Actual number of physicians/records where country complete		

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 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 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 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.

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.

8.8. SUBGROUP ANALYSIS

Exploratory stratifications will be conducted to explore differences between, 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:

- Analysis by country.

8.9. 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 where appropriate by the third party fieldwork agency, 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.

8.10. Limitations of the Research Methods

A key limitation of a study of this nature is the reliance on accurate, complete CRFs; 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 as first line therapy only. 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 CRFs, but will take into account the date of palbociclib approval for each indication. Patients who received off-label palbociclib are also 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.

8.11. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

The study will be submitted to a centralized independent IRB board for methodological review. The study will collect only secondary data, no protected health information (PHI) will be collected and all data will be de-identified. The centralized review is consistent with the Global IRIS study (WIRB approved number: 1256297).

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

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

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 party responsible for collecting data from the participant 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.

A global Word report will be provided on completion of the entire study and analysis provided in PowerPoint format. 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.

Additional country specific slide decks can be developed if required (additional fee). 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.

12. 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.

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14. LIST OF TABLES & FIGURES

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.