NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	**P**albociclib Combinations in H**R**+/HER2- M**e**tastatic Breast **C**ancer Pat**i**ents: A Non-Interventional Pr**o**spective Study on the Treatment Patterns & Clinical Outcomes in Africa Middle Eas**t** (**PRECIOUS)**
Protocol number	A5481150
Protocol version identifier	3.0
Date	8 November 2022
Active substance	Palbociclib
Medicinal product	Ibrance®

Research question and objectives	To describe patient demographics, clinical characteristics, treatment patterns and clinical outcomes of adult patients who have received palbociclib combination treatment in line with regional approved indications in real-world settings across Africa Middle East countries.
	Primary Objectives:
	• To determine clinical outcomes including (but not limited to):
	  • Proportion of patients who are progression free and alive at specific intervals (eg, 12, 18 months).
	  • Proportion of patients alive after 1- and 2-years post palbociclib combination initiation – depending on availability of follow- up data.
	Secondary Objectives:
	• To determine objective response rate (ORR) – depending on the availability of follow-up data.
	• To describe the demographic and clinical characteristics of patients who have received palbociclib combination treatment in line with locally approved indications.

	• To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice. • To describe supportive therapies received by patients while receiving palbociclib combination treatment. • To summarize adjuvant therapies received for the treatment of early or locally advanced breast cancer (Stages 0- IIIa). • To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use. • To assess quality of life of patients receiving palbociclib combination treatment. **Exploratory Objectives** • To evaluate time to response (TTR), time to progression (TTP)/progression free survival (PFS) associated with palbociclib combination treatment-depending on availability of follow up data. • To describe the first immediate subsequent treatment used following end of treatment with palbociclib.
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADL	Activities of Daily Living
AEM	adverse event monitoring
AfME	Africa Middle East
ASR	age-standardized rate
BC	breast cancer
BRCA	breast cancer gene
CBC	complete blood count
CRA	clinical research associates
CRF	case report form
CDK	cyclin-dependent kinase
CSA	clinical study agreement
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EDP	exposure during pregnancy
EMR	electronic medical record
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ER	estrogen receptor
ER+	estrogen receptor positive
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FPI	first patient in
G8	Geriatric 8
GPP	Good Pharmacoepidemiology Practices
HER2	human epidermal growth factor receptor 2

Abbreviation	Definition
HER2-	human epidermal growth factor receptor 2 negative
HIC	high-income countries
HR-	hormone receptor negative
HR+	hormone receptor positive
IRIS	Ibrance Real World Insights
IEC	Independent ethics committee
IRB	Institutional review board
ISMF	investigator site master file
ISPE	International Society for Pharmacoepidemiology
KSA	Kingdom of Saudi Arabia
LHRH	luteinizing hormone-releasing hormone
LMIC	lower-middle-income countries
LPI	last patient in
LPO	last patient out
MBC	metastatic breast cancer
ME	Middle East
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NI	non-interventional
NIS	non-interventional study
ORR	objective response rate
PFS	progression free survival
PI3K	phosphatidylinositol 3-kinase
PR+	progesterone receptor positive
POLARIS	Palbociclib in Hormone Receptor–Positive Advanced Breast Cancer: A Prospective Multicenter Noninterventional Study
Q	quarter
QoL	Quality of life
Rb	retinoblastoma

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SOP	standard operating procedure
TTP	time to progression
TTR	time to response
UAE	United Arab Emirates
US	United States

2. RESPONSIBLE PARTIES

All study investigators are listed as a stand-alone document in Annex 1.

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
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3. ABSTRACT

The Abstract is a stand-alone document, see Annex 1.

4. AMENDMENTS AND UPDATES

Amendment Number	Date	Protocol section(s) Changed	Summary of Amendment(s)	Reason
1	13 Dec2021	Responsible Parties	Added the Pfizer and IQVIA study teams	To reflect the complete study team
	13 Dec2021	Abstract	Removed from the protocol	It is a stand-alone document and should not be in the actual protocol. Added to Annex 1
	13 Dec2021	Milestones	Updated the milestones dates and removed the ones not applicable	To reflect the current situation and progress of the study
	13 Dec2021	Study Design	Updated the countries (Egypt, Jordan,, KSA, Lebanon, Morocco, Qatar and UAE) and the number of centers to 19	To reflect the changes in participating countries and the number of centers enrolled.
	13 Dec2021	Study Size (table 3)	Updated the planned number of subjects per centers per country	To reflect the changes in participating countries and the number of centers enrolled.
2	8 November 2022	Study Design	Extension of enrollment period 18 months instead of 12 months	Challenges in patients recruitment due to change of treatment protocols in some countries
	8 November 2022	Study Size (table 3)	Reducing sample size to 200 subjects instead of 340 subjects	Challenges in patients recruitment due to change of treatment protocols in some countries
	8 November 2022	Milestones	Updated the milestones dates	To reflect the current situation and progress of the study and the extension in the enrollment period

5. MILESTONES

Milestone	Planned Date
Start of data collection	15 July 2021
End of data collection	30 April 2025
Interim report 1	30 November 2023
Final study report	31 December2025

6. RATIONALE AND BACKGROUND

6.1. Background

Breast cancer (BC) is a complex, heterogenous disease encompassing multiple tumor entities with specific pathologic features and biological behaviors.[1] It is the most common neoplasm among women with an estimated incidence of 2.4 million cases and 523,000 deaths in the year 2015.[2] Approximately 6%-10% of new BC cases are diagnosed as stage IV metastatic disease and an estimated 20%-30% patients with early BC experience relapse with distant metastatic disease.[3]

Absolute rates of BC incidence are higher in high-income countries (HICs), however incidence rates are also increasing in lower-middle–income countries (LMICs).[2] The age- standardized rate (ASR) per 100,000 population for BC worldwide is 43.1.[4] The highest BC incidence rates are in North America, Australia, New Zealand, and Northern and Western Europe.[5] The incidence rate varies from 19.4 per 100,000 people in East Africa to 89.7 per 100,000 in West Europe.[6] Mortality rates of BC depend on the availability of early detection and treatment.[4] Hence, the mortality rates are higher in many LMICs, such as those in sub-Saharan Africa due to their late stage diagnosis and limited access to treatment as compared to HICs.[5] The 5 year survival rate is 85% or higher in the United States, Canada, Australia, Israel, Brazil, and many Northern and Western European countries, whereas it is 60% or lower in many LMICs, such as South Africa, Mongolia, Algeria, and India.[5]

Breast cancer is one of the most prevalent cancers in the Middle East (ME), where it is also the most common cause of death among females.[7] The BC cases diagnosed in this geography are more aggressive and associated with worse outcomes compared to cases evidenced in other parts of the world, which may partly be explained by late diagnosis.[7]

Indeed, most Arab women do not present themselves for regular medical examination due to social customs, leading to diagnosis of BC at an advanced stage, which is more challenging to treat.[7] According to Kuwait cancer registry, BC constitutes 36.4% of newly reported cancer cases among females.[7] In Kingdom of Saudi Arabia (KSA), BC constitutes 29.1% of all women's cancer, as reported by KSA cancer registry 2013.[8] The age-standardized incidence and mortality rate of BC in KSA was 22.4 and 10.4 per 100,000 women, respectively in the year 2008.[9] In United Arab Emirates (UAE), BC constitutes 43% of cancers diagnosed among females and 25% of all cases of cancer, with an incidence rate of

approximately 38 per 100,000 women.[10] Based on the National Population-Based Registry Program of Egypt (2008–2011), BC was the second most frequent cancer constituting 15.41% of all cancers with an age specific incidence rate of 35.8 per 100,000 women.[11] Similarly, in Algeria, BC represents 59% of all women's tumors with crude incidence rate of 54.4 per 100,000 women and a standardized incidence rate of 65.2 per 100,000 women.[12] In Lebanon, between the years 2003 and 2008, BC was the most commonly reported cancer in women, with an increase in age-standardized incidence rate from 78.3 to 95.7 per 100,000 women from year 2003 to 2008.[13] A similar trend was observed in Morocco where the age-standardized incidence rate of BC increased from 35.0 to 39.0 per 100,000 women between the years 2004 and 2008, showing an annual increase of 2.85 %.[14]

Molecular classification differentiates BC on the basis of gene expression pattern, clinical and biological properties, histologic correlation and response to treatment and prognosis.[15] The classification is on the basis of presence or absence of hormone receptors (HR) such as estrogen receptors (ER) or progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2). These receptors have an important role in the prognosis of the disease.[1] The 5 subtypes of BC are: luminal A (HR+/HER2−), luminal B (HR+/HER2+), HER2-enriched (hormone receptor negative [HR-]/HER2+), basal-like (80%–90% are triple negative), and normal breast-like/unclassified BC.[15] Approximately 70% of the BC express HR.[16] The majority of the diagnosed BC are estrogen receptor positive (ER+) and HER2-, and 75% of metastatic breast cancer (MBC) patients are HR+ (either ER+ or progesterone receptor positive [PR+]).[3,16]

Endocrine therapy is the major treatment of choice for HR+/HER2- MBC.[17] In premenopausal women with HR+ BC, endocrine therapy with or without ovarian ablation (by surgery, chemotherapy or luteinizing hormone-releasing hormone (LHRH)) is the preferred option.[18] In post-menopausal HR+/HER2- MBC (without extensive visceral involvement), anastrazole, letrozole and exemestane are the standard hormonal therapies along with selective estrogen receptor modulators like tamoxifen or selective estrogen receptor degraders like fulvestrant.[3] These treatment options are associated with a time to progression (TTP) and prolongation of progression free survival (PFS) ranging from 5 to 15 months.[18] These treatment options are supported by clinical practice guidelines published by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) as preferred first-line options in patients who are antiestrogen naïve or who had prior estrogen therapy within one year.[19] For MBC with significant visceral burden or rapid progression of disease, chemotherapy is recommended.[3] The response rates associated with these endocrine therapies as first-line agents are up to 40% with all initial responders eventually acquiring resistance over time.[3] Moreover, single-agent treatment with an aromatase inhibitor or tamoxifen has shown limited clinical benefit as well as selective ER degrader fulvestrant has modest activity in this patient population.[20-22] Hence, clinically it's important to identify new targets to develop effective therapies to improve patients' outcomes. Some potential molecular targets that are altered in BC patients are cyclin-dependent kinase 4 and 6 (CDK4/6), phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway, and poly adenosine diphosphate ribose polymerase.[16]

PI3K/mTOR and CDK4/6 inhibitors can reduce the resistance to endocrine therapy. CDK4/6 inhibitors control the cyclin D– CDK–retinoblastoma (Rb) pathway and may have a synergistic activity when combined with hormonal therapy, as well as, reduce the resistance acquired to that class of treatment.[16]

Palbociclib (IBRANCE®) is one such oral targeted agent that selectively inhibits cyclin-dependent kinases (CDKs) - CDK4 and CDK6 resulting in cell cycle arrest. It is indicated for the treatment of HR+/HER2-MBC in combination with letrozole as initial endocrine-based therapy in post-menopausal women.[23]

The efficacy and safety of palbociclib was assessed in PALOMA-1 trial: a randomized Phase 2 study of palbociclib in combination with letrozole versus letrozole alone. The study showed that participants who were treated with Ibrance® plus letrozole had median PFS of 20.2 months as compared to those treated with letrozole alone who reported median PFS of 10.2 months (p=0.0004).[24] Following its success, the Food and Drug Administration (FDA) granted accelerated approval of palbociclib in combination with letrozole in February 2015 and became the first CDK4/6 inhibitor to be approved as a cancer therapy by the FDA.[25] The label was later expanded to include aromatase inhibitor in this indication based on the follow-up of PALOMA-2 trial which was a Phase III study for post-menopausal patients with metastatic HR+/HER- BC receiving letrozole in combination with palbociclib versus patients receiving letrozole and placebo. The study showed that participants treated with Ibrance® in combination with letrozole had a greater PFS compared with patients treated with letrozole plus placebo (24.8 months vs. 14.5 months; p<0.001, respectively).[26] A regular approval was granted to palbociclib in February 2016 for a second indication: treatment of HR+, HER2-MBC in combination with fulvestrant in women with disease progression following endocrine therapy. This was following the success of Phase III PALOMA-3 trial, that showed that Ibrance® in combination with fulvestrant prolonged PFS (median PFS of 9.5 months) compared with placebo with fulvestrant (median PFS of 4.6 months; p <0.0001) in women with metastatic HR+/HER2- BC that had relapsed or progressed during endocrine therapy.[26]

Palbociclib utilization and clinical outcomes have been examined in the real-world setting in both retrospective and prospective studies. One retrospective real-world study, based on data from a US electronic medical record (EMR) database, assessed the settings in which palbociclib was being initiated and examined in the real-world occurrence of associated adverse events (AEs) like neutropenia.[27] The study reported that 80.2% of the patients received palbociclib concomitantly with letrozole. Overall, 39.5% of patients initiated palbociclib plus letrozole in first-line therapy while 15.7% in second-line therapy followed by 13.1% and 31.7% in third-line and fourth- line (or later) therapies, respectively. Overall, 74.6% of patients had a neutropenic event during follow-up including 47.3% and 8.0% of patients with a Grade 3 or 4 occurrence, respectively.[27] In other retrospective study based on EMR data from the Flatiron Health Analytic database, real-world best tumor responses, which occurred at least 30 days after the date of therapy initiation, were assessed.[28] For patients using palbociclib plus aromatase inhibitor, complete response was achieved in

9.5% of patients, and partial response was achieved in 50.5% of patients. For patients using palbociclib plus letrozole, complete response was achieved in 9.7% of patients, and partial response was achieved in 50.2% of patients.[28]

The Ibrance Real World Insights (IRIS) study, based on retrospective chart review, evaluated treatment patterns and clinical outcomes among patients using palbociclib in various countries globally. In the Argentina patient subgroup, the 6-month PFS rate was 94% for patients treated with palbociclib plus letrozole and 95% for patients treated with palbociclib plus fulvestrant.[29] Six-month survival rates were 98% for palbociclib plus letrozole and 98% for palbociclib plus fulvestrant; 93% and 89% of patients treated with palbociclib plus letrozole were alive at 12 and 18 months, respectively.[29]

In the United States (US) patient subgroup, the 12-month progression free rate was 84.1% for patients treated with palbociclib plus aromatase inhibitor and 79.8% for those treated with palbociclib plus fulvestrant; 12-month survival rates were 95.1% for palbociclib plus aromatase inhibitor and 87.9% for palbociclib plus fulvestrant.[30] In another retrospective chart review study conducted in the US, real- world effectiveness was evaluated among patients using palbociclib plus letrozole as first- line treatment; the 6-month, 12-month and 18-month PFS rates were 92.7%, 75.5%, and 51.6%, respectively, while the 6-month, 12-month, and 18-month overall survival rates were 97.5%, 95.3% and 92.5%, respectively.[31]

In a prospective real-world study, "Palbociclib in Hormone Receptor–Positive Advanced Breast Cancer: A Prospective Multicenter Noninterventional Study (POLARIS)", measures of functional status were assessed in adults aged ≥70 years who were using palbociclib combination therapy.[32] The results showed that measures of functional status (as assessed via the Activities of Daily Living [ADL] screening tool, Geriatric 8 [G8] screening tool, and Eastern Cooperative Oncology Group [ECOG] performance status) were generally maintained during the first 6 months of therapy, indicating that functional status was essentially preserved in elderly population receiving palbociclib combination therapy.[32]

In the AfME region, palbociclib was first approved in UAE in early 2015 in combination with letrozole for the treatment of post-menopausal women with ER+/HER2- MBC as initial endocrine-based therapy for their disease. Since then, approval in Lebanon and KSA followed, and now palbociclib is available in most AfME countries.

6.2. Rationale

Palbociclib is a novel first-in-class CDK 4/6 inhibitor, which is now globally available in more than 80 countries.[34] As palbociclib has only recently been approved, there is limited information on real-world treatment patterns and outcomes, particularly in the ME and Africa setting. It is important to collect real-world data as clinical trial populations may not be representative of the target populations of patients given the stringent enrollment criteria in clinical trials coupled with the focus on a single line of therapy. This study will provide prospective, observational data on patients initiating treatment with palbociclib to contribute

to the knowledge of metastatic/locally advanced BC disease management, clinical outcomes and quality of life (QoL) in the real-world ME and Africa setting.

7. RESEARCH QUESTION AND OBJECTIVES

With the introduction of palbociclib across different markets, this study aims to provide prospective, observational data of use of palbociclib in a real-world setting in terms of treatment patterns, clinical outcomes and QoL.

7.1. Primary Objectives

- To determine clinical outcomes including (but not limited to):
    - Proportion of patients who are progression free and alive at specific intervals (eg, 12, 18 months).
    - Proportion of patients alive 1- and 2-years post palbociclib combination initiation - depending on availability of follow-up data.

7.2. Secondary Objectives

- To determine objective response rate (ORR) – depending on availability of follow-up data.
- To describe the demographic and clinical characteristics of patients who have received palbociclib combination treatment in line with locally approved indications.
- To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice.
- To describe supportive therapies received by patients while receiving palbociclib combination treatment.
- To summarize adjuvant therapies received for the treatment of early or locally advanced BC (Stages 0-IIIa).
- To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use.
- To assess QoL of patients receiving palbociclib combination treatment.

7.3. Exploratory Objectives

- To evaluate time to response (TTR), time to progression (TTP)/PFS associated with palbociclib combination treatment – depending on availability of follow-up data.

- To describe the first immediate subsequent treatment used following end of treatment with palbociclib.

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, non-interventional (NI), multicenter study being conducted in Africa Middle East (AfME) countries. The aim is to understand palbociclib treatment patterns, clinical outcomes and QoL for patients with metastatic/locally advanced BC being treated in routine clinical practice in 7 AfME countries: Egypt, Jordan, KSA, Lebanon, Morocco, Qatar and UAE.

Approximately 200 patients from 19 centers across the 7 countries will be enrolled. The recruitment period (ie, from first patient into last patient in) will span over 18 months.

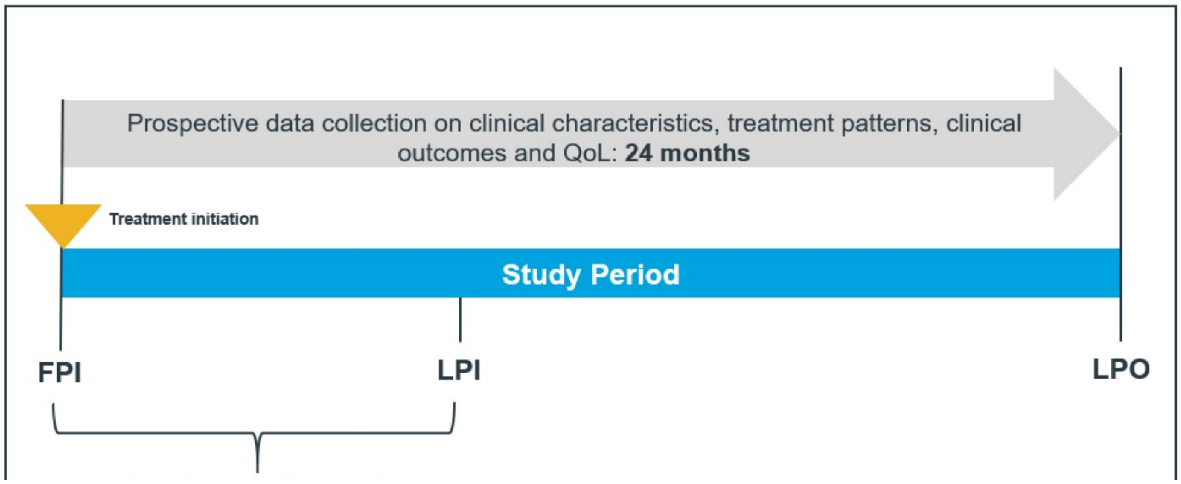
Patients will be enrolled at the time of treatment initiation with palbociclib and will be followed up over a 24-month period at time intervals per routine care, or until patient's withdrawal from the study or death (whichever comes first). Prospective data on clinical characteristics, treatment patterns, clinical outcomes and QoL will be collected (Figure 1).

Participation in this study is not intended to change the routine treatment patients receive, as determined by their prescribing physicians; all treatment decisions, type and timing of the disease monitoring are per routine clinical care, and at the discretion of treating physician and patient.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this non-interventional study is being conducted.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this non-interventional study is being conducted.

Figure 1. Study Design



Recruitment 18 months

8.2. Setting

Patients with HR+/HER2- metastatic/locally advanced BC within Egypt, Jordan, KSA, Lebanon, Morocco, Qatar and UAE will be enrolled from a geographically representative population as well as from diverse treatment settings (eg, academic and community sites). Patients whose treatment decision with palbociclib combination has been made by their treating physician and meet the eligibility criteria will be invited to participate in the study in a consecutive manner and over 18 months of recruitment. Data will be collected in accordance with routine standard of care visits. Eligibility will be assessed at the date of the enrollment. Data will be collected at enrollment (time of treatment initiation), during treatment with palbociclib and after treatment with palbociclib, over a 24-month period (at time intervals per routine care). After the end of treatment with palbociclib, data related to the first immediate subsequent treatment received will be collected. Patients included in the study will be followed up until the end of the follow-up, withdrawal or death, whichever occurs first.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study: Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Age ≥18 years or older with diagnosis of adenocarcinoma of the breast with evidence of metastatic/locally advanced disease not amenable to treatment with curative intent.

2. Documented HR+ (ER+ and/or PR+) tumor based on local standards.

3. Documented HER2- tumor based on local standards.

4. Will initiate treatment with palbociclib plus letrozole/aromatase inhibitor or palbociclib plus fulvestrant in line with the licensed indication(s), as first or second line therapy for metastatic/locally advanced BC at enrollment.

5. Patients who in the opinion of the investigator are willing and able to comply with regular clinic visits.

6. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients participating in any interventional clinical trial.

2. Patients on active treatment for malignancies other than metastatic/locally advanced BC at the time of enrollment.

3. Patients who are unable to understand the nature of the study and are unwilling to sign an informed consent.

8.3. Variables

Patient demographics, clinical characteristics, comorbid conditions and concomitant medications, early/locally advanced and metastatic BC treatment history, current BC treatment, performance status (ECOG), clinical outcomes, laboratory/other investigations and QoL will be collected. Detailed definitions of variables and the Data Entry Schedule is provided in Table 1 and Table 2.

Table 1. Study Variables

Variable	Operational Definition	Data Source(s)
Demographics	Age, ethnicity, weight, family history of BC (breast cancer (BRCA) gene testing performed).	Patient records
Clinical characteristics	Time since diagnosis, staging, node status, menopause status, diagnosis for which palbociclib combination was prescribed, sites of metastases, de novo versus recurrent disease.	Patient records

Variable	Operational Definition	Data Source(s)
Comorbid conditions and concomitant medications	Comorbid conditions and concomitant medications.	Patient records
Early or locally advanced BC treatment history	Adjuvant treatments received for early or locally advanced BC (Stages 0-IIIa). Time since end of adjuvant treatment. Surgery/radiotherapy received.	Patient records
MBC treatment history	Treatments and supportive therapies received since metastatic HR+/HER2- diagnosis. Duration of treatments.	Patient records
Current BC treatment	Starting dose, duration of treatment, changes in dose, interruptions, cycle delays and discontinuations. Line of treatment.	Patient records
Performance status (ECOG)	Eastern Cooperative Oncology group score.	Patient records
Clinical outcomes	• Proportion of progression free survival/time to progression (at intervals per standard of care). • Proportion of objective response rate (at intervals per standard of care). Complete response defined as complete reduction of all visible disease; partial response defined as partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease; stable disease defined as no change in overall size of visible disease, also including cases where some lesions increased in size and some lesions decreased in size; progressive disease defined as an increase in visible disease and/or presence of any new lesions, including cases where the clinician indicates progressive disease. • Time to response (at intervals per standard of care), defined as the time to first response among patients who achieved complete response or partial response. • Proportion of overall survival (1- and 2-years post-treatment initiation).	Patient records

Variable	Operational Definition	Data Source(s)
All lab investigations + other investigations	• All lab investigation conducted including complete blood count (CBC).	Patient records
Quality of life	• To be assessed via EORTC QLQ-C30 (Cancer Quality of Life Questionnaire).	Patient questionnaire

BC = breast cancer; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MBC = metastatic breast cancer.

Table 2. Data Entry Schedule

Data Collection and Entry[1] ►	Baseline	During Treatment with Palbociclib	Post Treatment with Palbociclib
	SOC Visit[1]	SOC Follow-up visits[2] through End of Treatment with Palbociclib	SOC Follow-up Visits through End of Study[3]
Informed Consent & Inclusion/Exclusion Criteria	x		
Patient Demographics, Medical History, Baseline Metastatic Disease Status	x		
BC Diagnosis and Recurrence History	x		
Comorbid conditions	x	x	
Concomitant Medications	x	x	
BC Treatment[4]	x	x	x[5]
Performance Status (ECOG)	x	x	
Clinical Outcomes[6]	x	x	
Laboratory investigations, including CBC[7]	x	x	
EORTC QLQ-C30[8]	x	x	

BC = breast cancer; SOC = standard of care; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

1. Data is collected in accordance with normal standard of care visits; enter all data available per Data Entry Schedule into the electronic data capture system.
2. For a visit to be considered a follow-up visit, clinical outcomes data must be collected at minimum, in accordance with SOC.
3. Follow-up through End of Study: Enter data at SOC visits post palbociclib treatment.
4. BC treatment: including surgery, radiation, systemic chemotherapy, hormone therapy, and/or targeted therapy, in both neoadjuvant/adjuvant and metastatic disease settings, prior to, during and after palbociclib treatment; supportive care is also collected in the metastatic setting.
5. Data on the first immediate subsequent treatment used after the end of palbociclib treatment should be collected.
6. Clinical outcomes: overall clinical response as judged by treating physician, at intervals per standard of care schedule: progression free survival/time to progression, objective response rate, time to response and overall survival.
7. CBC: Baseline and during palbociclib treatment, enter any CBC during the 1st 3 cycles, then enter Day 1 (or prior to start of a new cycle) CBC for the subsequent cycles as per standard of care.
8. EORTC QLQ-C30 will be collected at baseline (before starting palbociclib) then every 3 months ±2 weeks after initiating treatment with palbociclib for the first year of treatment. After the first year of treatment with palbociclib, EORTC QLQ-C30 will be collected every 6 months ±4 weeks until the end of treatment with palbociclib.

8.4. Data Sources

All data collected in this study are intended to capture the real-world treatment patterns and outcomes for patients with HR+/HER2- metastatic/locally advanced BC. An electronic case report form (eCRF) will be used for data collection. The eCRF must be signed by the investigator. The signature serves to attest that the information contained in the eCRF is true. At all times, the investigator has the final responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the eCRFs.

Data for this study will be obtained via the sources outlined below.

8.4.1. Patient Medical Charts

The investigator or authorized medical staff will record clinical and treatment data from patients' existing medical records into an eCRF following each patient's standard of care clinic visit.

8.4.2. Patient Questionnaires and Quality of Life

All patients enrolled in the study will be asked to participate in completing the Quality of Life Questionnaire, EORTC QLQ-C30, to be collected at baseline (before starting palbociclib) then every 3 months ±2 weeks after initiating treatment with palbociclib, for the first year of treatment, in accordance with routine standard of care visits. After the first year of treatment with palbociclib, EORTC QLQ-C30 will be collected every 6 months ±4 weeks until the end of treatment with palbociclib, in accordance with routine standard of care visits.

Patients will complete these questionnaires on a paper form.

8.5. Study Size

This is an observational study of drug usage without any pre-defined hypothesis to be tested; rather, it addresses descriptive objectives. Sample size calculations were performed per country taking into account population size, estimated MBC prevalence, and a margin of error of 5%. A minimum sample size of 15 patients per country (total sample size of 105 patients) was estimated on this basis.

A planned total sample size of approximately 350-410 patients (Table 3) will be applied to ensure adequate exploration of the objectives and sufficient generalizability.

Table 3. Planned Number of Subjects and Centers per Country

Country	Estimated Number of Centers	Estimated Number of Subjects
Egypt	5	60
Gulf (UAE/Qatar)	2	20
Jordan	1	20
Lebanon	6	65
Morocco	2	15
KSA	3	20
Total	19	200

8.6. Data Management

8.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered in the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs[/DCTs] must match those charts.

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

8.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for as long as they are retained.

If the investigator is unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

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

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

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

This is a descriptive study, and as such, no statistical testing will be conducted. Analyses will be conducted using Statistical Analysis System (SAS) (version 9.3 or higher). Summary statistics for patient demographics, clinical characteristics, treatment patterns and QoL will be performed. Summary statistics for continuous variables will include number of observations, mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum. Summary statistics for categorical data will include number of observations, counts and percentages. Kaplan-Meier analyses will be performed on time-to-event outcomes, eg, TTP, response and death.

Exploratory stratifications will be conducted (where adequate numbers of patients permit) to explore differences by eg, country, line of therapy, menopausal status, de novo versus recurrent disease, age (<55 years vs. ≥55 years), and combination therapy (ie, palbociclib plus letrozole/aromatase inhibitor vs. palbociclib plus fulvestrant). The data may also be evaluated and presented by other meaningful subgroups, as outlined in the SAP.

Should missing data occur, the data will be analyzed as they are recorded in the eCRFs, and no imputation of missing data will be performed. The amount of missing values for data elements will be reported.

8.8. Quality Control

Investigators will be trained with an initial on-site visit to the clinic on the protocol, electronic data capture (EDC) system (ie, eCRF), investigator site master file (ISMF), documentation, and any applicable study processes. Any new information relevant to the performance of this non-interventional study (NIS) will be forwarded to the medical staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of safety data, data integrity and consistency. The eCRFs for all included patients will be made available to the remote data monitor for review. A list of critical variables will be created as required elements for review during the remote data monitoring process. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

Monitoring visits may be made, if necessary, to monitor study process by Pfizer, Inc. or its delegate. In the event of a visit, direct access to original source data will be required for monitoring visits and/or inspections/audits, which will be carried out with due consideration for data protection and patient confidentiality.

Items routinely checked during on-site visits include:

- Documentation of the informed consent process.
- Compliance with patient eligibility criteria.
- Proper maintenance of records, such as study protocol.
- Completed eCRFs.
- Documentation of AEs, and transmission of serious adverse events (SAEs).
- Identification of patients lost to follow-up.
- Study correspondence.
- Compliance with Institutional review board (IRB)/ Independent ethics committee (IEC) approval requirements.
- Review of the ISMF.
- Archiving of the study documents will be performed accordingly to Pfizer standard operating procedures (SOPs).

8.9. Limitations of the Research Methods

A key limitation of a study of this nature is the reliance on accurate, complete CRFs, which is dependent on the correct completion of the CRFs and the availability of detailed, complete patient records. We have outlined a number of important quality control steps to be taken as part of the study procedures to minimize the impact of this. Notably, to reduce the administrative burden on all physicians, only data elements that are relevant for addressing the research objectives will be collected.

As this is a NIS, potential bias cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at prespecified time points, which may have an impact on the amount of data available and its interpretation.

8.10. Biases

Selection bias

In order to minimize selection bias, the sampling strategy that was designed for the proposed study will reflect real-life clinical practice since it will capture all possible treatment settings. In addition, selection bias due to sampling and participation will be assessed by comparing characteristics of the participating versus non-participating patients and prescribers.

Information bias

At the patient level, misclassification of drug exposure has to be considered. Medical records provide detailed information on prescribed and/or dispensed medications but may not contain information on the intended duration of use (days of supply) and often do not contain information on the actual use of the medications by the patient. Thus, patients may be classified as exposed to a drug although they actually have not taken the drug. For this reason, great care will be taken to ensure the quality of the information that is abstracted, and prescribers' follow-up by clinical research associates (CRAs) will be enforced.

Missing Data

Some limitations with regard to data completeness may occur in this study, mainly related to the information captured in the patients' medical records. Measures to minimize missing data will be implemented, including:

- Ensuring that primary variables of interest are those that are routinely collected as part of real-world clinical care.
- Collecting only critical data elements (ie, variables aligned with the study objectives) to minimize site/participant burden.
- Including "not applicable"/"not done" on CRFs to differentiate these from values that are truly missing.

- CRF completion guidelines will provide consistent instructions on completion of the CRF.

- All individuals performing data abstraction from medical records will be trained on appropriate data abstraction techniques in order to minimize possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.

- Missing data will be followed up on during monitoring visits.

- Checking for patterns of missing data and addressing any issues with targeted operational strategies.

8.11. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by a single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the CSA and applicable privacy laws.

9.2. Patient Consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

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

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

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decision ally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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

9.3. Patient Withdrawal

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

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

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

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

9.5. Ethical Conduct of the Study

The observational study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiological Practice (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Declaration of Helsinki and its amendments, and any applicable national guidelines.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Collecting Adverse Events is not a part of this protocol.

Table 4 summarizes the requirements for reporting safety events on the non-interventional study (NIS). NIS adverse event monitoring (AEM) Report Form to Pfizer Drug Safety Unit. These requirements are delineated for 3 types of events: (1) serious adverse events (SAEs); (2) non-serious adverse events (AEs) (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in Section 10.4 “Definitions of safety events”.

Table 4. Recording and Reporting of Safety Events

Safety event	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All
Non-serious AE	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see Section 10.4.2 "Serious adverse events").

Safety events listed in Table 4 must be reported to Pfizer within 24 hours of awareness of the event by the investigator regardless of whether the event is determined by the investigator to be related to palbociclib. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far-right column of Table 4 that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection tool (eg, case report form). In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.1. Single Reference Safety Document

The country specific product label will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

10.2. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of palbociclib or the time of the patient's informed consent if s/he is being treated with palbociclib at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. With agreement of the Pharmacovigilance Policy Committee (PvPC), the post-product-administration reporting period may be extended based on product characteristics (eg, for products with known extended half-life) or known safety profile; if approval for such an extension is obtained, replace "28" in the prior sentence with the approved number of days. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation if patients are screened for eligibility following informed consent, add: ", failed screening criteria"), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to palbociclib, the SAE also must be reported to Pfizer Safety.

10.3. Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to palbociclib, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that palbociclib caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether palbociclib caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that palbociclib did not cause the event, this should be clearly documented on the data collection tool eg, case report form and NIS AEM Report Form.

10.4. Definitions of Safety Events

10.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;

- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.4.2. Serious Adverse Events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a SAE with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by Pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.5. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).

- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

10.6. Scenarios Necessitating Reporting to Pfizer Safety within 24 Hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

10.6.1. Exposure during Pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) palbociclib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to palbociclib (maternal exposure).

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed, either due to treatment or environmental exposure to palbociclib prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective EDP reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with palbociclib, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to palbociclib in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is

provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the EDP may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

10.6.2. Exposure during Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

10.6.3. Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name);
- The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE;
- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE;
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

10.6.4. Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.6.5. Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

10.6.6. Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are not part of any planned regulatory/health technology assessment submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 3	8 November 2022	A5481150 NI Study Abstract V 3.0
2	List 1	13 December 2021	List of Study Investigators

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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