EU RISK MANAGEMENT PLAN FOR PALBOCICLIB

RMP Version number: 1.9

Data-lock point for this RMP: 02 August 2021 (for post-marketing data)

Date of final sign off: 25 February 2022

Rationale for submitting an updated RMP:

Update in response to Type II Variation Procedure No. EMEA/H/C/003853/II/0037.
Summary of significant changes in this RMP:

Throughout the RMP, the following changes were made:

Removal of the Important Identified risks (Myelosuppression [Neutropenia, Anaemia, Thrombocytopenia] and, ILD/Pneumonitis) and Important Potential Risks (QT prolongation, Hyperglycaemia) and Missing Information (Male patients) from all relevant sections

- Part I: No edits
- Part II Module SI: No edits
- Part II Module SII: No edits
- Part II Module SIII: Corrections to CT exposure tables (Correction: The placebo patients from study A5481023 were incorrectly included in all outputs, and the A5481027 Ibrance patients were mistakenly excluded from two dosing tables.)
- Part II Module SIV: No edits
- Part II Module SV: No edits
- Part II Module SVII: Removal of the above-mentioned risks and missing information from all relevant sections and corrections to applicable CT risk tables (See correction above included in Part II Module SIII)
- Part II Module SVIII: Removal of the above-mentioned risks and missing information
- Part III: Study A5481027 removed.
- Part V: Removal of the above-mentioned risks and missing information from all relevant sections.
- Part VI: Removal of the above-mentioned risks and missing information from all relevant sections
- Updates to Annexes 7,8

Other RMP versions under evaluation: None

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Details of the currently approved RMP:

Version number: 1.7

Approved with procedure: EMEA/H/C/003853/IB/0030

Date of approval (opinion date): 15 October 2020

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s applicant´s QPPV. The electronic signature is available.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count
BIG	Breast International Group
BMI	Body Mass Index
CCND1	Cyclin D1
CCR	California Cancer Registry
CDK	Cyclin-Dependent Kinase
CHF	Congestive Heart Failure
CI	Confidence Interval
CONFIRM	Comparison of Faslodex Recurrent or Metastatic Breast Cancer
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DM	Diabetes Mellitus
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Oestrogen receptor
EU	European Union
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
IIR	Investigator-Initiated Research
ILD	Interstitial Lung Disease
LHRH	Luteinising Hormone Releasing Hormone
MAH	Marketing Authorization Holder
mg	Milligramme
MHOS	Medical Health Outcomes Survey
MI	Myocardial Infarction
OR	Odds Ratio
PD	Pharmacodynamic
PFS	Progression Free Survival
PK	Pharmacokinetic
PL	Package Leaflet
PM	Post-Marketing
PR	Progesterone Receptor
PT	Preferred Term
PY	Person Year
QD	Once Daily
QTc	QT interval corrected for heart rate
QTcS	QT interval corrected for heart rate using a study-specific correction factor
RMP	Risk Management Plan
RR	Relative Risk
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

TTP	Time To Progression
US	United States
VTE	Venous Thromboembolic Events

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

TABLE OF CONTENTS

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

LIST OF TABLES

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Palbociclib
Pharmacotherapeutic group(s) (ATC Code)	Protein kinase inhibitors (L01XEXX)
Marketing Authorisation Holder Applicant	Pfizer Europe MA EEIG (BREXIT effect)
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Ibrance
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Palbociclib is a highly selective, reversible, small molecule inhibitor of CDK 4 and 6. The chemical name of the palbociclib free base is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one.
	Summary of mode of action Through inhibition of CDK 4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 to S Phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers.
	Important information about its composition: N/A
Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Current: Palbociclib is indicated for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer: • in combination with an aromatase inhibitor • in combination with fulvestrant in women who have received prior endocrine therapy In pre- or peri-menopausal women, the endocrine therapy should be combined with a LHRH agonist.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Dosage in the EEA	Current: The recommended dose is 125 mg of palbociclib QD for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment with IBRANCE should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. When co-administered with palbociclib, the recommended dose of letrozole is 2.5 mg taken orally QD continuously throughout the 28-day cycle. Please refer to the SmPC of letrozole. Treatment of pre/peri-menopausal women with the combination of palbociclib plus letrozole should always be combined with an LHRH agonist. When coadministered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the SmPC of fulvestrant. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/peri-menopausal women should be treated with LHRH agonists according to local clinical practice. Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.
Pharmaceutical form(s) and strengths	Current: Opaque hard gelatin capsules of the following strengths: 75, 100, and 125 mg. Proposed: Film-coated tablets of the following strengths: 75, 100 and 125 mg.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = Anatomical Therapeutic Chemical; CDK = Cyclin-Dependent Kinases; EEA = European Economic Area; ER = Oestrogen receptor; EU = European Union; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor; INN = International Nonproprietary Name; LHRH = Luteinising Hormone Releasing Hormone; mg = Milligramme; N/A = Not Applicable; QD = Once Daily; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication

Palbociclib (IBRANCE®), an oral, Cyclin-Dependent Kinase (CDK) 4/6 inhibitor, is indicated for the treatment of Hormone Receptor (HR)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor
- in combination with fulvestrant in women who have received prior endocrine therapy

In pre- or peri-menopausal women, the endocrine therapy should be combined with a Luteinising Hormone Releasing Hormone (LHRH) agonist.

Incidence:

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million cases diagnosed in 2012.[1] In Europe (EU-27), the age-adjusted annualised incidence is 108.8/100,000[2] females. In the United States (US), breast cancer represents 14% of all new cancer cases in men and women with an estimated 231,840 new breast cancer cases in 2015.[3] In the US, the age-adjusted annualised incidence is 124.6/100,000 females, and the overall estimated prevalence (2011) is 1,223/100,000 females.[4] The most common breast cancer subtype is HR-positive, HER2-negative, which is also associated with better prognosis.[5]

There were no studies identified that reported incidence rates for HR-positive, HER2-negative post-menopausal advanced breast cancer. However, several population-based studies were identified that evaluated the proportion of all incident invasive breast cancers that were HR-positive, HER2-negative, including advanced stage (at diagnosis) HR-positive, HER2-negative breast cancer; these results are summarised in Table 1.[5, 6, 7,8,9,10] Using information from these studies to calculate pooled averages, an estimated 65.7% of all incident breast cancers (all stages) are HR-positive, HER2-negative, and an estimated 9.3% of all incident breast cancers are advanced stage HR-positive, HER2-negative. Based on these data, in the EU, from 15.6% to 17.4% of all incident breast cancers are advanced HR-positive, HER2-negative[5,8] and in the US, an estimated 8.8% of all incident breast cancers are advanced stage HR-positive, HER2-negative.[10] Although the rates from these studies were not specific to only post-menopausal women, the proportion of post-menopausal women ranged from approximately two-thirds to three-quarters (Table 1).

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 1. Proportion of Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative Female Breast Cancer from Various Population-based Studies

Region or Country	N	Design	Population	Proportion of HR-positive, ER2-negative patients (Advanced Stage)	Proportion of HR-positive, HER2-negative patients that were Post-menopausal or Age 50+ Years[‡]	Proportion of HR-positive, HER2-negative patients (All Stages)
Global[a]	10159	Combination of 12 population-or hospital-based studies of breast cancer conducted in various geographic regions (Blows, et al. 2010)[7]	Breast cancer	Not reported	4826 (66.6%) ‡	7243 (71.3%)
Spain	3480	Population-based study from 10 Spanish cancer registries; most cases diagnosed in 2005 (Puig-Vives, et al. 2013)[5]	Females with invasive breast cancer classified by molecular subtype	286/1647 (17.4%)	1357 (71.2%) †	1905 (68.7%)
Switzerland	1,214	Population-based Ticino Cancer Registry (Southern Switzerland) with cases ascertained between 2003-2007 (Spitale, et al. 2009)[8]	All 1st primary invasive breast cancers	119/764 (15.6%)	683 (76.9%) †	888 (73.2%)
Poland	804	Population-based case control study of breast cancer cases ascertained between 2000-2003 (Yang, et al. 2007)[9]	Women ages 20-74 years with invasive breast cancer and molecular analysis results available	Not reported	366 (66.3%) †	552 (68.7%)
US	33199	Population-based CCR with 99% ascertainment of California cancer cases and SEER (Kurian, et al. 2010)[6]	All invasive breast cancer cases diagnosed between 2006-2007 with HR and HER2 information available	Not reported	Overall (HR-positive, HER2-negative proportion not reported): 25,151 (75.8%) ‡	22382 (67.4%)

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 1. Proportion of Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative Female Breast Cancer from Various Population-based Studies

Region or Country	N	Design	Population	Proportion of HR-positive, ER2-negative patients (Advanced Stage)	Proportion of HR-positive, HER2-negative patients that were Post-menopausal or Age 50+ Years‡	Proportion of HR-positive, HER2-negative patients (All Stages)
US	61309	Population-based CCR with 99% ascertainment of California cancer cases (Parise, et al. 2009)[10]	1st primary event of invasive breast cancer diagnosed between 1994-2004 with HR and HER2 information available	3113/35320 (8.8%)	Overall (HR-positive, HER2-negative proportion not reported): 27,198/35,320 (77.2%) ‡	39366 (64.2%)
Totals	**110165**			**3518/37731 (9.3%)**		**72336 (65.7%)**

CCR = California Cancer Registry; ER = Oestrogen Receptor; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor; SEER = Surveillance, Epidemiology, and End Results.
†Post-menopausal females with HR-positive, HER2-negative breast cancer
‡Females ages ≥50 years (proxy for post-menopausal since not collected in the study) with HR-positive, HER2-negative breast cancer
a. North America, Europe, Australia

Using the 2015 overall age-adjusted annualised incidence rates of female breast cancer in the EU and US, and the pooled average rates for the proportion of females with HR-positive, HER2-negative breast cancer based on rates obtained from the literature (Table 1), incidence rates of HR-positive, HER2-negative female breast cancer are estimated to be:

- Europe

Stage	Estimated Annual Incidence	Calculation
HR-positive, HER2-negative (all stages)	71.5/100000 females	65.7% of 108.8/100000 females
ER-positive, HER2-negative (advanced stage at diagnosis)	10.1-18.3/100000 females	9.3-16.8% of 108.8/100000 females

ER = Oestrogen Receptor; HER2 = Human Epidermal Growth Factor Receptor 2.

- US

Stage	Estimated Annual Incidence	Calculation
HR-positive, HER2-negative (all stages)	81.9/100000 females	65.7% of 124.6/100000 females
HR-positive, HER2-negative (advanced stage)	11.6/100000 females	9.3% of 124.6/100000 females

ER = Oestrogen Receptor; HER2 = Human Epidermal Growth Factor Receptor 2.

Since these incidence rates of HR-positive, HER2-negative female breast cancer were calculated using available published data and were not reported directly in the published literature, they should be interpreted with caution.

Prevalence:

The 1-year age-adjusted prevalence of breast cancer in the EU-27 is 149.8/100,000[2] and the overall estimated prevalence of female breast cancer in 2012 in the US is 2,975,314 females.[3] Several population-based studies were identified that evaluated the proportion (prevalence) of all incident invasive breast cancers that were HR-positive, HER2-negative, including advanced stage HR-positive, HER2-negative breast cancer (Table 1). No studies were identified that reported prevalence rates per unit population.

Prevalence rates per unit population for persons living with cancer vary substantially depending on the interval considered since the initial cancer diagnosis. For example, in Europe (EU-27), the 1-year, 3-year, and 5-year age-adjusted prevalences for female breast cancer were 149.8/100,000, 423.4/100,000, and 665.6/100,000, respectively.[2] Interval-specific prevalence rates will vary substantially by stage at diagnosis, because survival rates are shorter for advanced stage breast cancer. Additionally, interval-specific prevalence rates will also vary based on cancer subtype (more aggressive subtypes will have shorter survival) as well as period effects (as new treatments become available, survival rates for specific stages/subtypes may increase). Because the palbociclib target population is advanced stage HR-positive, HER2-negative breast cancer, and because period effects will likely affect this subgroup of breast cancer patients due to the approval of several new

090177e1997610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

targeted cancer treatments for this subgroup in the last few years, estimating period prevalence rates for advanced stage HR-positive, HER2-negative breast cancer, in the same manner in which incidence rates were estimated, is likely to be substantially flawed. As such, no prevalence rates per unit population were estimated.

Demographics of the Target Population –Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

Age

A few studies described in Table 1 reported the mean or median age at diagnosis for HR-positive, HER2-negative breast cancer. In the Ticino Cancer Registry (Southern Switzerland), amongst the 888 women with HR-positive, HER2-negative breast cancer, the median age at diagnosis was 63.4 years (Standard Deviation [SD] ± 13.7), with 80.5% of women with HR-positive, HER2-negative breast cancer ≥50 years of age.[8] The mean age for HR-positive, HER2-negative breast cancer in the Spain study (n = 1905) was 60.2 years (SD ± 14.4);[5] and in the Poland study (n = 552), the mean age was 56.3 years (SD ± 9.9).[9] A retrospective cohort study of women with HER2-negative advanced breast cancer from a single centre in France reported a median age of 52 years (range 24-75) for the subgroup of women with advanced stage HR-positive, HER2-negative breast cancer (n=133).[11]

In the US, 83.2% of all breast cancers are diagnosed in women between 45 and 84 years of age, with the most frequent age at diagnosis (25.5%) between 55 to 64 years, and a median age at diagnosis of 61 years.[4] In the Nurses' Health Study which followed 66,145 women from 1980 through 2000 and measured incident cases of breast cancer for which information on ER/Progesterone Receptor (PR) status was available the number of ER-positive, PR-positive breast tumours increased at a faster rate than the number of ER-negative, PR-negative tumours both before and after menopause.[12]

Gender

The vast majority of breast cancers occur in women[4] and thus the majority of cancer registries and publications report information only for female breast cancer. Therefore in general the information described for the overall breast cancer incidence reflects the rates for women. The occurrence of breast cancer in men is not discussed here given the target population (pre/peri- and post-menopausal women) for palbociclib.

Race/Ethnic origin

The incidence of female breast cancer in the US by race/ethnicity, overall and for women aged ≥50 years with advanced stage disease, is provided in Table 2.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 2. Age-adjusted Incidence of Female Breast Cancer by Race/Ethnicity (United States)

Race/Ethnicity[4,13]	Overall Incidence[a,4]	Incidence of Advanced Stage in Women ≥50 Years of Age[13]
White	128.0	50.5
Black	122.8	67.0
Asian/Pacific Islander	93.6	30.7
American Indian/Alaska Native	79.3	34.9
Hispanic	91.3	40.6

a. age-adjusted incidence per 100,000.

The incidence of invasive female breast cancer in 2012 in the US among women overall, women under 50 years of age and women 50 years and over by race/ethnicity are provided in Table 3.

Table 3. Incidence of Female Breast Cancer (United States) in 2012 by Race/Ethnicity (United States) Stratified by Age[14,a]

Age	All races	White	Black	Asian/ Pacific Islander	American Indian/ Alaskan Native	Hispanic
Overall (all ages, all races)	124.7					
<50 years	42.7	42.9	44.0	39.6	22.1	33.3
≥50 years	339.2	348.2	340.0	247.0	239.3	246.9

a. age-adjusted incidence per 100,000.

Only 1 study provided information on the incidence/prevalence of HR-positive, HER2-negative breast cancer in racial/ethnic subgroups. Table 4 describes the prevalence and lifetime risk of HR-positive, HER2-negative breast cancer (all stages, n = 22,382) by race/ethnicity from a study of 33,199 women from the US California Cancer Registry (CCR).[6]

Table 4. Prevalence and Lifetime Risk of Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative Breast Cancer, by Race/Ethnicity (United States)

Race/Ethnicity[6]	Prevalence (%)[a]	Lifetime Risk
White	15713/21947 (71.6%)	8.10% (95% CI: 7.94-8.20)
Black	1098/2071 (53.0%)	4.70% (95% CI: 4.41-5.02)
Asian	2296/3658 (62.8%)	5.06% (95% CI: 4.81-5.34)
Hispanic	3275/5523 (59.3%)	4.60% (95% CI: 4.41-4.80)

CI = Confidence Interval.
a. Percentage of HR-positive, HER2-negative breast cancer among all cancers in each racial/ethnic category.

There are several well-established risk factors for breast cancer, including older age, non-Hispanic white race/ethnicity, family history of breast cancer, obesity, moderate to high consumption of alcohol, low physical activity, and exposure to reproductive hormones (either endogenous or exogenous).[15]

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Obesity is a well-established risk factor for post-menopausal breast cancer, especially in the absence of post-menopausal hormone use.[12,16] In a prospective cohort study conducted in 99,039 US-based post-menopausal women, the Relative Risk (RR) of developing breast cancer increased with increasing Body Mass Index (BMI), ranging from a RR for women with BMI 25.0-27.4 of 1.35 (95% Confidence Interval [CI] 1.08-1.68) to a RR for women with BMI ≥40 of 2.08 (95% CI 1.44-2.99).[17] While obesity has a less pronounced role in the risk of breast cancer in pre-menopausal women, it significantly increases the risk of dying of breast cancer in pre-menopausal women with HR-positive early disease.[18] When compared to normal weight counterparts, obese women with these characteristics have a 34% higher risk of breast cancer mortality, based on a large retrospective study. In terms of mechanism of action, obesity is thought to promote breast carcinogenesis through increased exposure to endogenous estrogens in adipose tissue, and particularly increases the risk of developing HR-positive, HER2-negative types of breast cancer.[16]

Several additional factors related to increased cumulative exposure to exogenous or endogenous oestrogens are also associated with increased risk of developing HR-positive breast cancer, including use of hormonal therapy, low or nulliparity, early age of menarche, late age at first birth, and late age of menopause.[12,15,19]

The Main Existing Treatment Options:

Currently, anti-endocrine therapy is the preferred option for HR-positive breast cancer, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease requiring a fast response. For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice. The additional anti-endocrine agent should be tamoxifen unless tamoxifen resistance is proven. An aromatase inhibitor is also a viable option, but absolutely mandates the use of ovarian suppression/ablation.[20]

Typically treatment in the HR-positive, HER2-negative advanced breast cancer population includes anti-endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen[21] with Time To Progression (TTP) and prolongation of Progression Free Survival (PFS) both ranging from 5 to 15 months.[21,22,23]

Letrozole is an oral non-steroidal aromatase inhibitor approved worldwide for the first-line treatment of post-menopausal women with HR-positive advanced breast cancer.[24,25] Letrozole is administered orally on a continuous 2.5 Milligramme (mg) Once Daily (QD) dosing regimen. Multiple clinical studies have shown that letrozole is well tolerated. In a multi-centre Phase 3 trial, 907 patients with HR-positive or HR-unknown advanced breast cancer were randomised to receive either letrozole or tamoxifen until disease progression.[24] Most of the patients (91%) had received no prior treatment for their advanced disease. Letrozole was superior to tamoxifen for time to tumour progression (median, 9.4 months versus 6.0 months, hazard ratio = 0.72; p <0.0001), time to treatment failure (median, 9 months versus 5.7 months, hazard ratio = 0.73; p <0.0001), objective response rate (32% versus 21%, Odds Ratio [OR] = 1.78; p-value of 0.0002), and clinical benefit rate (50% versus 38%, OR = 1.62; p-value of 0.0004).[25]

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Fulvestrant is a potent anti-estrogen drug that binds and degrades ER. Recent data with fulvestrant administered 500 mg monthly to patients with recurrent HR-positive, HER2-negative breast cancer indicate significant antitumor activity after both anti-oestrogen and aromatase inhibitor failure. In a Phase 2 study, the combination of fulvestrant and everolimus has shown efficacy in post-menopausal women after failure of aromatase inhibitor treatment similar to that of the combination of tamoxifen with everolimus (median TTP 7.4 months).[26] Fulvestrant is currently indicated for the treatment of post-menopausal women with metastatic HR-positive breast cancer following the failure of anti-oestrogen therapy. While not studied extensively in pre- or peri-menopausal women, based upon its mechanism of action and limited clinical data, it is expected to also add benefit to the treatment of pre- and peri-menopausal women when given concurrently with ovarian suppression/ablation.

Clinical experience demonstrates that ovarian ablation produces comparable outcomes to tamoxifen monotherapy and supports the use of goserelin (LHRH agonist) concurrently with fulvestrant in pre-menopausal women with metastatic breast cancer.[27,28] Ovarian suppression using LHRH analogues such as goserelin continue to grow in use and within the US have largely replaced ovarian ablation, due in part, to less morbidity and possible reversibility.[28] Courses of treatment in pre-menopausal patients with ovarian ablation/suppression do not differ from those used in post-menopausal patients.[21]

Despite the use of letrozole and other anti-endocrine therapeutic options in post-menopausal women with HR-positive, HER2-negative breast cancer at first relapse, median PFS generally remains less than 1 year.[21,24] Furthermore, despite the use of approved therapies, median PFS/TTP is less than 8 months in patients whose disease progressed after prior therapy. [29,30,31] The goal of therapy in any setting is prolongation of PFS by delaying progression, for which subsequent treatment options include chemotherapy with its associated toxicities and limited clinical benefit.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Morbidity/Complications

Important complications for patients with post-menopausal HR-positive, HER2-negative advanced breast cancer include thromboembolic events and osteoporosis/bone fracture/low bone mineral density.

Thromboembolic Events

A systematic review of 38 cohort studies published between 1966 and 2011 in patients diagnosed with one of 8 cancers, including breast, found an incidence rate of hospitalisation for venous thromboembolism of 5 per 1,000 Person Years (PYs) for average risk breast cancer patients, 55 per 1000 PY for high risk breast cancer patients and an incidence rate of 21 per 1000 PY for the overall risk of breast cancer patients.[32]

In a large population-based Danish study of 57,591 cancer patients compared to 287,476 control patients, the adjusted RR of hospitalisation for Venous Thromboembolic

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Events (VTE) among persons with breast cancer compared to the general population was 3.3 (95% CI 2.6, 4.2).[33] Advanced cancer stage, radiation and chemotherapy increased the absolute and RR of hospitalisation for VTE in breast cancer patients.

The incidence of pulmonary embolism in an outpatient cohort of oncology patients (n = 13,783) who had imaging studies from 2004-2009 was 2.87% (95% CI 2.59,3.16) overall and 1.50% (95% CI 1.02, 2.11) in breast cancer patients.[34]

In the Breast International Group (BIG) 1-98 study comparing 5 years of monotherapy with either tamoxifen (n = 2459) or letrozole (n = 2463) for post-menopausal HR-positive early breast cancer, the incidence of thromboembolic events in the letrozole arm was 2.0%.[35]

Effectiveness of fulvestrant as a second-line agent in patients with advanced disease was established by 3 large, multi-centre, parallel group studies (Studies 0020 and 0021) (combined N in fulvestrant arm = 428) of post-menopausal women with locally advanced or metastatic breast cancer who had experienced disease progression during adjuvant endocrine therapy or first-line anti-oestrogen therapy for advanced disease who were randomised to either fulvestrant or anastrozole. [36] Over a median follow-up of 27 months, the incidence of thromboembolic disease in the fulvestrant arm was 15 (3.5%). In the Comparison of Faslodex Recurrent or Metastatic Breast Cancer (CONFIRM) trial, a randomised double-blind multi-centre dose comparison efficacy trial comparing fulvestrant 500 mg versus 250 mg monthly in post-menopausal women with advanced HR-positive breast cancer who experienced disease progression on prior endocrine therapy, the incidence of thromboembolic disease in the fulvestrant 500 mg and fulvestrant 250 mg was 3/361 (0.8%) and 6/374 (1.6%) after a median duration of exposure 174 days and 145 days, respectively.[37]

Osteoporosis/Bone Fracture/Low Bone Mineral Density

Up to 80% of women with breast cancer develop “Cancer Treatment-Induced Bone Loss” during treatment due to the consequences of depletion of endogenous oestrogen.[38,39,40] Whereas post-menopausal women without breast cancer lose an average of 1% of their bone mineral density per year, post-menopausal women treated for breast cancer may lose up to 8% per year.[41,42,43] Breast cancer patients also have a 5-fold increased risk of fracture compared to women who are cancer-free.[44,45]

In the BIG 1–98 study previously described, the incidence of clinical fracture was significantly higher in the letrozole group compared with the tamoxifen group (8.6% versus 5.8% at a median follow-up of 51 months and 9.3% versus 6.5% at a median follow-up of 60 months).[35] Risk factors for fractures were age, prevalent fractures, diagnosis of osteoporosis at baseline and previous hormone replacement therapy.[46] The MA-17 trial was a Phase 3, randomised, double-blind, placebo-controlled trial of letrozole as extended adjuvant therapy for post-menopausal women with primary breast cancer who had completed approximately 5 years of adjuvant tamoxifen therapy.[47] After a median follow-up of 2.4 years, more women receiving letrozole than placebo reported a new diagnosis of osteoporosis (5.8% versus 4.5%, respectively, after 2 years, and 8.1% versus 6%, respectively after 3 years).

090177e1997610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

In the fulvestrant CONFIRM trial previously described, osteoporosis was reported in 1 patient (0.3%) in 250 mg arm and no patients in the 500 mg arm experienced osteoporosis.[37]

Among 93,676 generally healthy post-menopausal women followed for a mean of 136.7 months in the women's health initiative observational study, the annualised incidence of hip fracture was 0.20%.[48]

Mortality

The female breast cancer mortality rate in Europe (EU-27) is 22.4/100,000.[2] In the US, breast cancer is the third leading cause of cancer death in women, with a mortality rate across all breast cancer types of 22.6 per 100,000 women per year; the median age at death from breast cancer is 68 years, and 79.8% of all breast cancer deaths occur at ages 55 and older.[4] Six-percent (6%) of all breast cancer deaths occur at ages below 45 years of age and 14.3% occur at ages between 45-54 years.[4] Using data from 39,366 women from the US CCR with HR-positive, HER2-negative breast cancer (all stages), Parise, et al (2009) reported a 5-year relative survival for this subgroup of 91.9% (95% CI 90.1-93.7).[10]

A population-based study analysed the distribution, clinicopathological features, survival and excess risk of death among women diagnosed with breast cancer classified by molecular subtype in 10 Spanish-based cancer registries.[5] The 1, 3 and 5 year relative survival rates were estimated as the ratio of observed survival in the study population to the survival reported in the general population of the same age, sex, year and province. Among 3480 incident breast cancers diagnosed mainly in 2005, 2771 (79.6%) had molecular subtype data. Among these, 68.7% were HR-positive, HER2-negative breast cancer. The 1, 3 and 5 year relative survival was highest among women with this molecular subtype (Table 5). Survival estimates for HR-positive, HER2-negative breast cancer (all stages, n = 888) from the Swiss Ticino Cancer Registry were similar, with a 24-month overall survival of 96.5%.[8]

Table 5. Relative Survival Rates at 1, 3, and 5 Years, by Breast Cancer Subtype (All Stages)

Molecular Subtype[5]	1 Year (95% CI)	3 Years (95% CI)	5 Years (95% CI)
HR-positive, HER2-negative	98.8 (98.1-99.5)	95.4 (94.0–96.8)	91.5 (89.5–93.5)
HR-positive, HER2-positive	97.3 (95.2–99.4)	90.4 (86.7–94.3)	85.8 (81.2–90.7)
HER2-overexpressed (ER-negative, HER2-positive)	95.8 (92.7–99.1)	87.2 (81.9–92.8)	78.6 (72.0–85.8)
Triple-negative (ER-negative/PR-negative, HER2-negative)	93.2 (90.3–96.3)	79.8 (75.2–84.7)	76.3 (71.1–81.8)
Unclassified	87.3 (84.6–90.0)	81.0 (77.6–84.6)	77.0 (72.7–81.4)
Overall	95.7 (94.9–96.5)	90.1 (88.9–91.4)	85.9 (84.3–87.5)

CI = Confidence Interval; ER = Oestrogen receptor; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Important co-morbidities:

The epidemiology of selected important co-morbidities for the target indication is provided in this section. Search terms used to identify articles are presented in the related footnote.[1] In some instances, the articles did not specify if the patient received prior chemotherapy that may or may not have affected the incidence of co-morbidities.

Comorbid conditions reported more frequently in patients with cancer were hypertension, angina/coronary artery disease, Congestive Heart Failure (CHF), Myocardial Infarction (MI), other heart condition, stroke, emphysema/asthma/chronic obstructive pulmonary disease, Crohn's Disease/irritable bowel disease, arthritis of the hip, and diabetes.

In addition, people 65 years of age and older not only bear a disproportionate burden of cancer, but advanced age is associated with increased vulnerability to other age–related health problems.[49] In a large national linked database of 126,685 participants in the Medical Health Outcomes Survey (MHOS) and 14,897 patients from the Surveillance, Epidemiology, and End Results (SEER) programme, cancer patients were significantly more likely to report a higher prevalence for 10 of 12 comorbid conditions than patients without cancer.[50] According to the SEER–MHOS linked data, of the 3237 patients >65 years of age with breast cancer, 22.1% reported at least 1 comorbid condition and 65.4% reported 2 or more comorbid conditions.

Co-morbidities considered in this review included:

- Heart disease (CHF, MI, myocardial ischaemia, hypertension)
- Hypercholesterolaemia
- Uterine malignancies (endometrial cancer, uterine sarcoma)
- Hyperglycaemia/Diabetes Mellitus (DM)
- Obesity/BMI >30 kg/m^2

[1] Throughout the literature review, the following search terms were used for comorbidities: PubMed – (*see previously specified search terms for the target indication*) AND (*see previously specified search terms for epidemiology*) AND heart arrest [MeSH] OR ("heart" AND ("arrest" OR "attack")) OR heart failure [MeSH] OR "heart failure" OR myocardial ischemia [MeSH] OR "myocardial ischemia" OR cardiomyopathies [MeSH] OR "cardiomyopathies" OR hypertension [MeSH] or "hypertension" OR "congestive heart failure" OR (("high" OR "elevated" OR "increased") AND "blood pressure") OR hypercholesterolemia [MeSH] OR "hypercholesterolemia " OR endometrial neoplasms [MeSH] OR ("sarcoma" AND ("uterus" OR "uterine")) OR "endometrial neoplasms" or "hyperglycemia" OR "diabetes mellitus" OR "obesity" OR "BMI > 30." EMBASE –(*see previously specified search terms for the target indication*) AND (*see previously specified search terms for epidemiology*) AND heart infarction [Emtree] OR ("heart" AND ("arrest" OR "attack")) OR heart failure [Emtree] OR "heart failure" OR heart muscle ischemia [Emtree] OR "myocardial infarction" OR cardiomyopathy [Emtree] OR "cardiomyopathy" OR hypertension [Emtree] OR "hypertension" OR "congestive heart failure" OR (("high" OR "elevated" OR "increased") AND "blood pressure") OR hypercholesterolemia [Emtree] OR "hypercholesterolemia" OR endometrium cancer [Emtree] OR "endometrium cancer" OR uterus sarcoma [Emtree] OR (("uterus" OR "uterine") AND "sarcoma) OR "hyperglycemia" OR "diabetes mellitus" OR "obesity" OR "BMI > 30."

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Module SII. Non-Clinical Part of the Safety Specification

The non-clinical safety profile of palbociclib was evaluated in-vitro and in-vivo in rats and dogs. The rat and the dog were selected as the rodent and non-rodent species, respectively, for general toxicity studies because the ability to assess potential toxicities from both primary and secondary pharmacological targets, exposure profiles were sufficient and major metabolism pathways observed in humans. The oral route with QD dosing was selected for the majority of in-vivo studies based on the intended route of administration and dosing frequency necessary to achieve and maintain predicted therapeutic exposures. Repeat-dose toxicity studies up to 39 weeks of duration were performed using the clinical dosing regimen of 3 weeks of repeat dosing followed by a 1-week non-dosing period. In addition, safety pharmacology, genetic toxicity, carcinogenicity, fertility and early embryonic development, embryofoetal development, pre- and post-natal development, and phototoxicity studies were conducted.

The primary toxicities identified from these studies included hematolymphopoietic and male reproductive organ effects in rats and dogs; effects on bone and actively growing incisors, and glucose dysregulation with related effects on the pancreas, eye, kidney, and adipose tissue in rats only; and effects on embryofetal development in rats and rabbits. Other palbociclib-related findings included vacuolation in multiple tissues, and effects on the gastrointestinal tract, liver, kidney, adrenal gland, respiratory system, and coagulation times (prolonged) that were of limited severity and/or lacked degenerative features. Palbociclib also caused effects on cardiovascular function, was aneugenic in genetic toxicity assessments and carcinogenic in male rats.

Table 6 describes the non-clinical safety findings that have potential relevance to human use.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Hematolymphopoietic Bone marrow and lymphoid tissue hypocellularity were observed in rats and dogs following repeat-dose administration of palbociclib, and correlated with haematological changes that included decreases in leukocytes (neutrophils, monocytes, eosinophils, and lymphocytes), red blood cell parameters, and platelets. The hematolymphopoietic effects were observed in studies of ≥2 weeks in duration at sub-therapeutic exposures and multiples thereof, and were reversible.	Palbociclib has the potential to cause bone marrow and lymphoid organ toxicity in humans.
Altered Glucose Metabolism/Endocrine Pancreas Effects and Secondary Changes to the Eye, Kidney, and Adipose Tissue. Altered glucose metabolism was identified in male rats after repeat-dose administration of palbociclib starting at a young age. Hyperglycaemia and glucosuria were observed in male rats following 15 and 27 weeks of intermittent dosing at human clinical exposures and multiples thereof. The changes in glucose homeostasis did not reverse following a 12-week non-dosing period. No effects on glucose metabolism were identified in dogs in studies up to 39 weeks in duration at up to 3 times human clinical exposures. Pancreatic islet cell vacuolation was observed in male rats but not dogs following repeat-dose administration of palbociclib. The pancreatic vacuolation was identified in association with altered glucose metabolism following 15 and 27 weeks of intermittent dosing at human clinical exposures and multiples thereof. The vacuoles were determined to reflect a loss of beta cells with corresponding decreases in insulin and C-peptide. Reversibility was not shown for the effects on the pancreas following a 12-week non-dosing period. Cataracts/lens degeneration was identified in male rats but not in dogs following repeat-dose administration of palbociclib. Cataracts, consisting of anterior cortical, incomplete, or complete cataracts were identified from slit lamp ophthalmoscopy, and correlated with lens degeneration following 27 weeks of intermittent dosing at human clinical exposures and multiples thereof, and did not reverse following a 12-week non-dosing period. The effect on the eye was considered secondary to the endocrine changes/glucose dysregulation changes	Based on non-clinical safety studies in the rat, palbociclib may have the potential to alter glucose homeostasis in humans in association with effects on the endocrine pancreas. Effects on the eye, kidney, and adipose tissue are considered secondary to the endocrine changes/glucose dysregulation and therefore have low potential for occurrence with adequate glucose monitoring.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
observed in male rats following 15 and 27 weeks of intermittent dosing. Kidney tubule vacuolation was identified in male rats following repeat-dose administration of palbociclib. The kidney tubule vacuolation was identified following 15 and 27 weeks of intermittent dosing at ≥9 times human clinical exposure, and was considered secondary to the endocrine changes/glucose dysregulation observed in rats. The vacuolation of kidney tubular cells did not reverse following a 12-week non-dosing period. An effect on adipocytes was identified in male rats following repeat-dose administration of palbociclib. Adipose tissue atrophy in the skin/subcutaneous tissue and thymus were identified in rats following 27 weeks of intermittent dosing at 13 times human clinical exposure. The effect on adipocytes was considered secondary to the endocrine changes/glucose dysregulation observed in rats following 15 and 27 weeks of intermittent dosing. Partial reversibility was shown for the effects on adipose tissue following a 12-week non-dosing period.	
Reproductive and Developmental Palbociclib did not affect mating or fertility in male or female rats at exposures up to 13 times (projected in males) and 3 times human clinical exposure, respectively. In addition there were no effects on pre- and post-natal development of offspring from implantation through lactation and weaning. Palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion in studies of ≥3 weeks in duration at sub-therapeutic exposures and multiples thereof. Partial reversibility for male reproductive organ findings was observed following a 4- and/or 12-week non-dosing period. Palbociclib administration was associated with foetotoxicity in rats (reduced foetal body weights) concomitant with maternal toxicity at 3 times the human clinical exposure. In addition, an increase in skeletal developmental variations was observed in rats (cervical ribs) and rabbits (small forepaw phalanges) at 1 and 4 times human clinical exposure, respectively.	Based on non-clinical safety studies, palbociclib has the potential to impair male reproductive function and affect male fertility in humans. Based on non-clinical safety studies, palbociclib may cause foetal harm when administered to a pregnant woman. Please see Section Section SVII.3.1.1 , Reproductive and developmental toxicity (Important Potential Risk).

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
QT Prolongation Palbociclib is considered to have the potential to cause QT interval prolongation based on increases in APD_{90} at 10 μM (4475 ng/mL) in a dog Purkinje fibre assay, inhibition of the hERG potassium channel (IC50 of 3.2 μM [1432 ng/mL]), and QTc prolongation in conscious telemetered dogs at unbound plasma concentrations ≥67 ng/mL (4 times human clinical exposures). Haemodynamic effects were also noted at 8 times human clinical exposure in conscious telemetered dogs following a single dose, including decreases in heart rate (up to 8 beats per minute) that correlates with increases in RR interval, and modest increases in systolic blood pressure (up to 6 mm Hg).	Based on non-clinical safety studies, palbociclib has the potential to cause QTc prolongation. Decreases in heart rate up to 8 beats per minute or increases in systolic blood pressure up to 6 mm Hg are not considered to represent significant safety concerns in the PM setting.
Bone Effects on bone were observed in male rats following repeat-dose administration of palbociclib. Decreased trabeculae in the femur were observed in rats following 27 weeks of intermittent dosing at ≥3 times human clinical exposure. No recovery was observed for the bone effects following a 12-week non-dosing period.	Bone effects are not considered to represent a significant safety concern in the PM setting. The risk to adult humans who are no longer in a period of active growth is unclear, given that it could not be determined whether the effect on secondary spongiosa was a consequence of primary spongiosa loss or due to a direct effect.
Teeth Effects on actively growing incisors were observed in rats following repeat-dose administration of palbociclib. White (discolored) incisor teeth were noted and correlated histopathologically with minimal to moderate ameloblast degeneration/necrosis and/or minimal to mild pigmented mononuclear cell infiltrates following 27 weeks of intermittent dosing at 3 times the human clinical exposure. Partial to full reversibility of incisor teeth findings was observed after a 12-week non-dosing period.	Due to effects only on actively growing teeth, the odontopathy are not considered relevant to the adult human population.
Gastrointestinal GI effects were identified in rats and dogs following repeat-dose administration of palbociclib. Microscopic changes were noted in the intestines and stomach, including the appearance of abnormal epithelium (nuclear and cytoplasmic alterations), atrophy, and erosion, and were accompanied by clinical signs (faecal changes, emesis), in rats and/or dogs in studies up to 3 weeks duration at sub-therapeutic exposures and multiples thereof. Gastric changes (decreased	Based on non-clinical safety studies, palbociclib has the potential to cause GI effects in humans. However, GI effects are not considered to represent a significant safety concern in the PM setting as GI adverse effects in animals were not seen at clinically relevant doses.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
mucous in glands) were observed in rats at ≥9 times human clinical exposure following 27 weeks of intermittent dosing, for which recovery was not established. The GI effects were not considered adverse in the rat or dog at up to the highest tolerated doses based on the limited severity of findings.	
Respiratory Respiratory effects (including rales, dyspnoea, and tracheal mucosa atrophy) were noted in rats in toxicity studies ≤3 weeks duration at human clinical exposures and multiples thereof, but not in 15 and 27 week studies (at up to 18 times human clinical exposure). Additional effects (respiratory depression, apnoea) were noted in a respiratory safety pharmacology study in anesthetised dogs at ≥50 times human clinical exposure.	Respiratory effects are not considered to represent a significant safety concern in the PM setting given only short term limited effects in rats and likely anaesthetic complications in dogs.
Genotoxicity Palbociclib-induced micronuclei formation was observed in an in-vivo (rat) micronucleus assay at 19 times human clinical exposure, which through kinetochore staining was determined to be due to an aneugenic mechanism. A no effect level for micronuclei formation was identified at 7 times human clinical exposure.	The genetic toxicity profile of palbociclib suggests the potential to be aneugenic in humans.
Carcinogenicity Palbociclib was not carcinogenic in ras H2 transgenic mice following 6 months of repeat-dosing at ≥10 times human clinical exposure. A palbociclib-related increase in the incidence of microglial cell tumors was observed in the central nervous system (brain/spinal cord) of male rats in a 2-year carcinogenicity study. Microglial cell tumors originated in various locations of the CNS including the basal ganglia (striatum), midbrain, hypothalamus, hippocampus, amygdala, brain stem, and spinal cord, and they often infiltrated adjacent brain structures, especially the cortex. The relevance of the male rat neoplastic microscopic finding to humans is unknown; a no effect level for carcinogenicity was identified at ≥2 times human clinical exposure.	Based on the review of 300 cases of a second primary malignancy in the Pfizer Global Safety Database, the MAH does not consider that the aneugenic activity of palbociclib may lead to an increase in second primary malignancy tumors in patients with breast cancer.
Mechanisms for drug interactions	
Cytochrome P450 (CYP)3A	Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady-state in humans.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Palbociclib and its lactam metabolite (PF-05089326) were shown to be time-dependent inhibitors of CYP3A activity in-vitro in human liver microsomes.	
Strong CYP3A Inhibitors or Inducers Palbociclib is metabolised mainly by CYP3A and sulfotransferase (SULT) 2A1 in-vitro.	Co-administration of palbociclib with strong CYP3A inhibitors or inducers may increase or decrease, respectively, the systemic exposure to palbociclib in humans.

CYP3A = Cytochrome P450 3A; GI = Gastrointestinal; hERG = Human Ether-à-go-go Related Gene; mg = Milligramme; mL = Millilitre; Ng = Nanograms; PM = Post-Marketing; RR = Relative Risk.

Module SIII. Clinical Trial Exposure[2]

Each protocol number in the palbociclib program consists of the clinical project number (e.g., 'A548') followed by a unique study number (e.g., '1003'); hence 'A5481003'. For simplicity throughout this report in text, each protocol will be referred to by just the study number (e.g., 'Study 1003').

The exposure data summarised below is based upon studies that evaluated patients with malignant disease, who were administered palbociclib and focuses on:

- Study 1003, a completed Phase 1/2 study to assess the efficacy, safety and PK of palbociclib in combination with letrozole and letrozole alone for first-line treatment of ER-positive, HER2-negative advanced breast cancer
- Study 1008, a completed Phase 3 study of palbociclib plus letrozole versus placebo plus letrozole for the first-line treatment of post-menopausal women with ER-positive, HER2-negative advanced breast cancer
- Study 1023, a completed Phase 3 study of palbociclib in combination with fulvestrant with or without goserelin versus placebo in combination with fulvestrant with or without goserelin in patients with HR-positive, HER2-negative advanced breast cancer whose disease progressed after prior endocrine therapy
- Study 1001, a completed Phase 1 study to assess the safety, PK and Pharmacodynamics (PDs)of palbociclib in patients with advanced cancer
- Study 1002, a completed pilot study of palbociclib in patients with previously treated mantle cell lymphoma
- Study 1004, a completed Phase 1/2 study who received palbociclib in combination with bortezomib and dexamethasone in patients with refractory multiple myeloma
- Study 1010, the completed Phase 1 portion assessed the efficacy, safety, and PK of palbociclib as single agent in Japanese patients with advanced solid tumours or in combination with letrozole for the first-line treatment of Japanese patients with advanced breast cancer

[2] Same principle applied as in EMEA/743133/2009: HMA/EMA Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs); available: http://www.ema.europa.eu

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Exposure to palbociclib in these patients is summarised in Table 7 – Table 10 below for the following studies:

- Patients with advanced breast cancer (1001 [3/1 schedule only][3], 1003, 1008, 1010, 1023)
- Patients with advanced cancer (1001 [both 3/1 and 2/1 schedule], 1002, 1003, 1004, 1008, 1010, 1023, 1027); please note that patients with advanced breast cancer enrolled in these studies are included amongst patients with advanced cancer

Table 7. Duration of Exposure (by Indication)

Duration of Exposure (at Least)[a]	Persons	Person Time (years)
Advanced breast cancer		
<6 months	283	68.27
≥6 months	825	2057.36
≥1 year	606	1891.28
≥2 years	388	1576.62
≥3 years	252	1247.49
Total (≥1 dose)	**1108**[b]	**2125.63**
Advanced cancer[c]		
<6 months	406	85.89
≥6 months	848	2092.10
≥1 year	617	1916.96
≥2 years	395	1597.12
≥3 years	254	1255.90
Total (≥1 dose)	**1254**[b]	**2177.98**

Study A5481001 subjects treated with Palbociclib (PD-0332991) (date of data cutoff: 02Jan2015). Studies A5481002 and A5481004 subjects treated with Palbociclib (PD-0332991) (clinical study report data). Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21Dec2017). Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 14May2021). Study A5481010 Phase 1 Part 1 and Part 2 (date of data cutoff: 07Feb2018) and Phase 2 (date of data cutoff: 28Nov2018). Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021). Study A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Exposure (person-time) is based on overall exposure to Palbociclib (PD-0332991), Palbociclib (PD-0332991) + Letrozole, or Palbociclib (PD-0332991) + Fulvestrant treatment.

a. A patient may be in more than one exposure category
b. Total number of patients that received at least 1 dose of palbociclib
c. Advanced cancer includes advanced breast cancer

[3] Please note that throughout this document, Schedule 3/1 refers to 3 weeks on palbociclib treatment followed by 1 week off treatment (21/28 days) and Schedule 2/1 refers to 2 weeks on palbociclib treatment followed by 1 week off treatment (14/21 days).

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 8. Exposure by Dose (by Indication)

Dose of Exposure[a]	Persons	Person Time (years)
Advanced breast cancer		
Dose <75 mg/day	7	0.6
Dose 75 mg/day	190	186.93
Dose 100 mg/day	447	360.64
Dose 125 mg/day	1101	1018.30
Dose >125 mg/day	6	0.2
Total	**1108[b]**	**1566.66**
Advanced cancer[c]		
Dose <75 mg/day	17	2.6
Dose 75 mg/day	222	191.99
Dose 100 mg/day	506	374.08
Dose 125 mg/day	1150	1038.02
Dose >125 mg/day	41	10.9
Total	**1254[b]**	**1617.59**

Study A5481001 subjects treated with Palbociclib (PD-0332991) (date of data cutoff: 02Jan2015). Studies A5481002 and A5481004 subjects treated with Palbociclib (PD-0332991) (clinical study report data). Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21Dec2017). Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 14May2021). Study A5481010 Phase 1 Part 1 and Part 2 (date of data cutoff: 07Feb2018) and Phase 2 (date of data cutoff: 28Nov2018). Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021). Study A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Subjects are counted once for each dose level they took during the study.
Exposure (person time) is based on overall exposure to Palbociclib (PD-0332991) doses only.
mg = Milligramme.

a. Patient may be in more than one exposure category as patients are counted once for each dose level they took during the study
b. Total number of patients that received at least 1 dose of palbociclib
c. Advanced cancer includes advanced breast cancer

Table 9. Exposure by Age Group and Gender (by Indication)

Age Group	Persons		Person Time (years)	
	Female	Male	Female	Male
Advanced breast cancer				
Age <18 years	0	0	0	0
Age ≤18 and ≤ 64 years	764	0	1401.04	0
Age ≥65 years	344	0	724.59	0
Age ≥75 years	86	0	154.34	0
Total[a]	**1108**	0	**2125.63**	0
Advanced cancer[b]				
Age <18 years	0	0	0	0
Age ≤18 and ≤ 64 years	799	53	1409.54	23.7
Age ≥65 years	371	31	732.99	11.8
Age ≥75 years	89	7	156.10	1.9
Total[a]	**1170**	**84**	**2142.52**	**35.5**

Study A5481001 subjects treated with Palbociclib (PD-0332991) (date of data cutoff: 02Jan2015). Studies A5481002 and A5481004 subjects treated with Palbociclib (PD-0332991) (clinical study report

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 9. Exposure by Age Group and Gender (by Indication)

Age Group	Persons		Person Time (years)	
	Female	Male	Female	Male

data). Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21Dec2017). Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff:14May2021). Study A5481010 Phase 1 Part 1 and Part 2 (date of data cutoff: 07Feb2018) and Phase 2 (date of data cutoff: 28Nov2018). Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021). Study A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Exposure (person-time) is based on overall exposure to Palbociclib (PD-0332991), Palbociclib (PD-0332991) + Letrozole, or Palbociclib (PD-0332991) + Fulvestrant treatment

a. Total accounts for mutually exclusive age groups (i.e., age group ≥75 years is not included in the Total).
b. Advanced cancer includes advanced breast cancer.

Table 10. Exposure by Ethnic or Racial Origin (by Indication)

Ethnic/Racial Origin	Persons	Person Time (years)
Advanced breast cancer		
White	686	1308.09
Black	21	25.46
Asian or Pacific Islander	363	708.69
Other[a]	23	58.05
Unspecified	15	25.34
Total	**1108**	**2125.63**
Advanced cancer[b]		
White	808	1347.92
Black	30	29.35
Asian or Pacific Islander	374	710.70
Other[a]	27	64.67
Unspecified	15	25.34
Total	**1254**	**2177.98**

Study A5481001 subjects treated with Palbociclib (PD-0332991) (date of data cutoff: 02Jan2015). Studies A5481002 and A5481004 subjects treated with Palbociclib (PD-0332991) (clinical study report data). Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21Dec2017). Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 14May2021). Study A5481010 Phase 1 Part 1 and Part 2 (date of data cutoff: 07Feb2018) and Phase 2 (date of data cutoff: 28Nov2018). Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021). Study A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Exposure (person-time) is based on overall exposure to Palbociclib (PD-0332991), Palbociclib (PD-0332991) + Letrozole, or Palbociclib (PD-0332991) + Fulvestrant treatment.

a. Race Other = Asian/Pacific Islander, East Indian, Egyptian, Hispanic, Indian, Mexican, Middle Eastern, Greek, Mixed, Panamanian, Spanish, South Pacific, Unknown.
b. Advanced cancer includes advanced breast cancer

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Module SIV. Populations Not Studied In Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

There has been limited exposure in special populations to palbociclib and no epidemiologic studies have been conducted in pregnant/lactating women, paediatric patients (age: ≤17 years) and specific subpopulations that were excluded from the CT developmental programme.

The following is the important exclusion criterion across the palbociclib development program:

Hypersensitivity to Palbociclib or to any of the excipients

Reason for exclusion**:** Unknown risk but standard wording for the administration of an exogenous substance.

Is it considered to be included as missing information? No

Rationale**:** there is no anticipated use of palbociclib where a patient has a known hypersensitivity reaction to palbociclib or excipients

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions (ARs) such as rare ARs.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 11 lists the patient populations that have been included or not in CTs in the palbociclib clinical development programme.

Table 11. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant Women	Given the known foetotoxic effects of palbociclib in animal studies, pregnant women were not enrolled in palbociclib clinical trials. No data on pregnant women using palbociclib are available to date. No studies have been conducted in humans to date to assess the effect of palbociclib on milk production, palbociclib presence in breast milk, or its effects on the breast-fed child. It is unknown whether palbociclib is excreted in human milk.
Breast-Feeding Women	Given the known foetotoxic effects of palbociclib in animal studies, breast-feeding women were not enrolled in palbociclib clinical trials. No studies have been conducted in humans to date to assess the effect of palbociclib on milk production, palbociclib presence in breast milk, or its effects on the breast-fed child. It is unknown whether palbociclib is excreted in human milk.
Patients/Subjects with Hepatic Impairment	Based on a population PK analysis that included 183 patients with cancer, where 40 patients had mild hepatic impairment based on NCI classification (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1.0-1.5 × ULN and any AST), mild hepatic impairment had no effect on the PK of palbociclib. Among patients with advanced breast cancer (Studies 1001, 1003, 1008, 1010, and 1023), there were 189 patients with mild hepatic impairment and 1 patient with moderate hepatic impairment treated with palbociclib representing 152.8 patient years and 0.2 patient years of exposure, respectively. In a Phase 1 study (Study 1013) of subjects with varying degrees of hepatic function (as defined by Child-Pugh classification), palbociclib PK was evaluated in 28 subjects (4 cohorts of 7 each: normal function, mild impairment, moderate impairment, and severe impairment). Plasma palbociclib exposure was higher in subjects with moderate or severe hepatic impairment than in subjects with normal hepatic function, while subjects with mild hepatic impairment had slightly lower exposures than the subjects with normal hepatic function. f_u of palbociclib increased incrementally with worsening hepatic function. As the unbound plasma concentration represents the pharmacologically effective exposure, the results from the ANOVAs for unbound exposure parameters were used to make the recommendations for dose adjustments for patients with hepatic impairment. The ratios of adjusted geometric means for $AUC_{inf,u}$[a] decreased by approximately 17% in subjects with mild hepatic impairment (Child-Pugh class A) and increased by approximately 34% and 77% in subjects with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C), respectively, relative to subjects with normal hepatic function. The ratios of the adjusted geometric means for $C_{max,u}$[b] increased by approximately 7%, 38% and 72% for mild, moderate and severe impairment, respectively, relative to subjects with normal hepatic function. The magnitude of the change in palbociclib exposure in subjects with mild and moderate hepatic impairment was not considered clinically relevant. Based on these results, no dose adjustment is required for patients with mild or moderate hepatic impairment

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 11. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	(Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib is 75 mg QD on Schedule 3/1.
Patients/Subjects With Renal Impairment	Based on a population PK analysis that included 183 patients with cancer, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. Among patients with advanced breast cancer (Studies 1001, 1003, 1008, 1010, and 1023), there were 352 patients with mild renal impairment and 138 patients with moderate renal impairment treated with palbociclib representing 393.0 and 152.5 patient years of exposure, respectively. In a Phase 1 study (Study 1014), of subjects with varying degrees of renal function (as defined by Cockcroft-Gault estimates of CrCl), palbociclib PK was evaluated in 31 subjects (4 cohorts: normal function [CrCl ≥90 mL/min; 8 subjects], mild impairment [60 mL/min ≤ CrCl <90 mL/min; 10 subjects], moderate impairment [30 mL/min ≤ CrCl <60 mL/min; 7 subjects], and severe impairment [CrCl <30 mL/min); 6 subjects]). Plasma palbociclib exposure was higher in subjects with renal impairment than in subjects with normal renal function; however, the exposures were similar across subjects with mild, moderate, and severe renal impairment. Since the observed f_u in this study was consistent with the in-vitro determined f_u in human plasma, and there appeared to be no obvious trend in the mean f_u with worsening renal function, the results of the comparisons based on total exposure parameters were used to make recommendations for dose adjustments for patients with renal impairment. The ratios of adjusted geometric means for AUC_{inf}, increased by 39%, 42%, and 31% with mild, moderate, and severe renal impairment, respectively; relative to subjects with normal renal function. The ratios of the adjusted geometric means for C_{max} increased by 17%, 12%, and 15% for mild, moderate, and severe impairment, respectively, relative to subjects with normal renal function. The magnitude of the increase in palbociclib exposure in subjects with renal impairment was not considered clinically relevant. Based on these results, no dose adjustment is required for patients with mild, moderate or severe renal impairment (CrCl ≥15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose recommendation.
Patients With a Disease Severity Different From the Inclusion Criteria in the Clinical Trial Population	Palbociclib has been studied in normal healthy volunteers, in patients with hepatic or renal impairment, in patients with advanced breast cancer as well as in other advanced cancer patients. There are no Pfizer-sponsored palbociclib studies in patients with early cancers. However, a number of IIR adjuvant or neoadjuvant pre-surgical studies are administering palbociclib in early-stage breast cancer. For example, palbociclib is currently being studied in the early breast cancer population at high risk of relapse in a non-Pfizer-sponsored, randomised, cooperative Phase 3 study, PENELOPE.
Sub-Populations Carrying Known and Relevant Polymorphisms	CCND1 and CYP19A1 polymorphism analysis did not show an association with palbociclib plus letrozole response.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 11. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients of Different Racial and/or Ethnic Origin	The majority of patients in both the palbociclib plus letrozole arm (76/84 [90.5%]) and the letrozole alone arm (72/81 [88.9%]) of the Phase 2 portion of advanced breast cancer Study 1003 were White. In the palbociclib plus letrozole arm, only 6 patients were Asian, 1 patient was Black, and 1 patient was classified as "Other" race. The vast majority of patients (69/74 [93.2%]) who received single agent palbociclib in first-in-patient Study 1001 were White. Only 3 patients were Black, 1 patient was Asian, and 1 patient was classified as "Other". Therefore, no conclusions can be made regarding the effect of race and/or ethnicity on the safety of palbociclib, alone or in combination with letrozole. The majority of patients in the palbociclib plus fulvestrant arm and in the placebo plus fulvestrant arm in Study 1023 were White (72.6% versus 76.4%, respectively). Both treatment arms were well balanced with regard to patient race and ethnicity. In the palbociclib plus fulvestrant arm, 12 (3.5%) patients were Black, 74 (21.3%) were Asian, 8 (2.3%) were considered Other, and 1 (0.3%) patient was unspecified. Study 1019 is a Phase 1 PK healthy volunteer study in Chinese patients, which was initiated after the closure date of Annex 4 (15 May 2015). Study 1032 is a completed Phase 1 healthy volunteer study in Japanese patients and non-Asian patients. Study 1010 Phase 1 portion is a completed study, which consists of Part 1 (dose-escalation cohort) of palbociclib alone in 12 Japanese patients with solid tumours and Part 2 in 6 Japanese women with advanced breast cancer treated with palbociclib plus letrozole. Study 1010 was expanded to Phase 2 in Japanese women with advanced breast cancer being treated with palbociclib plus letrozole as a single arm, which is currently on-going. Based on PK data from Study 1010 that included only 12 Japanese patients, of whom 6 received palbociclib 100 mg QD and 6 received palbociclib 125 mg QD, the geometric mean AUC and C_{max} values were more than 2-fold greater after administration of the 125 mg single and multiple QD doses of palbociclib, compared with those after administration of the 100 mg single and multiple QD doses. The $t_{½}$ values were comparable between the 100 mg and 125 mg doses. However, the safety profile was consistent between patients who received the 100 mg and 125 mg doses. No new safety signals in the Japanese population participating in the Phase 1 Part 1 portion of the study were identified as the safety profile of palbociclib in Japanese patients was comparable to that in non-Japanese patients. A separate Phase 1 study (Study 1032) was conducted to further evaluate the effect of Japanese ethnicity on the PK of a single 125 mg oral palbociclib dose given to healthy Japanese subjects and demographically-matched healthy non-Asian subjects. Palbociclib geometric mean AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects when compared with demographic-matched non-Asian subjects. The ratios of adjusted geometric means (90% CI) for palbociclib AUC_{inf} and C_{max} were 130% (112%, 151%) and 135% (111%, 165%), respectively, for Japanese subjects relative to non-Asian subjects. In Study 1023, comparison of the within-subject mean steady-state palbociclib pre-dose plasma concentration during

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 11. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	multiple dosing (C_{trough}) in Japanese, Asian (except for Japanese) and non-Asian patients in the Study 1023 demonstrated relative consistency in the central tendency and range of the observed values across sub-populations, indicating similar palbociclib exposure in these sub-populations. Geometric mean values of the within-subject mean steady-state palbociclib C_{trough} values were similar for Japanese, Asian (except for Japanese), and non-Asian patients (84.4 ng/mL, 86.3 ng/mL and 74.8 ng/mL, respectively). While palbociclib geometric mean AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese healthy subjects compared with those in demographic-matched non-Asian healthy subjects, palbociclib geometric mean steady-state C_{trough} values were similar in Japanese, Asian (except for Japanese), and non-Asian advanced breast cancer patients. In addition, the safety profile of palbociclib in Japanese patients was similar to that in non-Japanese patients following administration of palbociclib 125 mg QD according to the dosing schedule of 3 weeks on treatment/1 week off treatment. Study 1034 is an on-going open-label, single arm, multicenter clinical trial designed to provide access to palbociclib in the US for post-menopausal women with HR-positive, HER2-negative advanced breast cancer who are deemed to be an appropriate patient population for receiving letrozole therapy. Palbociclib 125 mg QD is given according to Schedule 3/1 in combination with letrozole 2.5 mg QD continuously in this study. Of note, 28 (12%) of patients were non-Caucasians, comprised of 19 (8%) Black, and 9 (4%) Other (i.e., Aboriginal, Asian, Filipino Caucasian, Hispanic, or Middle Eastern) patients. Study 1027 is an ongoing randomized (1:1), double-blind, placebo-controlled, parallel-group phase 3 trial comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo plus letrozole in Asian postmenopausal women with ER-positive/HER2-negative advanced brest cancer. As of the primary completion date (PCD - 31 August 2020) a total of 340 participants were randomized in the study. The demographic characteristics were well-balanced between the 2 treatment arms; in particular, the ratial designation was Chinese in 83.8% of patients (83.4% in palbociclib+letrozole and 84.2% in placebo+letrozole arm, respectively) and “Other” in 16.2% (16.6% in palbociclib+letrozole and 15.8% in placebo+letrozole arm, respectively). Overall, palbociclib plus letrozole was safe and well-tolerated and no unexpected safety findings were observed in this Asian population.
Children	Palbociclib is in development for the treatment of pre-, peri- and post-menopausal women with advanced breast cancer. There is no significant experience of palbociclib treatment in paediatric patients. The safety and efficacy of palbociclib in children and adolescents ≤18 years of age have not been established.
Male Patients	There is limited experience in palbociclib treatment of male patients. Based on a population PKs analysis (50 male and 133 female patients), gender had no effect on the exposure to palbociclib and no new findings have been identified in palbociclib treatment of male patients.

Table 11. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure

AST = Aspartate Transaminase; AUC = Area Under the Concentration Curve; AUC_{inf} = Area Under the Concentration-Time Curve from 0 to Infinity; CCND1 = Cyclin D1; CI = Confidence Interval; C_{max} = Maximum Plasma Concentration; $C_{max,u}$ = Unbound Maximum Plasma Concentration; CrCl = Creatinine Clearance; C_{trough} = Predose plasma concentration during multiple dosing; CYP = Cytochrome P450; Fu = The mean fraction of unbound drug in plasma; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor; IIR = Investigator-Initiated Research; mg = Milligramme; mL = Millilitre; NCI = National Cancer institute; PK = Pharmacokinetic; QD = Once Daily; t½ = Half-Life; ULN = Upper Limit of Normal; US = United States

a. $AUC_{inf,u}$ refers to the unbound area under the plasma concentration-time profile from time 0 extrapolated to infinite time.
b. $C_{max,u}$ refers to the unbound maximum plasma concentration.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Cumulatively through 02 August 2021, it is estimated that 502,043 patients were exposed to palbociclib worldwide from marketing experience since the product was first approved on 03 February 2015.

SV.1.1. Method Used to Calculate Exposure

The estimation of the palbociclib patient exposure counts was done through a 3-step process calculation methodology:

1. US patient estimates - based on patient-level prescription data provided by the MAH's network of palbociclib-distributing customers (including specialty pharmacies, selected group purchasing organizations and large group practices, etc.), a total number of new patients per month in the US (excluding clinical trial patients and patients receiving free drug from MAH patient assistance programs) was derived. IQVIA aggregated these data and provided unique patient counts for analysis. These patient counts were subsequently rounded up to account for any patients whose payers block data sharing with the MAH and for any patients receiving drug outside of the MAH's network of palbociclib-distributing customers (e.g., dispensing hospitals, large group practices with on-site pharmacies, etc.).

2. European/Japan patient estimates - based on actual sales volumes relative to long-range forecasts.

3. To calculate the ROW patient estimates, the ratio of ROW to US and EU MAH unit shipment data is used to estimate the number of ROW patients (sourced supply chain group). The ratio is then applied to actual US and EU patients to estimate ROW patients. For markets where not yet launched, units shipped via named patient program or shipped with special approval (minimal) are not captured.

   For months where a patient count estimate is required for contribution and no data was available, a rolling average of the patient count from the previous 3 months or the previous month, as appropriate, may be utilized.

   Specifically, it should be noted for this RMP that:

   - Actual shipment data (provided by the MAH global supply department) are available only through the end of July 2021, and the forecast shipment data have been considered for the 2 days of August 2021.

   - Because actual patient estimates by market are available only through the end of July 2021, the forecast patient data have been calculated based on the previous rolling 3-month average.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

The cumulative estimated patient exposure by indication, gender, age group, dose, formulation, and region is based on and calculated from data provided by IQVIA Prescribing Insights Medical for the period of the second quarter of 2009 through the first quarter of 2021. The IQVIA demographics data reported during this period were applied to the cumulative from commercial launch to 02 August 2021 and are summarized in Table 12.

SV.1.2. Exposure

Table 12. Cumulative Estimated Patient Exposure for Palbociclib from Commercial Launch through 02 August 2021

Indication	Sex		Age (years)			Dose (mg/day)				Form.	Region			
	M	F	2-16	17-65	> 65	25	75	100	125	Oral	US	EU	Japan	ROW
Breast Cancer	5207 (1%)	496,837 (99%)	NA	248,637	253,406	60,939	57,350	114,858	268,896	502,043	148,381	231,545	40,602	81,515

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for misuse for illegal purposes

Palbociclib does not have characteristics that would make it attractive for use for illegal purposes; therefore, there is only a low potential for palbociclib misuse for illegal purposes. Only minimal penetration of palbociclib through an intact blood brain barrier to central nervous system tissues is anticipated, based on results of a tissue distribution study. In addition, palbociclib lacks functional secondary PD activity associated with the potential for abuse liability.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The Safety concerns listed in the relevant sections below are those included in the Initial endorsed EU-RMP 11 September 2016 (v 1.3).

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

None.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concerns in the initial endorsed EU-RMP version 1.3 are below in Table 13:

Table 13. Summary of Safety Concerns Included in the Initial Endorsed EU-RMP

Important Identified Risks	Myelosuppression (Neutropenia, Anaemia, Thrombocytopenia)
Important Potential Risks	QT prolongation
	Interstitial lung disease (ILD)/Pneumonitis
	Hyperglycaemia
	Reproductive and Developmental Toxicity
Missing Information	Male patients
	Hepatic impairment
	Renal impairment
	Long-term use

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

SVII.2.1. New Important Risks Added to the List of Safety Concerns

No new important potential risks have been identified for palbociclib since the last palbociclib EU RMP (Version 1.7, dated 01 September 2020) was submitted.

SVII.2.2. Important Risks Removed from the List of Safety Concerns

Based on the EMA Guidance on Good Pharmacovigilance Practices, Module V – Risk Management Systems (Rev 2) 28-Mar-2017, the MAH has reassessed and reclassified the above mentioned safety concerns and is hereby proposing the removal of the following:

- Myelosuppression (Neutropenia, Anaemia, Thrombocytopenia), currently classified as an important identified risk in the RMP, is proposed for removal from the list of safety concerns

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

in the RMP. Myelosuppression is a known risk for Palbociclib that has been fully characterised, and for which clinical measures to manage the risk as described in the product label are adequate to support risk minimization and have been integrated into standard medical practice.

- ILD/pneumonitis, currently classified as an important identified risk in the RMP, are proposed for removal from the list of safety concerns in the RMP. ILD/pneumonitis are known risks for Palbociclib that have been fully characterised, and for which clinical measures to manage the risks as described in the product label are adequate to support risk minimization and have been integrated into standard medical practice.

- QT prolongation is currently classified as an important potential risk for palbociclib in the RMP based on a dog Punkinje fibre assay showing a small but statistically significant increase on APD90 at 10 μM (4475 ng/mL) and an IC50 of 3.2 μM (1432 ng/mL) in a hERG assay. In clinical study A5481002, palbociclib in combination with letrozole did not prolong QT interval to a clinically meaningful extent compared to placebo plus letrozole. No new significant safety information pertaining to QT prolongation with palbociclib use has been identified from post-marketing data and there is no expectation that any pharmacovigilance activity can further characterise the risk.

- The MAH considered that the potential risk hyperglycaemia can be removed from the list of safety concerns based on the completion of Study A5481027. This study included the evaluation of hemoglobin A1c (HbA1c), fasting glucose and fasting insulin levels at baseline, during treatment and at the end of treatment, AEs relevant to hyperglycemia and ocular AEs in previously untreated Asian postmenopausal women with ER+HER2- advanced breast cancer treated with palbociclib plus letrozole versus placebo plus letrozole. The analysis showed comparable incidence and exposure-adjusted incidence of abnormal laboratory results, AEs relevant to hyperglycemia and ocular AEs between treatment groups. Overall, the results demonstrated that palbociclib plus endocrine therapy, when compared to placebo plus endocrine therapy, is not associated with increased risk of developing hyperglycaemia or worsening of diabetes.

No unexpected AE findings were observed based upon the known AE profile of palbociclib and letrozole. Overall, palbociclib plus letrozole was safe and well-tolerated.

SVII.2.2.1. Missing Information Removed from the List of Safety Concerns

Use of palbociclib in male patients with metastatic breast cancer is currently classified as missing information in the RMP. Palbociclib is indicated for the treatment of HR+HER2- locally advanced or metastatic breast cancer (including male patients) in combination with an aromatase inhbitior (EMA SPC May 2021). Real-world duration of treatment and response assessments based on electronic health care claims for breast cancer in male patients showed duration of treatment (DOT) by the Kaplan-Meier estimation for palbociclib plus letrozole in the first-line setting was approximately 3 times longer than the median DOT for letrozole alone (9.4 months [95% CI: 4.4, 14.0] vs.3.0 months [95% CI: 1.8, 4.8]). The response rate across all lines of therapy reported in the palbociclib cohort (N=12) was 33.3% vs. 12.5% for the non-palbociclib cohort (N=8). Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with palbociclib is consistent with

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

the safety profile in women. There is no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile of the product in male patients.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

The important identified and potential risks have been determined based on the safety and tolerability of palbociclib in the development programme with the characterisation of these risks based primarily on the data from the Phase 2 and Phase 3 pivotal study conducted in ER-positive, HER2-negative advanced breast cancer in post-menopausal women (Studies 1003 and 1008) and the Phase 3 pivotal study conducted in HR-positive, HER2-negative metastatic breast cancer (Study 1023), supplemented by safety data from non-clinical and other clinical palbociclib studies as well as PM reports. Additionally, the available published data from other Phase 1 studies for drugs in class (CDK 4/6 inhibitors) have been included in the overall risk assessment. Please see Section Module SIII, Clinical trial exposure for the list of included clinical studies.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Potential Risk: Reproductive and Developmental Toxicity

SVII.3.1.1.1. Potential Mechanisms

Testicular degeneration produced by palbociclib is consistent with CDK inhibition and alteration of cell cycle kinetics, given the rapid and continuous cycling of germ cells. CDK4 expression has been shown in normal human spermatogonia.[51] In addition, pathways involving CDKs appear to play a role in spermatogenesis.[52]

Palbociclib administration was associated with reduced foetal body weights in the rat and increase in foetal developmental variations in the rat (cervical ribs) and rabbit (small forepaw phalanges) embryofoetal development studies.

There are no adequate and well-controlled studies using palbociclib in pregnant women. Based on the mechanism of action of palbociclib, palbociclib can cause foetal harm when administered to a pregnant woman. In animal studies, palbociclib was foetotoxic at maternally toxic doses with exposure ≥3 times the human clinical exposure based on AUC.

SVII.3.1.1.2. Evidence Source and Strength of Evidence

Evidence Source: Palbociclib clinical and non-clinical studies. No reports were identified from the Pfizer safety database.

Strength of Evidence: Reproductive and developmental toxicity is considered an Important Potential Risk given adverse effects of palbociclib on male reproductive organs in rats and dogs as well as foetotoxicity in embryofoetal development studies.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

SVII.3.1.1.3. Characterisation of the Risk

Frequency with 95% CI The frequency of related AEs compatible with reproductive and developmental toxicity has not been assessed in humans.

Seriousness/outcomes

Table 14. Studies A5481001, A5481003, A5481008, A5481010 (Part 1 + Part 2 and Phase 2), A5481023 and A5481027 - Patients with Advanced Breast Cancer only Number (%) of All-Causality AEs consistent with possible reproductive or developmental toxicity by Outcome

Preferred Term	Total Events (N= 6)		Serious		Recovered		Not recovered		Fatal
	N1	%	n	%=n/N1	n	%=n/N1	n	%=n/N1	
Amenorrhoea	1	12.5	0	0	0	0	1	100.0	0
Duane's syndrome	1	12.5	0	0	0	0	1	100.0	0
Epidermolysis	2	25	0	0	2	100	0	0	0
Hypertrophic cardiomyopathy	1	12.5	0	0	0	0	1	100.0	0
Pyloric stenosis	2	25	1	50	1	50	1	50	0
Syringomyelia	1	12.5	0	0	0	0	1	100.0	0
Total Events	**8**	**NA**	**1**	**12.5**	**3**	**37.5**	**5**	**62.5**	**0**

Study A5481001 Patient ID: [redacted] (date of data cutoff: 02 January 2015).
Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21 December 2017).
Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 14May2021).
Study A5481010 Part 1 PIDs: [redacted] and all subjects from Part 2 (date of data cutoff: 07 February 2018); and Phase 2 (date of data cutoff: 28 November 2018)
Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021).
A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Includes all causalities treatment-emergent adverse events (data up to 28 days after last dose of study drug).
N= number of subjects with risk factor. N1= number of events reported for the risk factor. n = number of events for preferred term. NA = not applicable.
Percentages for Total Events column are based on total events. Percentages for Serious, Recovered, Not Recovered, and Fatal Events are based on N1.
MedDRA (v24.0) coding dictionary applied.

Severity and nature of risk

The frequency of related AEs compatible with reproductive and developmental toxicity has not been assessed in humans.

There were no effects on estrous cycle or mating and fertility in female rats in non-clinical studies. Based on non-clinical safety findings, male fertility may be compromised by treatment with palbociclib. At present, the clinical target population is female.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 15. Studies A5481001, A5481003, A5481008, A5481010 (Part 1 + Part 2 and Phase 2), A5481023 and A5481027 - Patients with Advanced Breast Cancer only Number (%) of All-Causality AEs consistent with reproductive or developmental toxicity by Severity (CTCAE grade)

Preferred Terms	Maximum Severity					Any Severity Grade (N=6)	
	Severe or Grade 3		Life-threatening or Grade 4		Fatal or Grade 5		
	n	%	n	%	n	n	%
Amenorrhoea	0	0	0	0	0	1	16.7
Duane's syndrome	0	0	0	0	0	1	16.7
Epidermolysis	0	0	0	0	0	1	16.7
Hypertrophic cardiomyopathy	0	0	0	0	0	1	16.7
Pyloric stenosis	0	0	2	33.3	0	2	33.3
Syringomyelia	1	16.7	0	0	0	1	16.7

Study A5481001 Patient ID: [redacted] (date of data cutoff: 02 January 2015).
Study A5481003 Phase I and Phase II subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 21 December 2017).
Study A5481008 subjects treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 14May2021).
Study A5481010 Phase 1 Part 1 PIDs: [redacted] and all subjects from Part 2 (date of data cutoff: 07 February 2018); and Phase 2 (date of data cutoff: 28 November 2018).
Study A5481023 subjects treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 17May2021). A5481027 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 31Aug2020).
Includes all causalities treatment-emergent adverse events (data up to 28 days after last dose of study drug) by maximum CTCAE grade.
N= number of subjects with risk factor. n = number of subjects with preferred term. Percentages are based on N.
MedDRA (v24) coding dictionary applied.
CTCAE version 4.0 was used for the palbociclib RMP v1.8 2021

Post-Marketing

The safety database was searched through 02 August 2021 for cases reporting adverse events consistent with reproductive and developmental toxicity. The search identified 11 cases reporting 11 relevant events. The PTs included Maternal exposure during pregnancy (7), Complication of pregnancy, Death neonatal, Unintended pregnancy and Abortion (1 each). The outcome of the 3 exposure in utero cases included a live birth (fetal outcome normal), an abortion (unknown if it was elective or spontaneous) and 5 was unknown at the time of the report. The case of unintended pregnancy described a 33-year-old female who had received palbociclib for approximately 2 months when the pregnancy was discovered. The patient was on birth control (unspecified) and had been educated about the importance of taking precaution prior to starting the palbociclib. "The baby had severe birth defects (details not provided) this fetus was aborted." Of note Complication of pregnancy was described as "she went from pregnancy to a menopausal state" and Death neonatal occurred in a 34-week infant who lived 24 hours then died (no details provided).

SVII.3.1.1.4. Risk Factors and Risk Groups

No risk groups have been identified.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

SVII.3.1.1.5. Preventability

Restricting use to females would avoid impact on spermatogenesis. In the event that men are to be treated with palbociclib, sperm preservation prior to beginning therapy with palbociclib should be considered.

If females of childbearing potential or partners of females of childbearing potential receive palbociclib, adequate contraceptive methods should be used during therapy and for at least 21 days for females and 97 days for males after completing therapy. Additionally, restricting use of palbociclib in combination with letrozole to postmenopausal females should avoid treatment of women of child-bearing potential.

SVII.3.1.1.6. Impact on the Risk-Benefit Balance of the Product

There does not appear to be a significant public health impact resulting from the potential of reproductive and developmental toxicity in patients treated with palbociclib.

SVII.3.1.1.7. Public Health Impact

The potential effect on public health cannot be precisely determined at this time. Reproductive toxicity may potentially be associated with a significant impact on public health should foetal or developmental abnormalities be encountered as a result of palbociclib exposure.

SVII.3.2. Presentation of the Missing Information

None

Module SVIII. Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Reproductive and Developmental Toxicity
Missing information	None

ILD = Interstitial Lung Disease.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities include adverse drug reaction (ADR) reporting and signal detection.

- **Specific adverse reaction follow-up questionnaires for safety concerns:**
  None.
- **Other forms of routine pharmacovigilance activities for safety concerns:**
  None.

III.2. Additional Pharmacovigilance Activities

None proposed.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Not applicable.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

Table 17. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified risk: None	
Important Potential risk:	
Reproductive and Developmental Toxicity	Routine risk communication: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Preclinical safety data (excerpts) Pregnancy and breast-feeding and fertility of the SmPC PL
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Fertility, pregnancy and lactation data for reproductive and developmental toxicity is included in SmPC Section 4.6. Preclinical safety data for reproductive and developmental toxicity is included in SmPC Section 5.3. Information about Pregnancy and breast-feeding and fertility for reproductive and developmental toxicity is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None
Missing Information: None	

PL = Package Leaflet; SmPC = Summary of Product Characteristics.

V.2. Additional Risk Minimisation Measures

None proposed.

V.3. Summary of Risk Minimisation Measures

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk: None		
Important Potential Risks		
Reproductive and Developmental Toxicity	Routine risk minimisation measures: SmPC Section 4.6, 5.3 Pregnancy and breast-feeding and fertility of the SmPC PL Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	None	Additional pharmacovigilance activities: None
Missing information: None		

PL = Package Leaflet; SmPC = Summary of Product Characteristics.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Ibrance

This is a summary of the RMP for Ibrance. The RMP details important risks of Ibrance, how these risks can be minimised and how more information will be obtained about Ibrance's risks and uncertainties (missing information).

Ibrance's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Ibrance should be used.

This summary of the RMP for Ibrance should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ibrance's RMP.

I. The Medicine and What It Is Used For

Ibrance is authorised for treatment of HR-positive, HER2 negative locally advanced or metastatic breast cancer. It contains Palbociclib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Ibrance's benefits can be found in Ibrance's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Ibrance, together with measures to minimise such risks and the proposed studies for learning more about Ibrance's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public with prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ibrance is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Ibrance are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ibrance. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 19. List of important risks and missing information

Important identified risks	None
Important potential risks	Reproductive and Developmental Toxicity
Missing information	None

II.B. Summary of Important Risks

Table 20. Summary of Important Risks or Missing Information

Important Identified Risk: None	
Important Potential Risk: Reproductive and Developmental Toxicity	
Evidence for linking the risk to the medicine	Palbociclib clinical and non-clinical studies.
Risk factors and risk groups	No risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6, 5.3 PL Section: Pregnancy and breast-feeding and fertility Additional risk minimisation measures: None
Missing information: None	

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for palbociclib.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2-Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3-Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4-Specific Adverse Drug Reaction Follow-Up Forms

Annex 5-Protocols for proposed and on-going studies in RMP Part IV

Annex 6-Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7-Other Supporting Data (Including Referenced Material)

Annex 8-Summary of Changes to the Risk Management Plan over Time

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

REFERENCES:

1 World Cancer Research Fund International. Breast cancer statistics. Available: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics. 05 Oct 2015.

2 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374-403.

3 Surveillance Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Breast Cancer. Available: http://seer.cancer.gov/statfacts/html/breast.html. Sep 2015.

4 Surveillance Epidemiology and End Results (SEER) Program. SEER Cancer Statistics Review, 1975-2011. Available: http://seer.cancer.gov/csr/1975_2011/. Apr 2014.

5 Puig-Vives M, Sanchez MJ, Sanchez-Cantalejo J, et al. Distribution and prognosis of molecular breast cancer subtypes defined by immunohistochemical biomarkers in a Spanish population-based study. Gynecol Oncol 2013;130(3):609-14.

6 Kurian AW, Fish K, Shema SJ, et al. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. Breast Cancer Res 2010;12(6):R99.

7 Blows FM, Driver KE, Schmidt MK, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: A collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 2010;7(5):e1000279.

8 Spitale A, Mazzola P, Soldini D, et al. Breast cancer classification according to immunohistochemical markers: Clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. Ann Oncol 2009;20(4):628-35.

9 Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev 2007;16(3):439-43.

10 Parise CA, Bauer KR, Brown MM, et al. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1994-2004. Breast J 2009;15(6):593-602.

11 Goncalves A, Deblock M, Esterni B, et al. Docetaxel first-line therapy in HER2-negative advanced breast cancer: A cohort study in patients with prospectively determined HER2 status. Antican Drugs 2009;20(10):946-52.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

[12] Colditz GA, Rosner BA, Chen WY, et al. Risk factors for breast cancer according to estrogen and progesterone status. J Natl Cancer Inst 2004;96(3):218-28.

[13] Surveillance, Epidemiology, and End Results (SEER) Program. SEER Statistics Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (2000-2011) <Katrina/Rita Population Adjustment> – Linked to County Attributes – Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch. Available: http://seer.cancer.gov/data/seerstat/nov2013/. 07 May 2014.

[14] Surveillance Epidemiology, and End Results (SEER) Program. Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. Available: http://seer.cancer.gov/faststats. Sep 2015.

[15] Althius MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-33defined breast cancer: A systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13(10):1558-68.

[16] Phipps AI, Malone KE, Porter PL, et al. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomark Prevent 2008;17(8):2078-86.

[17] Ahn J, Schatzkin A, Lacey JV Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med 2007;167(19):2091-102.

[18] Pan H, Gray RG. Effect of obesity in premenopausal ER + early breast cancer: EBCTCG data on 80,000 patients in 70 trials. J Clin Oncol 2014;(Suppl):Abstract 503.

[19] Setiawan VW, Monroe KR, Wilkens LR, et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: The multiethnic cohort study. Am J Epidemiol 2009;169(10):125-9.

[20] Cardoso F, Costa A, Norton L, et al. 1st international consensus guidelines for advanced breast cancer (ABC 1). Breast 2012;21(3):242-52.

[21] Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii11-9.

[22] Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: An open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012;30(16):1919-25.

[23] Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med 2012;367(5):435-44.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

[24] Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001;19(10):2596-606.

[25] Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the international Letrozole Breast Cancer Group. J Clin Oncol 2003;21(11):2101-9.

[26] Massarweh S, Romond E, Black EP, et al. A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER) positive breast cancer after aromatase inhibitor (AI) failure. Breast Cancer Res Treat 2014;143(2):325-32.

[27] Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: An intergroup study. J Clin Oncol 1998;16(3):994-9.

[28] Prowell TM, Davidson NE. What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? Oncologist 2004;9(5):507-17.

[29] Faslodex. Summary of Product Characteristics. Cheshire, United Kingdom: AstraZeneca UK Limited. Mar 2015.

[30] Afinitor. Package Insert. East Hanover, New Jersey, United States. Jun 2016.

[31] Arimidex. Package Insert. Wilmington, Delaware, United States. May 2014.

[32] Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: A systematic review and meta-analysis. PLoS Med 2012;9(7):e1001275.

[33] Cronin-Fenton DP, Søndergaard F, Pederson LA, et al. Hospitalization for venous thromboembolism in cancer patients and the general population: A population-based cohort study in Denmark, 1997-2006. Br J Cancer 2010;103(7):947-53.

[34] Shinagare AB, Guo M, Hatabu H, et al. Incidence of pulmonary embolism in oncologic outpatients at a tertiary cancer center. Cancer 2011;117(16):3860-6

[35] Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared to tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98. J of Clin Oncol 2007;25(5):486-92.

[36] Howell A, Pippen J, Elledge RM, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials. Cancer 2005;104(2):236-9.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

[37] Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor positive advanced breast cancer. J Clin Oncol 2010;28(30):4594-600.

[38] Twiss JJ, Waltman N, Ott CD, et al. Bone mineral density in postmenopausal breast cancer survivors. J Am Acad Nurse Pract 2001;13(6):276-84.

[39] Chen Z, Maricic M, Pettinger M, et al. Osteoporosis and rate of bone loss in postmenopausal survivors of breast cancer. Cancer 2005;104(7):1520-30.

[40] Lindsey AM, Gross G, Twiss JJ, et al. Postmenopausal survivors of breast cancer at risk for osteoporosis: Nutritional intake and body size. Cancer Nurs 2002;25(1):50-6.

[41] Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen alone or in combination trial 18233230. J Clin Oncol 2008;26(7):1051-7.

[42] Eastell R, Hannon RA, Cuzick J, et al. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial (18233230). J Bone Miner Res 2006;21(8):1215-23.

[43] Hirbe A, Morgan EA, Uluckan O, et al. Skeletal complications of breast cancer therapies. Clin Cancer Res 2006;12(20 Pt 2):6309s-14s.

[44] Chen Z, Maricic M, Bassford TL, et al. Fracture risk among breast cancer survivors: Results from the Women's Health Initiative Observational Study. Arch Intern Med 2005;165(5):552-8.

[45] Kanis JA, McCloskey EV, Powles T, et al. A high incidence of vertebral fractures in women with breast cancer. Br J Cancer 1999;79(7-8):1179-81.

[46] Rabaglio G, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 2009;20(9):1489-98.

[47] Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;394(19):1793-802.

[48] Women's Health Initiative. Outcomes summary tables: Confirmed outcomes in HT: by age. Available: https://www.whi.org/data/Outcomes%20Summary%20Tables/Table%202.2.pdf. 20 Sep 2013.

[49] World Health Organization. Chronic disease and their common risk factors. Available: http://www.who.int/chp/chronic_disease_report/media/Factsheet1.pdf. 05 Oct 2015.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

[50] Smith AW, Reeve BB, Bellizzi KM, et al. Cancer, comorbidities, and health-related quality of life in older adults. Health Care Financ Rev 2008;29(4):41-56.

[51] Bartkova J, Lukas C, Sorensen CS, et al. Deregulation of the RB pathway in human testicular germ cell tumors. J Pathol 2003;200(2):149-56.

[52] Ravnik SE, Wolgemuth DJ. Regulation of meiosis during mammalian spermatogenesis: the A-type cyclins and their associated cyclin-dependent kinases are differentially expressed in the germ-cell lineage. Dev Biol 1999;207(2):408-18.

090177e19977610c\Approved\Approved On: 28-Feb-2022 12:44 (GMT)

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

Not applicable.

090177e1987acc97\Approved\Approved On: 08-Nov-2021 16:51 (GMT)

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

090177e1987ace88\Approved\Approved On: 08-Nov-2021 16:51 (GMT)