**VERSION HISTORY**

| Version | Effective Date | Change Type (New, Revise, Admin) | Summary of Revisions |
|---|---|---|---|
| 1.0 | 24-Sep-2018 | New | New statistical analysis plan template required for non-interventional primary data collection study. Replaces CT24-GSOP-SD-GL04 1.0 NI Study Statistical Analysis Plan Template 31-Dec-2013. Converted from a supporting document to a required form and added to the instructions that an equivalent document may be used as long as the equivalent includes the core statistical elements. |
| 2.0 | 25-Oct-2018 | Revise | Some minor edits as a result of Pfizer Statistical review |
| 3.0 | 16-Dec-2020 | Revise | Edits to align with protocol updates and analysis suggestions from Pfizer and investigators. |
| 4.0 | 21-Dec-2020 | Revise | Edits based on review comments |
| 5.0 | 17-Jan-2022 | Revise | Updates to reflect decisions made by the CI and Pfizer regarding the analyses. |

# Non-Interventional Study Protocol
# X9001194

# 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)

## Statistical Analysis Plan
## (SAP)

**Version**: 5.0

**Author**: PPD

**Date**: 17-Jan-2022

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# 1 AMENDMENTS FROM PREVIOUS VERSION(S)

Updated to reflect decisions since the last version (4 0) made regarding the analyses by the CI and Pfizer. Amendments mainly focus on Sections 6 and 8 of this SAP.

# 2 INTRODUCTION

Note: in this document any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

*Palbociclib was recommended for use with an aromatase inhibitor in patients with locally advanced and metastatic breast cancer (MBC) in the NHS in England by the National Institute for Health and Care Excellence (NICE) in November 2017 and by the Scottish Medicine Consortium (SMC) in December 2017[1,2]. In order to provide access to palbociclib in the UK during the NICE/SMC appraisal period, the Ibrance® Patient Program (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), Hormone Receptor Positive (HR+)/Human Epidermal Growth Factor 2 Negative (HER2-) MBC[3].*

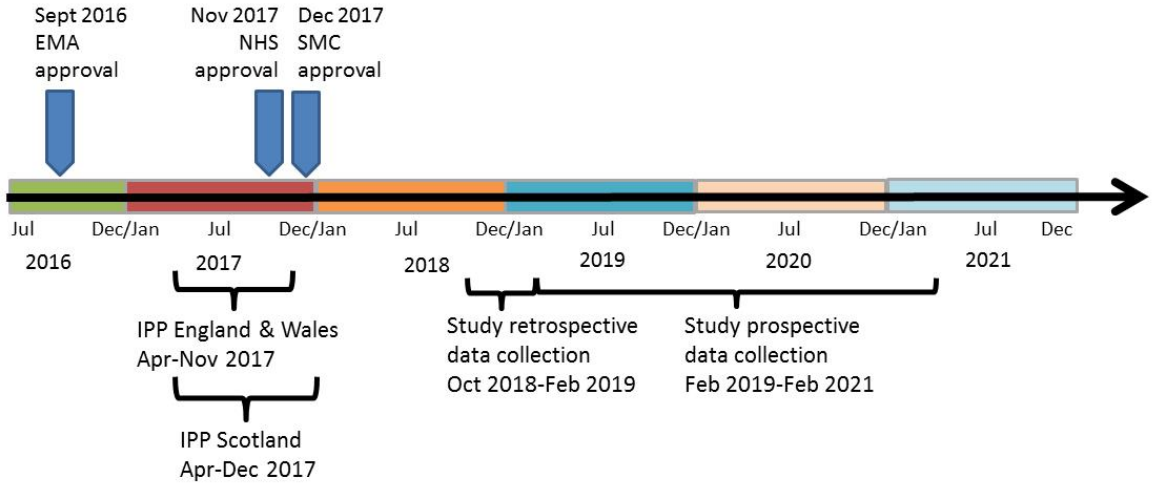
*Pfizer are interested in the opportunity to collect data from patients who received palbociclib as part of the IPP, to better understand effectiveness and safety of palbociclib when used in routine care in a UK context, with a focus on treatment persistence and dose management, patients' characteristics, 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.*

## 2.1 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 enrolment into the IPP.*

*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**




**Study population**

*Across the entire UK, 846 women received palbociclib as part of the IPP. In the sites selected for this study, approximately 200 patients received palbociclib as part of the IPP* and consented to participate in the study.

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

- *Patients enrolled into the IPP at one of the selected*
- *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 enrolment into the IPP*

*All eligible patients within the selected sites will be recruited into the study (and who provide informed consent, in the case of living patients, at sites where data collection is performed by pH Associates).*

*Data will be retrospectively collected from the point of patient's enrolment into the IPP until initial data collection, expected to take place between November 2018 and February 2019. After the initial retrospective data collection, data will be collected prospectively up to a maximum of 3 years from enrolment 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.*

**Data source**

*The study will be conducted in 8 or 9 NHS Trusts. Sites will be selected on the basis that:*

- *They are geographically dispersed across the UK.*
- *Their cancer service participated in the IPP.*
- *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) metastatic breast cancer subcommittee and 2) had patients on the IPP. All members of the steering committee meet this criterion. The NCRI subcommittee is an independent committee from Pfizer, and Pfizer has not input into the committee as part of this study.*
- *They have an interest in taking part in the study.*
- *They have appropriate and sufficient personnel available locally to identify eligible patients, collect the required data from medical records and to appropriately conduct the study in accordance with applicable legal and regulatory requirements.*

*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); which will subsequently be updated by members of the direct care team.*

## 2.2 STUDY OBJECTIVES

*What are the real-world treatment patterns, patients' characteristics, clinical outcomes, and healthcare resource utilisation associated with palbociclib treatment in* the 2 *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 [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 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.*

## 3 INTERIM ANALYSES

Interim analyses and analyses for manuscripts produced during the will be produced as per contracts between Pfizer and OPEN VIE. Endpoints to be evaluated will be defined prior to the commencement of analysis through discussions between Pfizer, OPEN VIE and the Chief Investigator.

## 4 HYPOTHESES AND DECISION RULES

### 4.1 STATISTICAL HYPOTHESES

*This is a descriptive study and there is no a priori hypothesis specified.*

### 4.2 STATISTICAL DECISION RULES

N/A

## 5 ANALYSIS SETS/POPULATIONS

*Across the entire UK, 846 women received palbociclib as part of the IPP. In the sites selected for this study, approximately 250 patients received palbociclib as part of the IPP. All eligible patients within the selected sites will be recruited into the study (and who provide informed consent, in the case of living patients, at sites where data collection is performed by pH Associates).*

### 5.1 FULL ANALYSIS SET

The full analysis set will be comprised of medical records extracted for the purpose of the study from all eligible patients who are enrolled into the study (either deceased with access to their medical records via their direct care team or living and having provided written informed consent to access of their medical records as part of the study). Analysis will be conducted on the 2-year follow-up data.

## 5.2 SAFETY ANALYSIS SET

N/A

## 5.3 OTHER ANALYSIS SET

N/A

## 5.4 SUBGROUPS

Subgroup analyses will be conducted on the whole dataset according to the treatment lines groups defined below:

- First Line (palbociclib prescribed as the first line treatment for metastatic breast cancer)
- First line palbociclib added to letrozole (palbociclib prescribed as the first line treatment and added to letrozole which is ongoing at index and prescribed more than 3 months prior to initiation on palbociclib)
- Second line (palbociclib prescribed as the second or later treatment line (in the clinician's/Pfizer's opinion) for metastatic breast cancer)

# 6 ENDPOINTS AND COVARIATES

The following endpoints will be estimated for the final report. Additional endpoints evaluated as a result of decisions made by the CI and Pfizer have been italicized. This list is designed to reflect the analyses conducted.

**Primary Objective: To describe patient demographic and clinical characteristics at initiation of palbociclib.**

- Age at initiation of palbociclib.
- Distribution of treatment lines
- Time to letrozole – 1st line palbociclib group
- Sex (male/female)
- Ethnicity of patients initiated on palbociclib.
- Menopausal status at initiation of disease
- Menopausal status at recurrence of disease
- Menopausal status at diagnosis of metastatic disease
- Disease free interval
- Summary measures of MBC history, including:
  - Whether cancer is primary or recurrent diagnosis.
  - Site and grade of disease.
  - Lymph node involvement (including number of lymph nodes) at initial BC diagnosis and by de novo status
  - Oestrogen-receptor, progesterone-receptor and HER2 status at initiation of disease

- Oestrogen-receptor, progesterone-receptor and HER2 status in the metastatic setting
- Proportion of patients (non de-novo metastatic only) who had a rebiopsy
- Oestrogen-receptor, progesterone-receptor and HER2 status at recurrence of disease out of those patients who were rebiopsied.
- Tumour stage at initial disease diagnosis and by de novo status
- Nodal status at initial disease diagnosis and by de novo status
- Metastatic at initial disease diagnosis and by de novo status
- Tumour size at initiation of disease and by de novo status
- Tumour grade at initiation of disease and by de novo status
- Proportion of patients who had Ki67 measured
- Summary of Ki67 values out of those patients with Ki67 measured.
- ECOG performance score at initial disease diagnosis
- ECOG performance score at recurrent disease diagnosis
- ECOG score at metastatic diagnosis
- Type of recurrence
- Number of metastatic sites.
- Location of metastases
  - Non-visceral location of metastases
  - Metastatic sites with locoregional recurrence
- Duration of BC disease at initiation of palbociclib.
  - Defined as date of diagnosis to date of initiation of palbociclib.
- Treatment history of MBC
  - Proportion of patients treated with chemotherapy in the neoadjuvant or adjuvant setting
    - Chemotherapy name
  - Proportion of patients treated with chemotherapy in the advanced/disease modification/metastatic setting
    - Chemotherapy name
    - Number of lines of prior chemotherapy for metastatic disease
  - Proportion of patients for whom an LHRH was used
  - Proportion of patients treated with endocrine therapy in the neoadjuvant or adjuvant setting
    - Endocrine therapy name
  - Proportion of patients treated with endocrine therapy in the advanced/disease modifying/metastatic setting
    - Endocrine therapy name
    - Number of lines of prior endocrine therapy for metastatic disease
  - Proportion of patients treated with radiotherapy in the advanced/disease modifying/metastatic setting
- Concomitant medications (defined as medications prescribed whilst on palbociclib)
- Concomitant medications prescribed alongside goserelin

- Number of prior treatments in the metastatic setting, all prior therapies as well as chemotherapy/endocrine therapy combined and separately

**Secondary Objective 1: 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:
  - Starting Dose.
  - Endocrine partner prescribed alongside palbociclib
  - Proportion of patients with dose reductions at 1, 2 and 3 years after initiation.
  - Proportion of patients with palbociclib treatment discontinuation at 1, 2 and 3 years after initiation.
  - Reasons for discontinuation of palbociclib
  - Proportion of patients with temporary discontinuations
  - Time to dose reduction in number of days (from start of treatment) – 1st line treatment group only
  - Time to palbociclib discontinuation ('drug survival') in number of days (from start of treatment) in those patients permanently discontinuing palbociclib
  - Reasons for discontinuation.
  - 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.
  - Number of completed 28-day cycles per patient.
  - Proportion of patients co-administered letrozole at palbociclib initiation.
  - Proportion of patients co-administered fulvestrant at palbociclib initiation.

**Secondary Objective 2: 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 2-years following initiation of palbociclib who:
  - Are free from disease progression.
  - Are alive
  - Achieved PR
  - Achieved CR
  - Had stable disease
- Median (95% confidence interval [CI]):
  - PFS

  - OS
  - Time to achieving best overall response
- Length of follow-up
- Best response to palbociclib, overall and by de novo and relapse status
- Time to best response – by de novo and relapse status
- Time to first response – overall and by de novo and relapse status

**Secondary Objective 3: To describe the occurrence of neutropenia during the first-year post-initiation observation period.**

- In the 6 months post-palbociclib initiation, proportion of patients who experience,
  - Neutropenia (overall and by grade, recorded and inferred from ANC measurements).
  - Worst neutropenia experienced within 3 months of palbo initiation
  - Febrile Neutropenia.

**Secondary Objective 4: 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 who experience Gastro-intestinal toxicity, including:
  - Diarrhoea.
    - Severity
  - Nausea.
    - Severity
  - Vomiting.
    - Severity

    - Proportion of patients experiencing an AE during follow-up

**Secondary Objective 5: To describe progression of clinical indicators, including biochemical and radiological indicators at each time-point available during the first year following palbociclib treatment initiation.**

- Summary measures of full blood counts in the first 6 months following initiation:
  - Haemoglobin.
  - White cell counts.
  - Absolute neutrophil counts.
  - Platelet counts.
- Summary measures of liver function tests in the first 6 months following initiation:
  - aspartate transaminase (also called aspartate aminotransferase).
  - alanine transaminase (also called alanine aminotransferase).
  - alkaline phosphatase.
  - Albumin
  - Bilirubin

- Summary measures of bone profile in the first 6 months following initiation:
  - Calcium.
  - Phosphate.
- Summary measures of urea and electrolytes in the first 6 months following initiation:
  - Creatinine
  - Potassium
  - Sodium
  - Urea
- Summary measures of radiological indicators in the first 6 months following initiation including the proportion of patients with:
  - Stable disease.
  - Progressive disease.
  - CR or PR.

**Secondary Objective 6: To describe BC-related healthcare resource utilisation during the first year following palbociclib initiation.**

- Summary measures of hospital admissions for each line of therapy, including:
  - Proportion of patients with at least one inpatient admission recorded
  - Inpatient admissions per patient.
    - Elective or non-elective.
    - Reasons for admission (including day cases).
  - Length of stay per inpatient admission.
  - Proportion of patients with at least one outpatient visit recorded
  - Outpatient visits per patient.
  - Reason for outpatient visit
  - Type of HCP seen during outpatient visits
- Proportion of patients with at least one interaction with CNS
- Number of CNS interactions per patient
- Type of CNS interaction
- Reason for CNS interaction
- Proportion of patients with at least one interaction with AOS
- Number of AOS interactions per patient
- Type of AOS interaction
- Reason for AOS interaction

For the estimation of endpoints, *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* (as documented in the radiological assessment section of the eCRF) *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).*

# 7 HANDLING OF MISSING VALUES

*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).* The 15th of August will only be used for missing dates that are related to the IPP program, e.g., start date of palbociclib cycle. *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.*

# 8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

## 8.1 STATISTICAL METHODS

The following statistical methods will be used:

Full analysis will be conducted on 2-year follow up data not 3-year follow up data.

### 8.1.1 Analysis for quantitative data

Quantitative data will generally be analysed using basic summary statistics of central tendency (including means and medians) and dispersion (including standard deviations, the interquartile range [IQR] and the range). If distributions are normally distributed (evaluated through inspection of histograms), 95% confidence intervals will be calculated assuming a normal distribution, otherwise the median and IQR will be presented instead. Where appropriate, i.e., for ordinal endpoints frequency and percentages will be presented along with summary statistics.

### 8.1.2 Analysis for categorical data

For categorical data, frequency and percentage tables will be presented.

### 8.1.3 Analysis for binary endpoints

Most binary endpoints will be summarised using frequency tables with percentages. For survival-related endpoints, Kaplan-Meier analysis may be used with proportions of patients reaching an event after different time periods and median survival (the time at which 50% of patients have reached a given endpoint out of all patients that are still being followed-up at that point or have reached that given end point) with 95% confidence intervals estimated using the method of Brookmeyer and Crowley[6] or another appropriate method[7]. Swimmer plots will be used to show individual patient response to treatment over time (CR, PR, stable disease, progressive disease); these are plots that display a range of information with bars indicating the length of follow-up for each individual patient and symbols on the bars showing where CR and PR are reached and end.

## 8.2 STATISTICAL ANALYSES

*Definitions will be implemented as in section 8.1.3. 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.*

Note: Some analyses that were originally proposed were not conducted as per the decisions of the CI and Pfizer team, these have been kept in this section as a record.

### 8.2.1 Primary Objective: To describe patient demographic and clinical characteristics at initiation of palbociclib.

**Proposed:** Age, duration of MBC prior to palbociclib (calculated by subtracting the date of initial BC diagnosis from the date of palbociclib initiation), number of lymph nodes involved, tumour size at initial disease diagnosis and Ki67 values will be summarised as quantitative variables (see section 8.1.1) using measures of central tendency (mean and median) and dispersion (standard deviation, interquartile range [IQR] and range) will be calculated. All other variables analysed as part of the primary endpoint, whether categorical or binary, will be presented as frequencies and percentages.

**Actual:** Age was presented as both a quantitative variable as per section 8.1.1 and as a categorical variable (Categories: Less than 40 years old, between 40 and 50 years old,

between 50 and 65 years old and aged 65 and over). Disease free interval was defined as the time from last known date the patient was on (neo)adjuvant hormone therapy to the date of metastatic breast cancer diagnosis (non de novo patients only). Disease free interval was presented as a categorical variable as per section 8.1.2 (Groups: less than or equal to 12 months and greater than 12 months). Time from letrozole to palbociclib initiation was presented as a quantitative variable as per section 8.1.1 for the first line palbociclib added group only. Time from letrozole was calculated by subtracting the start date of letrozole (ongoing at palbociclib initiation) from the date of palbociclib initiation. Number of metastatic sites was presented as a categoric variable as per section 8.1.2 (Groups: 1,2,3, 4 or more). Number of lines of prior endocrine therapy and chemotherapy prescribed for metastatic disease were presented as quantitative variables as per section 8.1.1. All other variables, aside from those named in this paragraph or the paragraph directly above were analysed as categoric variables as per section 8.1.2.

**8.2.2 Secondary Objective 1: To describe treatment pattern (as per licence/IPP requirement); including the proportion of patients with dose modification and who switch treatment at 1 and 2 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.**

**Proposed:** Starting and mean dose of palbociclib and subsequent treatments after progression, length of treatments and time to dose reduction and discontinuation of palbociclib in days will be summarised as quantitative variables (see section 8.1.1). Times will be calculated in days through subtracting the time of first dose reduction/discontinuation from the date of palbociclib initiation. Treatment after progression and reasons for discontinuation, the proportion of patients completing a daily cycle, having dose reductions, treatment discontinuation and being co-administered letrozole and fulvestrant at palbociclib initiation will be summarised as categorical variables using frequencies and percentages (see section 8.1.2). Reasons for discontinuation of palbociclib will be presented as categorical data (see section 8.1.2) The proportions of patients with dose reductions and discontinuation will be calculated separately at 1 and 2 years after palbociclib initiation. Quantitative discrete variables (such as the number of completed cycles per patient) will be summarised using a combination of the approaches described in sections 8.1.1 and 8.1.2, if appropriate.

**Actual:** Starting dose of palbociclib was presented as a categoric variable as per section 8.1.2. Endocrine partner prescribed alongside palbociclib, proportion of patients with recorded dose reductions, proportion of patients who discontinued palbociclib and the associate reasons, proportion of patients with temporary interruptions to palbociclib treatment were presented as categoric variables as per section 8.1.2. Time to dose reduction was presented as a categoric variable as per section 8.1.2 (Categories: Patient did not have a dose reduction, dose reduction occurred within 3 months of palbociclib initiation, dose reduction occurred between 3 and 6 months after palbociclib initiation and dose reduction occurred over 6 months after palbociclib initiation). Number of patients

prescribed treatment in the 1st, 2nd, and 3rd line after palbociclib discontinuation was presented as a categoric variable as per section 8.1.2. Dose, duration of subsequent treatments and number of completed 28-day cycles per patient were presented as quantitative variables as per section 8.1.1. Number of completed 28-day cycles (categories: 1-6 cycles, 7-12 cycles, 13-18 cycles, 19-24 cycles, 25-27 cycles and No completed cycles) and the proportion of patients co-administered letrozole or fulvestrant were presented as categoric variables as per section 8.1.2. All other endpoints were evaluated as proposed.

**8.2.3 Secondary Objective 2: 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 and 2 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".**

**Proposed:** 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 (e.g., 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 and 2 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.

**Actual:** Proportion of patients free from disease progression, are alive, achieved PR, CR or stable disease were analysed separately at the 2-year timepoint only. Length of follow-up, and time to best response and first response were presented as quantitative variables as per section 8.1.1. Best response to palbociclib, overall and by de novo and relapse status was treated as a categoric variable and analysed according to section 8.1.2.

**8.2.4 Secondary Objective 3: To describe the occurrence of neutropenia during the first-year post-initiation observation period.**

**Proposed:** The proportion of patients developing neutropenia and febrile neutropenia in the first 6 months post-palbociclib initiation will be summarised as a binary variable (see section 8.1.3), while occurrences per patient will be summarised as a quantitative variable (see section 8.1.1). Analyses for occurrences of neutropenia will be analysed overall and sub-divided by grade. Incidences of neutropenia will be presented in two ways. Firstly, neutropenia in the 6 months post-palbociclib initiation will be presented. Absolute neutrophil count, recorded as part of full blood counts or as part of the neutropenia dataset collected, will be used to determine incidences of neutropenia according to the CTC version 2.0 criteria (http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf]). Only absolute neutrophil counts from the neutropenia dataset that are within 6 months of palbociclib initiation will be included. Secondly, incidences of neutropenia as recorded in the notes will be presented as a quantitative variable (see section 8.1.1). The time from palbociclib initiation to first incidence of neutropenia will be presented as a quantitative variable (see section 8.1.1) with the categories to be determined after visualisation of the data.

**Actual:** Neutropenia, overall and by grade, was presented from two different sources on the eCRF (as recorded in the notes and inferred from the ANC measurements recorded in the 6 months post-palbociclib initiation) as a categoric variable as per section 8.1.2. Proportion of patients experiencing febrile neutropenia and the worst grade of neutropenia experienced within 3-months of palbociclib initiation were also presented as a categoric variable as per section 8.1.2.

### 8.2.5 Secondary Objective 4: To describe the occurrence of gastro-intestinal toxicity, including diarrhoea, nausea and vomiting during the first-year post-initiation observation period.

**Proposed:** The proportion of patients developing diarrhoea, nausea and vomiting in their first year will summarised as a categorical variable (see section 8.1.2), while occurrences per patient will be summarised as a quantitative variable (see section 8.1.1). All the above will be assessed at 1, 15 and 22 days into the treatment cycle, for each cycle, as well as after 1 year of follow-up post-initiation of palbociclib.

**Actual:** Proportion of patients experiencing diarrhoea, nausea and vomiting as well as the associated grade were presented as categoric variables as per section 8.1.2. Proportion of patients experiencing an AE (at least one of neutropenia, diarrhoea, nausea, and vomiting) was presented as frequencies and proportions.

### 8.2.6 Secondary Objective 5: 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 etc.).

**Proposed:** The first, mean, median, minimum, and maximum results per patient of all full blood counts, results of liver function tests and bone profile during the 6 months following palbociclib initiation will be summarised as quantitative variables (see section 8.1.1). For radiological indicators, proportions of patients with stable disease, progressive disease and who achieve CR/PR will be treated as binary variables (see section 8.1.3); the first or modal measurement will be used if there is more than one observation per patient. All the above will be assessed at 1, 15 and 22 days into the treatment cycle as well as after 1 year.

**Actual:** Baseline full blood counts, liver function tests, bone profile measurements and urea and electrolytes will be presented as quantitative variables as per section 8.1.1. To account for different number of test values in the 6 months post-palbociclib initiation, blood values were summarised per patient and then presented as quantitative variables as per section 8.1.1. Radiological indicators were presented as categoric variables as per section 8.1.2.

### 8.2.7 Secondary Objective 6: To describe BC-related healthcare resource utilisation (hospital admissions, outpatient visits and calls to CNS) during the first year following palbociclib initiation.

**Proposed:** The total number of inpatient, emergency department visits and outpatient visits will be calculated in the first year palbociclib initiation. The number of visits to each of these clinics per patient will be summarised as a quantitative variable (see section 8.1.1). Reasons for admission for each of these will be compiled and treated as a categorical variable (see section 8.1.2). For inpatient admissions, the proportion of visits that were planned/elective or non-elective/accident and emergency will be described using frequencies and percentages (see section 8.1.3). Length of stay per inpatient admission will be treated as a quantitative variable (see section 8.1.1). The number of phone calls to CNS will be compiled with the distribution of reasons analysed as a categorical variable (see section 8.1.2). The number of contacts with the AOS with distributions of reasons and types of contact (phone calls or visits) will also be compiled and displayed using a frequency table with percentages (see section 8.1.2).

**Actual:** Proportion of patients with at least one inpatient admission, reasons for admission, elective or non-elective admission were presented as a categoric variable as per section 8.1.2. Inpatient, outpatient, CNS and AOS interactions per patient as well as length of inpatient admission were presented as per quantitative variables as per section 8.1.1. All other endpoints were presented as categoric variables as per section 8.1.2.

### 8.2.8 Safety Analyses

No safety analyses planned.

### 8.2.9 Summary of Analyses

| Outcome | Analysis Set | Supports Protocol Objective Number | Subgroups | Statistical Method | Missing Data |
|---|---|---|---|---|---|
| Summary of age at initiation of palbociclib | Full Analysis set | Primary Objective | Overall and treatment Line | Calculated by subtracting Date of palbociclib initiation from Date of Birth. Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) | Day of birth assumed to be the 15th. If month is missing, birthday assumed to be 1st July. Otherwise excluded. |
| Distributions of categorical, binary, and ordinal demographical and clinical characteristics | Full Analysis set | Primary Objective | Overall and treatment Line | Frequency tables and percentages | Excluded |
| Summary measures of MBC statistics | Full Analysis set | Primary Objective | Overall and Treatment Line | Frequency tables and percentages<br>Summary statistics for Ki67 proliferation index (incl. Mean/Median/SD/IQR/Range) | Excluded |
| Duration of MBC at palbociclib initiation | Full Analysis set | Primary Objective | Overall and Treatment Line | Calculated by subtracting Date of palbociclib initiation from Date of MBC diagnosis. Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) | Standard imputation for dates (section 7), otherwise exclude. |
| Treatment for MBC diagnosis prior to palbociclib initiation | Full Analysis set | Primary Objective | Overall and Treatment Line | Frequency tables and percentages | Excluded |
| Summaries of comorbidities and Charlson comorbidity index of patients at palbociclib initiation | Full Analysis set | Primary Objective | Overall and Treatment Line | Frequency tables and percentages for each comorbidity type<br>Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) for Charlson comorbidity index | Excluded |
| Palbociclib prescribed as on or off-label | Full Analysis set | Primary Objective | Overall and Treatment Line | Frequency tables and percentages | Excluded |
| Summary measures of palbociclib treatment patterns | Full Analysis set | Secondary Objective 1 | Overall and Treatment Line | Frequency tables and percentages for proportions and categorical variables such as proportion of patients with dose reductions or discontinuation and reasons for discontinuation<br>Summary statistics calculated (incl. | Excluded |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Mean/Median/SD/IQR/Range) for doses, time to dose reduction and discontinuation and length of treatment | |
| Describing treatment patterns 1,2 and 3 years after palbociclib initiation | Full Analysis set | Secondary Objective 1 | Overall and Treatment Line | Frequency tables and percentages for proportions of patients completing a 28-day cycle, co-administered letrozole and fulvestrant at palbociclib initiation. Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) for number of completed 28-day cycles | Excluded |
| Proportion of patients free from disease progression | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Frequency tables and percentages | Excluded |
| Proportion of patients alive | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Frequency tables and percentages | Excluded |
| Proportion of patients achieving PR/CR/with stable disease | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Frequency tables and percentages | Excluded |
| Median PFS | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Kaplan-Meier analysis, median PFS measured as being time from the date of palbociclib initiation to the date of first document disease progression or death. 95% confidence intervals calculated for median. | Standard imputation for dates (section 7), otherwise exclude. |
| Median OS | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Kaplan-Meier analysis, median OS measured as being time from the date of palbociclib initiation to the date of death. 95% confidence intervals calculated for median. | Standard imputation for dates (section 7), otherwise exclude. |
| Median time to best overall response (CR or PR) | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Kaplan-Meier analysis, time to first best overall response (partial/complete response) measured as being time from the date of palbociclib initiation to the date of first response. 95% confidence intervals calculated for median. | Standard imputation for dates (section 7), otherwise exclude. |
| Swimmer plots | Full Analysis set | Secondary Objective 2 | Overall and Treatment Line | Swimmer plots used to represent patient response (CR / PR/ stable disease / progressive disease) to treatment for patients responding to treatment (CR or PR). | |
| Duration of response (PR/CR) | Patients enrolled achieving PR/CR | Secondary objective 2 | Overall and Treatment Line | Kaplan-Meier analysis, median duration of response measured as being time from the | Standard imputation for dates (section 7), |

| | | | | | |
|---|---|---|---|---|---|
| | during follow-up in Full Analysis set | | | date of CR/PR to documented disease progression or death. 95% confidence intervals calculated for median. | otherwise exclude. |
| Proportion of patients experiencing neutropenia and febrile neutropenia for first year post-observation period | Full Analysis set | Secondary objective 3 | Overall and by grade of neutropenia. Treatment Line | Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) and frequency and percentages of proportions of patients with neutropenia and febrile neutropenia. | Excluded |
| Proportion and summary measures of patients experiencing gastro-intestinal toxicity during first year observation period | Full Analysis set | Secondary objective 4 | Overall and Treatment Line | Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) and frequency and percentages of proportions of patients with experiencing gastro-intestinal toxicity including diarrhoea, nausea, and vomiting. | Excluded |
| Summary measures of full blood counts in the first year of initiation | Full Analysis set | Secondary objective 5 | Overall and Treatment Line | Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) of haemoglobin, white cell counts, absolute neutrophil counts, and platelet counts. The mean, median, minimum, and maximum reading will be used where multiple tests are taken within the study period. | Excluded |
| Summary measures of liver function tests in the first year following initiation of palbociclib | Full Analysis set | Secondary objective 5 | Overall and Treatment Line | Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) aspartate transaminase, alanine transaminase and alkaline phosphatase. The mean, median, minimum, and maximum reading will be used where multiple tests are taken within the study period. | Excluded |
| Summary measures of bone profile in the first year of initiation | Full Analysis set | Secondary objective 5 | Overall and Treatment Line | Summary statistics calculated (incl. Mean/Median/SD/IQR/Range) of calcium and phosphate. The mean, median, minimum, and maximum reading will be used where multiple tests are taken within the study period. | Excluded |
| Summary measures of radiological indicators in the first year of initiation | Full Analysis set | Secondary objective 5 | Overall and Treatment Line | Frequency and percentages for proportions of patients with stable and progressive disease or CR or PR. Where there is more than one test, the first, most common and most favourable test results will be used. | Excluded |
| Summary measures of hospital admissions for each | Full Analysis set | Secondary objective 6 | Overall and Treatment Line | Frequency and percentages of inpatient, outpatient and emergency department visits | Excluded |

| | | | | | |
|---|---|---|---|---|---|
| line of therapy | | | | and summary measurements of visits per patient (incl. Mean/Median/SD/IQR/Range) and lengths of inpatient stay | |
| Summary of phone calls from patient to Cancer National Services | Full Analysis set | Secondary objective 6 | Overall and Treatment Line | Frequency and percentages for phone calls and reasons for visit | Excluded |
| Summary of phone calls from patient to Acute Oncology Services | Full Analysis set | Secondary objective 6 | Overall and Treatment Line | Frequency and percentages for phone calls, reasons for visit and contact types | Excluded |

## 9 LIST OF TABLES AND TABLE SHELLS

As per documents sent to Pfizer over the course of the project.

## 10 REFERENCES

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## 11 APPENDIX - ADDITIONAL INFORMATION

### Details about the Charlson Comorbidity Index

The Charlson comorbidity index[4] is a weighted index for predicting mortality that considers the number and seriousness of comorbid disease. An updated index from work by Steadman et al. will be used for this analysis[5].

| Co-morbidity | Weight |
|---|---|
| Acute Myocardial infarction | |
| History of Myocardial infarction | |
| Cardiovascular disease (CVD) | |

| | |
|---|---|
| Congestive heart failure | 2 |
| Peripheral vascular disease | 0 |
| Cerebrovascular disease | 0 |
| Dementia | 2 |
| Chronic pulmonary disease | 1 |
| Rheumatologic disease | 1 |
| Peptic ulcer disease | 0 |
| Mild liver disease | 2 |
| Diabetes without chronic complications | 0 |
| Diabetes with chronic complications | 1 |
| Hemiplegia or paraplegia | 2 |
| Renal disease | 1 |
| Moderate or severe liver disease | 4 |
| AIDS/HIV | 4 |
| **Maximum score** | |

**Dataset to be collected according to study time points**

| | **Study time points** | | | |
|---|---|---|---|---|
| **Variables** | **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) | | | | ✓ |

| Variables | Study time points | | | |
|---|---|---|---|---|
| | **Baseline (From disease diagnosis to index date)** | **Index date** | **Post-initiation observation period** | **Other** |
| M/F | | | | ✓ |
| Ethnicity (categories in eCRF) | | | | ✓ |
| Patient status at the end of data collection period (alive/dead)<br>• date of death / last clinic visit<br>• 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:<br>• Date of diagnosis.<br>• Primary / recurrent disease<br>• 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:<br>• (neo)-adjuvant chemotherapy: pathological complete response achieved Y/N, date start, and date stopped<br>• type of surgery: wide local, mastectomy<br>• (neo)adjuvant oestrogen therapy: date start and stopped | ✓ | | | |
| Relevant comorbidities documented within baseline period (to include all individual components of the Charlson | ✓ | | ✓ | |

| Variables | Study time points | | | |
|---|---|---|---|---|
| | **Baseline (From disease diagnosis to index date)** | **Index date** | **Post-initiation observation period** | **Other** |
| comorbidity index, 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 | | | ✓ | |
| Haemoglobin 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 | | | ✓ | |
| Progression: sites, dates | | | ✓ | |

| Variables | Study time points | | | |
|---|---|---|---|---|
| | **Baseline (From disease diagnosis to index date)** | **Index date** | **Post-initiation observation period** | **Other** |
| 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)