Job bag number: REF-IBR6928, date of preparation October 2018

Study information

Title	Observational cohort study of patients with hormone receptor-positive metastatic breast cancer treated with palbociclib (Ibrance®) as part of the United Kingdom Ibrance® Patient Program (IPP); the Real Outcomes Ibrance® Study (ROIS)
Protocol number	X9001194
Protocol version identifier	1.0 Final
Date	12 November 2018
Active substance	Palbociclib - L01XE33
Medicinal product	Ibrance®
Research question and objectives	What are the real-world treatment patterns, patients' characteristics, clinical outcomes and healthcare resource utilisation associated with palbociclib treatment in the 3 years following initiation in United Kingdom patients with hormone receptor-positive, human epidermal growth factor 2-negative metastatic breast cancer treated as part of the IPP? **Primary objectives:** • To describe patient demographic and clinical characteristics at initiation of palbociclib. **Secondary objectives:** • To describe treatment pattern (as per licence/IPP requirement); including the proportion of patients with dose modification

	and who switch treatment 1, 2 and 3 years after palbociclib initiation, and median time to dose modification and treatment discontinuation ('drug survival'). For patients who progress, to describe the 1st/2nd /3rd line of treatment after progression. • To describe overall survival and progression-free survival, response (complete response, partial response), stable disease. This includes estimating the proportion of patients achieving those endpoints at 1, 2 and 3 years following palbociclib initiation; median survival, time to response and duration of response. In patients who respond to treatment, to describe partial response and complete response using "swimmer plots". • To describe the occurrence of neutropenia during the first year post-initiation observation period. • To describe the occurrence of gastro-intestinal toxicity, including diarrhoea, nausea and vomiting during the first year post-initiation observation period. • To describe progression of clinical indicators, including biochemical and radiological indicators at each time-point available during the first year following palbociclib treatment initiation (e.g. full blood counts, liver function tests, bone profile). • To describe breast cancer related healthcare resource utilisation (hospital admissions, outpatient visits, calls to Cancer National Services and contacts with the

	Acute Oncology Service) during the first year following palbociclib initiation.
Author	Dr PPD PhD, MBBS, BSc (Hon), MRCP Onc. Oncology Medical Affairs Manager, PPD UK; PPD Email: PPD Mobile: PPD PPD

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS....4
2. LIST OF ABBREVIATIONS....6
3. RESPONSIBLE PARTIES....8
4. ABSTRACT....9
5. AMENDMENTS AND UPDATES....12
6. MILESTONES....13
7. RATIONALE AND BACKGROUND....13
8. RESEARCH QUESTION AND OBJECTIVES....15
9. RESEARCH METHODS....16
9.1. Study design....16
9.2. Setting....18
9.2.1. Inclusion criteria....18
9.3. Variables....18
9.4. Data sources....23
9.5. Study size....23
9.6. Data management....23
9.6.1. Case Report Forms (CRFs)....24
9.6.2. Record Retention....25
9.7. Data analysis....25
9.8. Quality control....27
9.9. Limitations of the research methods....27
9.10. Other aspects....28
10. PROTECTION OF HUMAN SUBJECTS....28
10.1. Patient Information....29
10.2. Patient Consent....29
10.3. Patient Withdrawal....30
10.4. Institutional Review Board (IRB)/Research Ethics Committee (REC)....30
10.5. Ethical Conduct of the Study....30

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 30
11.1. Single Reference Safety Document....32
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS....33
13. REFERENCES 33
14. LIST OF TABLES....36
15. LIST OF FIGURES 36
CCI
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 36
ANNEX 3. ADDITIONAL INFORMATION....37

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
IPP	Ibrance® Patient Program
ROIS	Real Outcomes Ibrance® Study
HR+	Hormone Receptor Positive
BC	Breast Cancer
PFS	Progression-Free Survival
HER2(-)	Human Epidermal Growth Factor 2 (Negative)
MBC	Metastatic Breast Cancer
EU	European Union
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SMC	Scottish Medicines Consortium
UK	United Kingdom
CR	Complete Response
PR	Partial Response
OS	Overall Survival
AE	Adverse Event
CNS	Cancer National Service
AOS	Acute Oncology Service
IRB	Institutional Review Board
REC	Research Ethics Committee
CDK	Cyclin-Dependent Kinase
PALOMA	Palbociclib Ongoing Trials in the Management of Breast Cancer
US	United States
FDA	Food and Drug Administration
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

GDPR	General Data Protection Regulation
ISPE	International Society for Pharmacoepidemiology
eCRF	electronic Case Report Form
NCRI	National Cancer Research Institute
Y	Yes
N	No
NCI-DCI	National Cancer Institute - Deyo-Charlson Comorbidity Index
CI	Confidence Interval
A&E	Accident and Emergency
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
EMA	European Medicines Agency
GDPR	General Data Protection Regulation
MHRA	Medicines and Healthcare products Regulation Regulatory Authority Agency
SRSD	Single Reference Safety Document
STROBE	Strengthening The Reporting of Observational studies in Epidemiology
ICMJE	International Committee of Medical Journal Editors

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD PhD, MBBS, BSc (Hon), MRCP Onc	Doctor	Oncology Medical Affairs Manager PPD	PPD
PPD MPharm	Ms.	Senior Medical Advisor, Pfizer Oncology UK	PPD
PPD , BSc, MB BS, PhD, FRCP	Professor	PPD	PPD
PPD PhD	Doctor	PPD	PPD PPD
PPD PhD, Msc, MPhil	Doctor	PPD	PPD PPD

4. ABSTRACT

Title: Observational cohort study of patients with hormone receptor-positive metastatic breast cancer treated with palbociclib (Ibrance®) as part of the United Kingdom Ibrance® Patient Program (IPP); the Real Outcomes Ibrance® Study (ROIS)

Subtitle: the Real Outcomes Ibrance® Study (ROIS)

Hormone receptor positive (HR+) breast cancer (BC) represents the largest therapeutic subtype of the disease, accounting for 60 to 65% of all malignant neoplasms of the breast. Palbociclib (Ibrance®) is a small-molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) which in clinical trial settings has been shown to increase progression-free survival (PFS) for patients with HR+, human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (MBC). Palbociclib first received a European Union (EU) marketing authorisation in September 2016, to be commercialised as Ibrance® by Pfizer. Palbociclib was recommended for use with an aromatase inhibitor in patients with HR+/HER2- locally advanced and MBC in the National Health Service (NHS) in England by the National Institute for Health and Care Excellence (NICE) in November 2017 and by the Scottish Medicines Consortium (SMC) in December 2017. In order to provide access to palbociclib in the United Kingdom (UK) during the NICE/SMC appraisal period, the Ibrance® Patient Program (IPP) was initiated and run by Pfizer between April 2017 until a positive NICE/SMC appraisal in November 2017 (for England and Wales) or December 2017 (for Scotland).

Pfizer are interested in the opportunity to collect data from patients who received palbociclib as part of the UK IPP, to better understand patients' characteristics in a routine care setting, treatment persistence and dose management, clinical outcomes, and healthcare resource utilisation. This study will provide real-world evidence on patients' clinical progression and experience of treatment with palbociclib in routine clinical settings in a UK context.

Research question:

What are the real-world treatment patterns, patients' characteristics, clinical outcomes and healthcare resource utilisation associated with palbociclib treatment in the 3 years following initiation in United Kingdom patients with HR+/HER2- MBC treated as part of the IPP?

Primary objectives:

- To describe patient demographic and clinical characteristics at initiation of palbociclib.

Secondary objectives

- To describe treatment pattern (as per licence/IPP requirement); including the proportion of patients with dose modification and who switch treatment 1, 2 and 3 years after palbociclib initiation, and median time to dose modification and treatment

discontinuation ('drug survival'). For patients who progress, to describe the 1st /2nd /3rd line of treatment after progression.

- To describe overall survival (OS) and progression-free survival (PFS), response (complete response [CR], partial response [PR]), stable disease. This includes estimating the proportion of patients achieving those endpoints at 1, 2 and 3 years following palbociclib initiation; median survival, time to response and duration of response. In patients who respond to treatment, to describe PR and CR using "swimmer plots".

- To describe the occurrence of neutropenia during the first year post-initiation observation period.

- To describe the occurrence of gastro-intestinal toxicity, including diarrhoea, nausea and vomiting during the first year post-initiation observation period.

- To describe progression of clinical indicators, including biochemical and radiological indicators at each time-point available during the first year following palbociclib treatment initiation (e.g. full blood counts, liver function tests, bone profile).

- To describe BC related healthcare resource utilisation (hospital admissions, outpatient visits, calls to Cancer National Services and contacts with the Acute Oncology Service) during the first year following palbociclib initiation.

This is an observational cohort study with retrospective and prospective data collection to obtain medical data covering the 3 year period following palbociclib initiation.

The study will be conducted in 8-9 NHS trusts across different regions within the UK (list of hospitals provided in Annex 1). In the hospitals selected for this study, approximately 250 patients received palbociclib as part of the IPP out of a total of 846 women who received palbociclib in the UK. Site selection was based upon a minimum of 15 patients being enrolled onto the IPP, except for one site selected) due to lead clinician's membership in the steering committee. Membership of the steering committee was based upon two criteria 1) membership of the National Cancer Research Institute (NCRI) MBC subcommittee and 2) had patients on the IPP. All members of the steering committee meet this criteria. The NCRI subcommittee is an independent committee from Pfizer, and Pfizer has no input into the committee as part of this study.

Patients will be eligible for this study if: (1) they received ≥1 dose of palbociclib as part of the IPP at one of the selected hospitals; (2) at sites where the data is collected by external researchers, patients provide consent for an external researcher to access their medical records (for living patients only). Patients were eligible for the IPP if palbociclib was used in combination with an aromatase inhibitor and patients had previously untreated HR+/HER2- locally advanced or MBC.

The following data will be collected from patients' medical records: demographic characteristics at time of initiation, medical history prior to palbociclib initiation, clinical

indicators of progression and response to treatment, occurrence of neutropenia and gastro-intestinal toxicity post-palbociclib initiation, and healthcare resource utilisation. PFS and OS will be estimated for patients from the date of initiation of palbociclib.

The analysis will be descriptive. Demographic characteristics and medical history will be described at the time of palbociclib initiation (baseline). Qualitative variables will be described by the absolute and relative (%) frequency of each class. Missing data will not be taken into account in the calculation of percentages (counts of missing observations will be included in a separate category). Quantitative variables will be described by their mean, standard deviation, median, 1st and 3rd quartiles, and extreme values (minimum and maximum), where applicable and the number of missing and non-missing values. The Kaplan-Meier method will be used to obtain estimates of median PFS, OS, CR, PR and time to discontinuation of palbociclib, with corresponding two-sided 95% confidence intervals.

Completion of retrospective data collection is planned for the 1st of February 2019. Completion of the prospective data collection is planned for the 1st of February 2021. An interim report on descriptive characteristics of patients already enrolled into the study (primary objective) will be produced in January 2019. Delivery of a 1-year report on the analysis of patients with 1-year follow-up post-initiation period (primary and secondary objectives) is planned for the 1st of July 2019. An additional 3-year report on the analysis of patients with up to 3-year follow-up post-initiation period (primary and secondary objectives) may be provided in July 2021.

5. AMENDMENTS AND UPDATES

Amendments must be made only by prior agreement between Pfizer, pH Associates and the Chief Investigator. The institutional review board (IRB)/research ethics committee (REC) must be informed of all amendments and give approval for substantial amendments. The Chief Investigator must send a copy of the approval letter from the REC/IRB to Pfizer.

pH Associates, Pfizer, and the participating organisation(s) reserve the right to terminate participation in the study according to the study contract. pH Associates will notify the REC/IRB in writing of the study's completion or early termination and send a copy of the notification to Pfizer and the Chief Investigator.

Not applicable

6.

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	July 2018
Start of data collection	November 2018 for retrospective data collection February 2019 for prospective data collection
End of data collection	February 2019 for retrospective data collection February 2021 for prospective data collection
Interim report on descriptive analysis of patients already enrolled into the study (primary objective)	February 2019
1-year report (primary and secondary objectives)	01 of July 2019 [based on 1-year post initiation observation period, including all patients with up to 1-year follow-up post initiation]
3-year report (primary and secondary objectives)	01 of July 2021 [based on 3-year post initiation observation period, including all patients with up to 3 year follow-up post-initiation]

7. RATIONALE AND BACKGROUND

BC is the most frequently occurring cancer in women and is a major public health problem, with 1.7 million new cases diagnosed globally in 2012, representing 25% of all incident cancer cases (1). In Europe, more than 464,000 new cases of BC were diagnosed in 2012. The UK incidence rate is the sixth highest in Europe, with around 54,900 new BC cases every year (2). HR+ BC represents the largest therapeutic subtype of the disease and accounts for over 80% of cases in the UK (4).

Annually, approximately 6-7% of new BC cases present as *de novo m*etastatic disease and approximately 30% of women with early BC go on to develop metastatic disease (2). Survival from BC largely depends on the stage at diagnosis; the 1-year survival is 100% for patients diagnosed at stage I, versus 63% for patients diagnosed at stage IV; and five-year survival is 99% and 15% respectively for stage I and IV (5,6).

Up until the addition of palbociclib, low survival rates reflected that current therapies were generally unsuccessful in treating MBC, and as such that there was a significant unmet need for the development of better treatment options (7). Traditional treatment selection for MBC is based on biomarkers including hormone receptor positivity and HER2 status, and individual patient and clinical characteristics that may include tumour burden, timing of disease recurrence, and the type of prior adjuvant therapies (8). HR+ BCs are generally receptive to hormonal therapy. However, their clinical benefit is limited in the case of patients with MBC who are diagnosed as HER2- (9). Considering the multiple pathways involved in the hormone receptor network, targeting other components of pathologically activated intracellular signalling in BC has provided a direction for the development of novel therapies. The cyclin-dependent kinases (CDKs) are a large family of serine-threonine kinases that play an important role in regulating cell-cycle progression (10). The CDK4 and CDK6 inhibitors act at the transition from G1 phase of the cell cycle to S phase. This transition checkpoint is tightly controlled by the D-type cyclins and CDK4 and CDK6. When CDK4 and CDK6 are activated by D-type cyclins, they phosphorylate the retinoblastoma-associated protein. This suspends suppression of the E2 factor transcription factor family by the protein and ultimately allows the cell to proceed through the cell cycle and divide. In HR+ BC, cyclin D overexpression is common and loss of retinoblastoma-associated protein is rare, therefore making the transition checkpoint a potential therapeutic target. The CDK4 and CDK6 inhibitors prevent progression through this checkpoint, leading to cell cycle arrest, and have changed the treatment landscape for patients with HR+/HER− MBC (11).

Palbociclib, a CDK4/6 inhibitor, first received a EU marketing authorisation in September 2016, to be commercialised as Ibrance® by Pfizer to be used in women in the first line setting as well as in those who have received prior endocrine therapy in combination with letrozole (an aromatase inhibitor)) or fulvestrant (an estrogen receptor down regulator) (12).

Palbociclib was approved for use as first-line treatment of HR+/HER2− advanced BC in postmenopausal women, based on the phase II study Palbociclib Ongoing Trials in the Management of BC (PALOMA) PALOMA-1(13) and the phase III study PALOMA-2 (10). Palbociclib was approved for use with fulvestrant as second- or later-line treatment of HR+/HER2− advanced BC based on the phase III study PALOMA-3 (14,15). In PALOMA-1, median PFS was 20.2 months for the palbociclib-letrozole group versus 10.2 months for the placebo-letrozole group (hazard ratio [HR] for risk of progressing: 0.488, 95% confidence interval 0.319-0.748) (13); and In PALOMA-2, it was respectively 24.8 months versus 14.5 months (hazard ratio 0.58; 0.46 to 0.72) (10). In PALOMA-3, median PFS was 9.5 months in the palbociclib-fulvestrant group versus 4.6 months in the placebo-fulvestrant (hazard ratio (HR): 0.46, 0.36-0.59)(14); and specifically for patients with prior resistance to hormonal therapy and visceral metastases, it was respectively 9.2 months versus 3.4 (HR, 0.47; 0.35–0.61) (15).

Palbociclib was recommended for use with an aromatase inhibitor in patients with locally advanced and MBC in the NHS in England by NICE in November 2017 and by the SMC in December 2017 (16,17). In order to provide access to palbociclib in the UK during the

NICE/SMC appraisal period, the IPP was run by Pfizer between April 2017 and November 2017 for England and Wales, and December 2017 for Scotland. The IPP provided free access to treatment to NHS patients with previously untreated (or >12 month since discontinuation of adjuvant or neoadjuvant treatment with a nonsteroidal aromatase inhibitor), HR+/HER2- MBC (18).

Palbociclib and other CDK4/6 inhibitors have been generally well tolerated by patients. Based on pooled data from 3 randomised studies in patients who received palbociclib in combination with endocrine therapy (N=872), one most common side effect has been neutropenia soon after initiation of therapy which affects 80.6% of patients, including 10.1% experiencing grade 4 neutropenia and 1.6% experiencing febrile neutropenia (19). Palbociclib-induced neutropenia has also been shown to reverse rapidly with dose interruption and/or dose reduction (11).

Several real-world observational studies focusing on the real-world treatment pattern of palbociclib have been conducted in the United States (US) since its approval by the US Food and Drug Administration (FDA) in February 2015 for patients with advanced or MBC (3,18,19). A retrospective observational study using a US electronic medical record database was conducted in 763 patients with advanced BC treated with palbociclib (8). More than two thirds (69.9%) of patients had a confirmed HR+/HER2- tumor. Of those, 612 (80.2%) received palbociclib concomitantly with letrozole. Mean follow up was 6.4 months and mean age at palbociclib initiation was 64 years. Dose reductions were observed in 20.1% of patients and 74.6% of patients had a neutropenic event during follow up (47.3% grade 3 and 8.0% grade 4). In another US study in 1242 postmenopausal women with HR+/HER- MBC in the Symphony Health Solutions database, mean age at initiation of palbociclib was 62.7 years and median follow-up was 8.7 months (20). During the 12-month post-index period, 32–34% of patients reduced dose and 64–81% reduced or changed treatment.

Pfizer are interested in the opportunity to collect data from patients who received palbociclib as part of the IPP, to better understand effectiveness and safety of palbociclib when used in routine care in a UK context, with a focus on treatment persistence and dose management, patients' characteristics, clinical outcomes, and healthcare resource utilisation. This study will evaluate patients' clinical progression and experience of treatment with palbociclib in routine clinical practice in the UK. This study may be of benefit to the NHS and patients in supporting assessments of the benefit of palbociclib in routine care; and will also help contextualise evidence on safety of palbociclib previously generated from the real-world studies in US populations.

8. RESEARCH QUESTION AND OBJECTIVES

What are the real-world treatment patterns, patients' characteristics, clinical outcomes and healthcare resource utilisation associated with palbociclib treatment in the 3 years following initiation in UK patients with HR+/HER2- MBC treated as part of the IPP?

Primary objectives:

- To describe patient demographic and clinical characteristics at initiation of palbociclib.

Secondary objectives

- To describe treatment pattern (as per licence/IPP requirement); including the proportion of patients with dose modification and who switch treatment 1, 2 and 3 years after palbociclib initiation, and median time to dose modification and treatment discontinuation ('drug survival'). For patients who progress, to describe the 1st /2nd /3rd line of treatment after progression.

  To describe overall survival and progression-free survival, response (CR, PR), stable disease. This includes estimating the proportion of patients achieving those endpoints at 1, 2 and 3 years following palbociclib initiation; median survival, time to response and duration of response. In patients who respond to treatment, to describe PR and CR using "swimmer plots".

- To describe the occurrence of neutropenia during the first year post-initiation observation period.

- To describe the occurrence of gastro-intestinal toxicity, including diarrhoea, nausea and vomiting during the first year post-initiation observation period.

- To describe progression of clinical indicators, including biochemical and radiological indicators at each time-point available during the first year following palbociclib treatment initiation (e.g. full blood counts, liver function tests, bone profile).

- To describe BC related healthcare resource utilisation (hospital admissions, outpatient visits, calls to Cancer National Services (CNS) and contacts with the Acute Oncology Service (AOS)) during the first year following palbociclib initiation.

9. RESEARCH METHODS

The study is designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; (22)) International Society for Pharmacoepidemiology (ISPE; (23)) guidance, European Union General Data Protection Regulation (GDPR; (24)) and national data protection legislation and regulations, as appropriate.

9.1. Study design

This study will be a UK-wide, multi-centre, non-interventional cohort study (Figure 1). The study will involve secondary use of hospital medical records (paper-based or electronic, as

appropriate), collected both retrospectively and prospectively, from patients' medical records. Data will be collected for a maximum of 3 years following enrollment into the IPP.

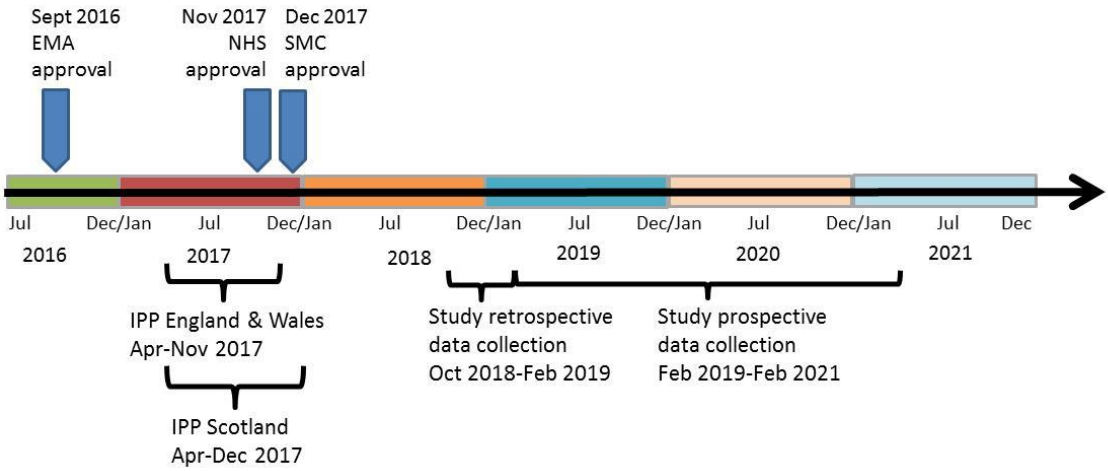
Consent from living patients will be required if data are collected by pH Associates. In that case, patients will be provided with information about the study and approached for consent by members of the direct care team, either by post or in person at a routine hospital visit. Since no consent can be obtained if the patient is deceased, identifiable medical records of deceased patients will be accessed for study data collection by the direct care team only, to preserve confidentiality and avoid bias arising from exclusion of deceased patients.

Data will be collected retrospectively from the point of patient's enrollment into the IPP until initial data collection, expected to take place between November 2018 and February 2019. Members of the direct care team, or researchers from pH Associates (for living patients only), will collect existing (retrospective) data from the medical records of eligible patients in an electronic case report form (eCRF).

After the initial retrospective data collection, data will be collected prospectively up to a maximum of 3 years from enrollment in the IPP by members of the direct care team by updating the eCRF with any subsequent therapeutic and progression data available in the medical records until the end of the 3 year follow-up period.

The palbociclib initiation date will be defined as the index date. The baseline period will extend from the date of diagnosis up to palbociclib initiation (index date). The post-initiation observation period will be defined as the period from the index date until the end of the 3 year follow-up period. Patients will contribute data up to the time that they are lost to follow-up (for example due to discharge, death or other reasons) or 3-year post-index observation period, whichever is sooner.

Figure 1. Schematic of study design



9.2. Setting

The study will be conducted in 8 or 9 NHS Trusts (See Annex 1). Sites have been selected on the basis that:

- They are geographically dispersed across the UK.
- Their cancer service participated in the IPP.
- They have appropriate and sufficiently trained personnel available locally to identify eligible patients and support the study delivery in accordance with applicable legal and regulatory requirements.
- They treated at least 15 patients as part of the IPP, so that collectively the total number of patients across the selected sites approximates 250 patients. One site was also selected due to the lead clinician's membership in the steering committee. Membership of the steering committee was based upon two criteria 1) membership of the National Cancer Research Institute (NCRI) MBC subcommittee and 2) had patients on the IPP. All members of the steering committee meet this criteria. The NCRI subcommittee is an independent committee from Pfizer, and Pfizer has no input into the committee as part of this study.
- They have an interest in taking part in the study.

9.2.1. Inclusion criteria

All patients meeting the following eligibility criteria will be included in the study:

- Patients enrolled into the IPP at one of the selected hospitals (see **Annex 1 for IPP enrolment letter**).
- Patients who received ≥1 dose of palbociclib as part of the IPP at one of the selected sites.
- For sites where data collection is performed by pH Associates, written informed consent will be required from living patients to access their medical records.
- Patient aged ≥18 years old at enrollment into the IPP

9.3. Variables

The endpoints associated with each of the study objectives are described below, along with the variables that will be collected in order to address the objectives. Response options for each variable will be further detailed in the eCRF. A list of variables is available in Annex 2.

Endpoints to address the objective	Variables required to address objective
Primary objective: To describe patient demographic and clinical characteristics at initiation of palbociclib.	

• Demographic characteristics of patients, including summary measures of age, sex, ethnicity and menopausal status at initiation of palbociclib.
• Summary measures of BC characteristics at the time closest prior to initiation of palbociclib:
  o recurrence, stage and grade of disease, Ki-67 protein proliferation index, site of metastases, lymph node involvement (including number of lymph nodes), oestrogen-receptor status, progesterone-receptor status, and HER2 status.
• Duration of BC disease at initiation of palbociclib.
• Treatment for BC diagnosis prior to palbociclib initiation.
• Summary measures of relevant comorbidities diagnosed at or prior to initiation of palbociclib.
• Palbociclib prescribed as on-label or off/label use according to Summary of Products Characteristics(19)
	• Sex (male / female).
	• Month and year of birth.
	• Ethnicity (categories to be defined in eCRF).
	• Menopausal status (Yes [Y]/No [N]).
	• For latest BC diagnosis prior to initiation of palbociclib:
	  o Date of BC diagnosis.
	  o Recurrence: Loco-regional, local, regional, distant, newly diagnosed.
	  o Stage of disease: I, I, III, IV.
	  o Grade of disease: 1,2, 3.
	  o Biopsy results: Ki-67 proliferation index.
	  o Site of metastases: lung, liver, other visceral, brain, bone, other non-visceral.
	  o Lymph node involvement: Y/N, if Y report number of lymph nodes.
	  o Oestrogen-receptor status: Y/N.
	  o Progesterone-receptor status: Y/N.
	  o HER2 status: Positive/ Negative.
	• Treatment for BC diagnosis prior to palbociclib initiation :
	  o (neo)-adjuvant chemotherapy: pathological complete response achieved Y/N, date start and date stopped.
	  o Type of surgery: wide local, mastectomy.
	  o (neo) adjuvant oestrogen therapy: date start and stopped.
	• Relevant comorbidities documented within baseline period (to include all individual components of the Deyo-Charlson comorbidity index from the National Cancer Institute [NCI-DCI] (25)), to be further defined in full in the eCRF).

Secondary objective: To describe treatment pattern (as per licence/IPP requirement); including the proportion of patients with dose modification and who switch treatment 1, 2 and 3 years after palbociclib initiation, and median time to dose modification and treatment discontinuation ('drug survival'). For patients who progress, to describe the 1st /2nd /3rd line of treatment after progression.	

• Summary measures of palbociclib treatment patterns, including: o Starting dose. o Proportion of patients with dose reductions at 1, 2 and 3 years after initiation. o Proportion of patients with palbociclib treatment discontinuation at 1, 2 and 3 years after initiation. o Mean (Standard Deviation [SD]) dose intensity over the course of treatment in patients who complete treatment of palbociclib o Median time to dose reduction in number of days (from start of treatment) and in terms of number of cycles (completed or interrupted). o Median time to dose increase in number of days (from start of treatment) and in terms of number of cycles (completed or interrupted); only in patients with previously reduced dose o Median time to palbociclib discontinuation ('drug survival') in number of days (from start of treatment) and in terms of number cycles (completed or interrupted). o Reasons for discontinuation. o 1st, 2nd and 3rd line of treatment after progression: number of patients prescribed each medication, dose, and length of treatment. • Description of the number of patients which are being prescribed as per posology of treatment (19): o Proportion of patients who complete a 28-day cycle (21 days daily dose followed by 7 days off treatment). o Mean (SD) of completed 28 day cycles. o Proportion of patients co-administered letrozole at palbociclib initiation. o Proportion of patients co-administered fulvestrant at palbociclib initiation.	• Palbociclib: date on initiation, initial dose, date of dose reduction, subsequent dose, dates of cycle initiation and completion, date of discontinuation (indicate whether last cycle is interrupted or completed), reasons for palbociclib dose reduction / increase / discontinuation. • Date of start and end of concomitant medication treatment: letrozole, fulvestrant, osteo-strengthening drugs (denosumab, zometa), other drugs. • First 3 lines of medication after palbociclib discontinuation: name, dose and length of treatment.
Secondary objective: To describe overall survival and progression-free survival, response (CR, PR), stable disease. This includes estimating the proportion of patients achieving those endpoints at 1, 2 and 3 years following palbociclib initiation; median survival, time to response and duration of response. In patients who respond to treatment, to describe PR and CR using "swimmer plots".	

• Proportion of patients at 1, 2 and 3 years following initiation of palbociclib who: o Are free from disease progression. o Are alive o Achieved PR o Achieved CR o Had stable disease • Median (95% confidence interval [CI]) : o PFS o OS o Time to achieving best overall response • Summary measures of duration of response (Kaplan-Meier analysis). • Representation of all radiological assessment of response (CR / PR / no response or stable disease / progressive disease) in patients responding to treatment (achieving CR or PR following initiation of palbociclib) using "swimmer plots".	• Date ((DD/MM/YYYY) unless specified otherwise) of start and end of palbociclib. • Date of data collection. • Patient status at the end of data collection period (alive/dead): o Date of death / last clinic visit. o If not known (i.e. lost to follow-up), date of last recorded hospital visit. • Radiological assessments of response during the follow-up period: date of assessment and outcome (CR / PR / no response or stable disease / progressive disease), as documented by the local investigator.
Secondary objective: To describe the occurrence of neutropenia during the first year post-initiation observation period.	
• For each cycle, proportion of patients at day 1 into the cycle, day 15 into the cycle, day 22 into the cycle (and number of patients assessed) who experience: o Neutropenia, overall and by grade. o Febrile neutropenia. • Summary measures of incidence of: o Neutropenia, overall and by grade. o Febrile neutropenia.	• Incidence (Y / N) and date(s) of occurrence of neutropenia (by grade) and febrile neutropenia.
Secondary objective: To describe the occurrence of gastro-intestinal toxicity, including diarrhoea, nausea and vomiting during the first year post-initiation observation period.	
• For each cycle, proportion of patients at day 1 into the cycle, day 15 into the cycle, day 22 into the cycle (and number of patients assessed) who experience Gastro-intestinal toxicity, including: o Diarrhoea o Nausea o Vomiting • Summary measures of incidence of: o Diarrhoea o Nausea o Vomiting	Incidence (Yes / No) and date(s) of occurrence of gastro-intestinal toxicity, including: o Diarrhoea o Nausea o Vomiting

<table>
<tr><td colspan="2">Secondary objective: To describe progression of clinical indicators, including biochemical and radiological indicators at each time-point available during the first year following palbociclib treatment initiation (e.g. full blood counts, liver function tests, bone profile).</td></tr>
<tr><td>• Summary measures of full blood counts in the first year following initiation: haemoglobin, white cell counts, absolute neutrophil counts, platelet counts.
• Summary measures of liver function tests in the first year following initiation: aspartate transaminase (also called aspartate aminotransferase), alanine transaminase (also called alanine aminotransferase), and alkaline phosphatase.
• Summary measures of bone profile in the first year following initiation: calcium, phosphate.
• Summary measures of radiological indicators in the first year following initiation: stable disease, progressive disease, CR/PR</td><td>• Date and laboratory results as clinically indicated for each full blood count: pre-first cycle, on day 1 of each cycle of treatment, on day 15 into cycles 1 and 2 and day 22 if abnormal results at day 15.
• Date and liver function test results for each test as above.
• Date and bone profile results for each test.
• Date and results of radiological examinations: stable disease, progressive disease, CR/PR</td></tr>
<tr><td colspan="2">Secondary objective: To describe BC-related healthcare resource utilisation (hospital admissions, outpatient visits and calls to CNS) during the first year following palbociclib initiation.</td></tr>
<tr><td>• Summary measures of hospital admissions for each line of therapy, including:
o Inpatient admissions per patient, including elective or non-elective and reasons (including day-case).
o Length of stay per inpatient admission.
o Emergency department visits per patient.
o Outpatient visits per patient.
• Summary of phone calls from patient to CNS.
• Summary of contacts to AOS.</td><td>• BC-related inpatient admission: dates, reason and duration (derived from dates of hospital entry and discharge) of hospitalisation:
o Type: planned (elective) or Accident and Emergency (A&E).
• BC-related outpatient admission: dates, reason.
• Phone calls from patients to CNS: dates, reason.
• Recorded contacts with AOS: dates, reason, type of contact (phone calls, visits).</td></tr>
</table>

The following definitions will be implemented. PFS will be defined as the time from the date of palbociclib initiation to the date of first documented disease progression (i.e. mention of disease progression or mixed response in the medical records, e.g. due to evidence of a new site of disease, or increasing disease, after treatment initiation) or death. OS will be defined as the time from the date of palbociclib initiation until death from any cause. Time to achieving best overall response will be defined in patients who respond to treatment as the time from the date of palbociclib initiation until achievement of the best overall response: CR, or PR if CR is not achieved during follow-up. Duration of response will be defined as the time from the date CR or PR was first documented (whichever is recorded first) to the date of first documented disease progression or death from any cause (whichever occurs first).

9.4. Data sources

Data for this study will be collected through retrospective and prospective patient chart review from 8-9 cancer services of NHS Trusts in the UK. A feasibility pilot for data collection will be carried out on 10 of the initial patients' data collected. These patients will be selected from one or two centres (dependent on the speed of data capture) to enable the data to be reviewed at the earliest opportunity. The purpose of this pilot will be to check the availability and quality of data that will be collected in the study, and to confirm the length of time required to collect the data.

Data on patient demographic and clinical characteristics, treatment patterns, outcomes, healthcare resource use and AEs will be collected in deidentified-coded form, from paper based and/or electronic hospital medical records (as applicable at each site) by members of the patients' direct care team or pH Associates.

9.5. Study size

This is a descriptive study and there is no *a priori* hypothesis specified. Therefore the sample size has been chosen pragmatically, based on the available patients from the IPP.

Across the entire UK, 846 women received palbociclib as part of the IPP. In the sites selected for this study, approximately 250 patients (exact number will be updated after site confirmation and patient consent) received palbociclib as part of the IPP. All eligible patients within the selected sites will be recruited into the study.

9.6. Data management

Data management and handling of data will be conducted according to the study specific data management plan and in accordance with ENCePP/ISPE/ guidance and the General Data Protection Regulation and applicable national data protection legislation and regulations. Data for the study will be collected via an electronic data capture system using a standardised eCRF designed specifically for the study in accordance with this protocol. All data will be collected from hospital medical records by members of the NHS direct care team or an external researcher from pH Associates.

Before the start of data collection, NHS staff collecting data from patients' hospital medical records will be trained in data entry into the eCRFs by study management staff from pH Associates and consistency checks will be built into the eCRF to ensure data quality.

Patients will be identified in all study records by a unique study code to link multiple study records for each participant and preserve patient confidentiality.

Data management for eCRFs will be carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with the International Council for Harmonization E6 Good Clinical Practice guidelines, FDA Information Governance standard 21 Code of Federal Regulations Part 11 and the EU Clinical Trials Regulation, and the UK Medicines and Healthcare products

Regulatory Agency requirements. The MACRO™ system has restricted access permissions for data entry and data management, and records an audit trail of all changes to data and activity in the system. Access to the study in MACRO™ will be restricted (by password protection) to only those members of staff directly involved with the study and assigned access permissions will control the level of access to that required for the role of each individual working on the study. If corrections are needed to an eCRF, queries will be raised in the electronic data capture system by the study data manager and these will be resolved by the responsible investigator (or designee) by reference to the source records or agreed assumptions.

After obtaining the appropriate local approvals for data release, the deidentified data for this study will be collated and transferred securely to pH Associates, who will be the Data Processor for data management, analysis and reporting on behalf of Pfizer, the Data Controller. Pfizer will not have access to individual patient level data.After the initial retrospective data collection, data will be collected prospectively up to a maximum of 3 years from enrollment in the IPP by members of the direct care team by updating the eCRF with any subsequent therapeutic and progression data available in the medical records until the end of the 3 year follow-up period.

9.6.1. Case Report Forms (CRFs)

As used in this protocol, the term eCRF should be understood to refer to an electronic data record.

An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorised representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the eCRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorised third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs 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 eCRFs must be signed by the investigator or by an authorised staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

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

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., eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, 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, 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.

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

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

9.7. Data analysis

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

Analyses will be performed by pH Associates using Stata (StataCorp LLC) and R. Data from all participating centres will be pooled for analysis.

According to the objectives, descriptive statistics will be presented using data at 1 year (using retrospective data collected) or 2 and 3 years (using the prospective data as well as the retrospective data collected) following initiation of palbociclib. Clinical measurements will be presented at each time-point available, as described in section 7.3. The interim study report will only present results for objectives which are relevant to the 1-year follow-up period and the final report will present results for objectives which are relevant up to the 3-year follow-up period.

Descriptive statistics (numbers, percentages, means, standard deviations [SD], medians, quartiles, minimum, and maximum), as appropriate to the data collected, will be used to describe baseline demographic and clinical characteristics for the overall study. Treatment patterns and hospital admissions will also be reported using descriptive statistics. The frequency and proportion of patients experiencing a neutropenia, febrile neutropenia event;

and gastro-intestinal toxicity including diarrhea, nausea and vomiting, during follow-up, will be presented.

Definitions will be implemented as described in section 9.3 Variables. Patients who are known to be alive at the date of data collection (1-year for interim report and 3-year for full study report) will be censored at the date of data collection, and patients who are lost to follow-up will be censored on the date they were last known to be alive (e.g. date of last recorded hospital visit). Patients who are alive and free from disease progression at the date of data collection and those lost to follow-up will be censored on the date they were last known not to have disease progression (i.e. the date of last documented response assessment). Patients remaining in CR or PR at the end of the post-initiation observation period or lost to follow-up will be censored on the date CR or PR was last documented.

For the estimation of the proportion of patients alive, and free from disease progression, the denominator will be all patients known to be alive at the selected time-points (1 years, 2 years and 3 years). For the estimation of the proportion of patients achieving PR, CR and with stable disease at the selected time-points (1 years, 2 years and 3 years), the denominator will be all patients with at least one assessment of response (CR / PR / no response or stable disease / progressive disease) in the past year. Estimation of time to achieving best overall response and duration of response; and representation using swimmer plots will be performed in patients who respond (achieve CR or PR during follow-up) only.

Median PFS, OS, time to achieving best overall response, time to palbociclib dose modification and time to palbociclib discontinuation, and corresponding 95% CIs, will be estimated using Kaplan-Meier curves. Assessments of response (CR / PR / no response or stable disease / progressive disease) in patients responding to treatment (achieving CR or PR following initiation of palbociclib) will be represented using “swimmer plots”.

All percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding.

Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st of July will be assumed unless data collected is in 2017 (year of initiation of IPP) in which case the 15th of August will be assumed (midpoint as IPP was initiated in April 2017). Where other types of data are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available and the number included in each analysis will be stated. The percentage of data missing will be reported for each study variable. The calculation of percentages will not contain the missing categories. Counts of missing observations will be presented in a separate category.

9.8. Quality control

All data collectors will be provided with Data Collection Guidelines to facilitate consistent completion of the eCRF and will receive training in the requirements of the study protocol and correct completion of the eCRF prior to commencement of data collection.
The accuracy and quality of data collection will be monitored by reference to source data (source data verification [SDV]).

SDV will be performed on the complete dataset of a random sample of at least 10% of patients from each centre. Any issues identified by pH Associates relating to quality, accuracy or consistency of data collection will be discussed with the data collector concerned and further training provided by pH Associates if required. If any subsequent issues are identified related to quality, accuracy or consistency of data collection, a random check of a further 10% of data collected by that data collector will be undertaken. Should any further issues be identified, 100% SDV will be undertaken at the centre. It is the centre Investigator's responsibility to ensure the accuracy of the data entered in the CRFs.

Where patient study data are collected by pH Associates, SDV will be performed by a pH Associates study monitor who did not collect data for that patient record. For patients whose entire dataset was collected by members of patients' direct care team, a 'back-to-back' SDV will be performed with a member of the direct care team, as these patients will not have provided consent to their data being accessed by external researchers from pH Associates. This will involve the direct care team member at the centre reciting data from the patient notes to the pH Associates study monitor so that they can verify the data in the eCRF without the need to look directly at the identifiable source records.. All people performing SDV will be trained by pH Associates.

All clinical data submitted will be checked for eligibility, completeness and accuracy by the pH Associates data management team using agreed manual and programmed validation checks and queries will be raised. Study centres will be required to co-operate with the data management team in the resolution of these queries.

Analysis of the primary endpoint will be independently reviewed by a member of the Data Analysis team at pH Associates who was not involved in the analysis of the final study data. No additional analysis checks will be carried out.
Investigators taking part in the study will have all required training for delivery of the study

9.9. Limitations of the research methods

- Comparisons of the results of this study with that of clinical trials and other real-world studies may be limited due to the presence of several potential sources of bias.

- Several sources of selection bias may be introduced in the study:

  - At sites where data are collected by pH Associates, consent from living patients will be required; and consequently a low rate of consent amongst living patients may introduce an over-representation of deceased patients (for whom consent is not required) at those sites, and also compared to sites where consent is not required as all data are collected by the direct medical care team.

  - Patients were treated as part of routine care and therefore patients enrolled in this study may have more diverse characteristics than in a clinical trial setting (for example with regard to menopausal status, ER and PR status, HER2 status), which may impact on the efficacy of palbociclib.

  - Patients will be recruited from larger centres enrolled in the IPP, which may differ from smaller centres in terms of demographic and clinical characteristics, and therefore may not be representative of all patients treated with palbociclib in routine care as part of the IPP.

- Patients may be lost to follow-up due to the occurrence of AEs, lack of efficacy or other reasons, introducing attrition bias. However, the use of Kaplan-Meier curves will be used to obtain estimates of median PFS OS, CR, PR and this takes into account patient attrition.

- Radiological results will be collected from medical notes recorded by radiologists who were unblended to patient's treatment, introducing potential measurement bias.

- The interpretation of data collected retrospectively will be dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records. However, SDV will be employed to identify and correct abstraction errors.

- This is a descriptive study and no analyses to control for confounding will be carried out; therefore, no definitive causal relationships between Ibrance® and study endpoints can be made.

- At sites where data are collected by pH Associates, a low consent rate may diminish sample size and the target of 250 patients enrolled into the study may not be achieved. If <200 patients are recruited into the study, an expansion of the study to other sites involved in the IPP will be considered.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

Not applicable

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational 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 or secured in a locked room to ensure that only authorised study staff members have access. The study site will implement appropriate technical and organisational 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 authorised 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

For deceased patients at the time of data collection, as this study involves deidentified structured or unstructured data sharing with researchers (the direct care team will produce deidentified research records from identifiable patients' records to preserve confidentiality), which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

For living patients at the time of data collection, the informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

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

The investigator must ensure that each study patient or his or her legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient or his or her legally acceptable representative is fully informed

about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/REC. The investigator will retain the original of each patient's signed consent document.

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

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

10.4. Institutional Review Board (IRB)/Research Ethics Committee (REC)

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

10.5. 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 the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, European Medicines Agency (EMA) ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and European Union General Data Protection Regulation (GDPR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition. A serious adverse event is any adverse drug reaction as defined above that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard.

A serious adverse drug reaction is a serious adverse event that is considered related to the medicinal product.

A hospitalisation meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.
"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

All AEs related to any *Pfizer product(s)* shall be reported to **Email Transmission:** GBR.AEReporting@pfizer.com; **Facsimile Transmission:** 0800 015 6401 (toll free) 0845 300 8032 (toll); **Telephone Contact:** 0845 300 8031 (toll free) 0845 300 8032 (toll); **Address**: Pfizer Pharmacovigilance, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS; *by the Principal Investigator at each centre or pH Associates* within 24 hours of discovery or notification. AE information must be recorded on the AE form emailed and/or faxed to **Email Transmission:** GBR.AEReporting@pfizer.com; **Facsimile Transmission:** 0800 015 6401 (toll free) 0845 300 8032 (toll); **Telephone Contact:** 0845 300 8031 (toll free) 0845 300 8032 (toll).

Adverse drug reactions for non-Pfizer products should be notified by the Principal Investigator at each centre to the appropriate Marketing Authorisation Holder and/or to the Medicines and Healthcare Regulatory Authority (MHRA).

All pregnancies occurring in female patients while taking Pfizer products, and all pregnancies occurring in female partners of male patients taking Pfizer products should be reported to **Email Transmission:** GBR.AEReporting@pfizer.com; **Facsimile Transmission:** 0800 015 6401 (toll free) 0845 300 8032 (toll); **Telephone Contact:** 0845 300 8031 (toll free) 0845 300 8032 (toll); **Address**: Pfizer Pharmacovigilance, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS.

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 AEs with

explicit attribution to any Pfizer drug that appears 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 adverse event monitoring 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 non-interventional study adverse event management report and reported, within 24 hours of awareness, to Pfizer Safety using the non-interventional study 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 non-interventional study adverse event monitoring Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training 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.

11.1. Single Reference Safety Document

The palbociclib Summary of Product Characteristics(19) will serve as the Single Reference Safety Document (SRSD) during the course of prospective data collection part of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study. The SRSD should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be reported according to the requirements of Strengthening the reporting of observational studies in epidemiology (STROBE) (26).

Authorship of publications arising from the study will follow the 2015 guidelines proposed by the International Committee of Medical Journal Editors (ICMJE) (27).). All authors will meet the criteria for authorship, and all people who meet the criteria will be authors. Potential conflicts of interest will be disclosed. All authors will have:

- made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND
- participated in drafting the article or revising it critically for important intellectual content; AND
- approved the final version to be published.

Each author will meet all of these conditions and all individuals meeting these criteria will be authors. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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.

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 Non Interventional study protocol that the investigator becomes aware of.

13. REFERENCES

1. Cancer today [Internet]. [cited 2018 May 31]. Available from: http://gco.iarc.fr/today/home

2. Breast cancer statistics [Internet]. Cancer Research UK. 2015 [cited 2018 May 31]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer

3. Rugo HS, Diéras V, Gelmon KA, Finn RS, Slamon DJ, Martin M, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol Off J Eur Soc Med Oncol. 2018 Apr 1;29(4):888–94.

4. Wishart GC, Greenberg DC, Chou P, Brown CH, Duffy S, Purushotham AD. Treatment and survival in breast cancer in the Eastern Region of England. Ann Oncol. 2010 Feb;21(2):291–6.

5. Cancer survival by stage at diagnosis for England (experimental statistics) - Office for National Statistics [Internet]. [cited 2018 Jun 7]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015

6. National Cancer Registration and Analysis Service (NCRAS) [Internet]. GOV.UK. [cited 2018 Jun 7]. Available from: https://www.gov.uk/guidance/national-cancer-registration-and-analysis-service-ncras

7. Bonotto M, Gerratana L, Poletto E, Driol P, Giangreco M, Russo S, et al. Measures of Outcome in Metastatic Breast Cancer: Insights From a Real-World Scenario. The Oncologist. 2014 Jun 1;19(6):608–15.

8. Kish JK, Ward MA, Garofalo D, Ahmed HV, McRoy L, Laney J, et al. Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval. Breast Cancer Res BCR. 2018 May 2;20(1):37.

9. Dalmau E, Armengol-Alonso A, Muñoz M, Seguí-Palmer MÁ. Current status of hormone therapy in patients with hormone receptor positive (HR+) advanced breast cancer. The Breast. 2014 Dec 1;23(6):710–20.

10. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 17;375(20):1925–36.

11. CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer? | Cancer Network [Internet]. [cited 2018 Jun 5]. Available from: http://www.cancernetwork.com/breast-cancer/cdk46-inhibitors-game-changers-management-hormone-receptorpositive-advanced-breast-cancer

12. European Medicines Agency - Human medicines - Ibrance [Internet]. [cited 2018 May 31]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003853/smops/Positive/human_smop_001032.jsp&mid=WC0b01ac058001d127

13. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25–35.

14. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425–39.

15. Turner NC, Finn RS, Martin M, Im S-A, DeMichele A, Ettl J, et al. Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases. Ann Oncol Off J Eur Soc Med Oncol. 2018 Mar 1;29(3):669–80.

16. All Wales Medicines Strategy Group (AWMSG) - palbociclib (Ibrance) [Internet]. [cited 2018 May 22]. Available from: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2392

17. Palbociclib (Ibrance®) is accepted for restricted use within NHS Scotland. [Internet]. Scottish Medicine Consortium. [cited 2018 May 15]. Available from: https://www.scottishmedicines.org.uk/medicines-advice/palbociclib-ibrance-fullsubmission/

18. McKee S. Pfizer offers Ibrance free to the NHS during NICE appraisal [Internet]. 2017 [cited 2018 May 31]. Available from: http://www.pharmatimes.com/news/pfizer_offers_ibrance_free_to_the_nhs_during_nice_appraisal_1192363

19. IBRANCE 75 mg hard capsules - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2018 Jun 28]. Available from: https://www.medicines.org.uk/emc/product/4449/smpc

20. Li N, Du EX, Chu L, Peeples M, Xie J, Barghout V, et al. Real-world palbociclib dosing patterns and implications for drug costs in the treatment of HR+/HER2- metastatic breast cancer. Expert Opin Pharmacother. 2017 Aug 13;18(12):1167–78.

21. Tang DH, Li N, Du EX, Peeples M, Chu L, Xie J, et al. First-line treatment disruption among post-menopausal women with HR+/HER2- metastatic breast cancer: a retrospective US claims study. Curr Med Res Opin. 2017;33(12):2137–43.

22. ENCePP Home Page [Internet]. [cited 2018 Jun 7]. Available from: http://www.encepp.eu/index.shtml

23. Resources - International Society for Pharmacoepidemiology [Internet]. [cited 2018 Jun 7]. Available from: https://www.pharmacoepi.org/resources/guidelines_08027.cfm

24. European Union. General Data Protection Regulation [Internet]. 2018 May [cited 2018 Apr 6]. Available from: http://eugdpr.org/the-regulation.html

25. Stedman MR, Mariotto AB, Klabunde CN, Doria P, Barrett MJ, Butcher MS, et al. A Revised SAS Macro for Computing the Charlson Score. Poster presented at the National Cancer Institute [Internet].[cited 2018 Oct 25]. Available from https://20tqtx36s1la18rvn82wcmpn-wpengine.netdna-ssl.com/wp-content/uploads/2016/11/P-32.pdf

26. STROBE Statement: Available checklists [Internet]. [cited 2018 Jun 7]. Available from: https://www.strobe-statement.org/index.php?id=available-checklists

27. International Committee of Medical Journal Editors (ICMJE). ICMJE uniform requirements for manuscripts [Internet]. 2017 [cited 2017 Sep 6]. Available from: http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

14. LIST OF TABLES

Not Applicable

15. LIST OF FIGURES

Figure. Schematic of study design

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Table 1. Dataset to be collected according to study time points

Variables	Study time points			
	Baseline (From disease diagnosis to index date)	**Index date**	**Post-initiation observation period**	**Other**
Palbociclib treatment: date start, dose, date dose modified (new dose), date end and reason for end		✓	✓	
Date of birth (MM/YY)				✓
M/F				✓
Ethnicity (categories in eCRF)				✓
Patient status at the end of data collection period (alive/dead) • date of death / last clinic visit • If not known (i.e. lost to follow-up), date of last recorded hospital visit.			✓	
Clinical response assessments during the follow-up period: date of assessment and outcome (complete response / partial response / no response or stable disease / progressive disease), as documented by the local investigator.			✓	
Date of data collection time points (to be specified in eCRF)			✓	
Menopausal status (Y/N)	✓			
BC Diagnosis: • Date of diagnosis. • Primary / recurrent disease • Site, grade, biopsy (site biopsied, categories to be provided in eCRF), lymph node involvement, oestrogen-receptor status, progesterone-receptor status, and HER2 status	✓			
Treatment for primary/ secondary BC: • (neo)-adjuvant chemotherapy: pathological complete response achieved Y/N, date start and date stopped • type of surgery: wide local, mastectomy • (neo)adjuvant oestrogen therapy: date	✓			

Variables	Study time points			
	Baseline (From disease diagnosis to index date)	**Index date**	**Post-initiation observation period**	**Other**
start and stopped				
Relevant comorbidities documented within baseline period (to include all individual components of the NCI-DCI, to be further defined in full in the eCRF).	✓		✓	
Date of start and end of concomitant medication treatment : letrozole, fulvestrant, osteo-strengthening drugs (denosumab, zometa), other (all medications to be included in eCRF)	✓		✓	
First 3 lines of medications after palbociclib discontinuation			✓	
Hemoglobin results to be extracted pre-first cycle, on day 1 of each cycle of treatment, on day 15 into cycles 1 and 2 and day 22 if available	✓	✓	✓	
White cell counts to be extracted as above	✓	✓	✓	
Absolute neutrophil counts to be extracted as above	✓	✓	✓	
Platelet counts to be extracted as above	✓	✓	✓	
Aspartate transaminase levels to be extracted as above	✓	✓	✓	
Alanine transaminase levels to be extracted as above	✓	✓	✓	
Alkaline phosphatase levels to be extracted as above	✓	✓	✓	
Calcium levels to be extracted at pre-first cycle, then at each cycle, in the first year following initiation	✓	✓	✓	
Phosphate levels to be extracted as above	✓	✓	✓	
Calls from patient to CNS: dates and reason			✓	
BC-related inpatient admissions to hospital: planned (elective), A&E, reasons, duration (dates of entry and discharge)			✓	
BC-related outpatient admission: dates, reason			✓	

Variables	Study time points			
	Baseline (From disease diagnosis to index date)	**Index date**	**Post-initiation observation period**	**Other**
Progression: sites, dates			✓	
AE: Neutropenia (Y/N), date start and end, grade			✓	
AE: Febrile Neutropenia (Y/N), date start and end			✓	
AE: Diarrhoea (Y/N), date start and end, grade			✓	
AE: Nausea (Y/N), date start and end, grade			✓	
AE: Vomiting (Y/N), date start and end, grade			✓	
Death: date, cause				✓

Note: All dates are DD/MM/YYYY for all patients, except for date of birth (MM/YY)