NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving Palbociclib + Aromatase Inhibitor (AI) Combination Therapy as First-Line Treatment
Protocol number	A5481155
Protocol version identifier	1.0
Date	21 April 2020
Active substance	Palbociclib (L01XE33)
Medicinal product	Palbociclib
Research question and objectives	**Primary Objectives:** Objective 1 - Among patients with HR+/HER2- advanced/metastatic breast cancer (A/MBC) receiving palbociclib +AI combination therapy as first-line therapy: a. Describe demographic and clinical characteristics. b. Describe treatment patterns (eg, dose changes, discontinuations). Objective 2 - Among patients receiving palbociclib + AI as first-line therapy, examine clinical effectiveness outcomes including real-world progression-free survival (rwPFS) and real-world overall survival (rwOS).
Author	PPD Ph.D. PPD [redacted]

	PPD Pharm.D. PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
A/MBC	advanced/metastatic breast cancer
ACS	American College of Surgeons
AE	adverse event
AEM	adverse event monitoring
AI	aromatase inhibitor
ASCO	American Society of Clinical Oncology
BC	breast cancer
BRCA	BReast CAncer susceptibility gene
CCI	Charlson Comorbidity Index
CDK4/6i	cyclin-dependent kinase 4/6 inhibitor
CI	confidence interval
CoC	Commission on Cancer
CPOE	computerized physician order entry
CR	complete response
CTR	Certified Tumor Registrar
DCT	data collection tools
DFI	Disease Free Interval
ECOG	Eastern Cooperative Oncology Group
EDW	electronic data warehouse
EHR	electronic health record
EMR	electronic medical record
ER	estrogen receptor
FDA	Food and Drug Administration
FHIR	fast healthcare interoperability resource
FORDS	Facility Oncology Registry Data Standards
H&P	history and physical
HEOR	Health Economics and Outcomes Research
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL7	health level seven international
HR	Hormone receptor; hazard ratio
ICD	International Classification of Diseases
ID	identification
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IRIS	Ibrance Real-World Insights Study
ISH	*In situ* hybridization

Abbreviation	Definition
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JSON	JavaScript object notation
KPS	Karnofsky Performance Score
LHRH	luteinizing hormone releasing hormone
LIS	laboratory information system
MA	manual abstraction
MBC	metastatic breast cancer
NAACCR	North American Association of Central Cancer Registries
NDI	National Death Index
NE	not evaluable
NGS	next generation sequencing
NI	non-interventional
NIS	non-interventional study
NOS	not otherwise specified
OS	overall survival
PACS	picture archiving and communication system
palbo	palbociclib
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PHI	protected health information
PR	Progesterone receptor; partial response
QC	quality control
RCT	randomized control trial
RWD	real world data
rwOS	Real-world overall survival
rwPFS	Real-world progression-free survival
rwTTD	Real-world time to treatment discontinuation
rwTTNT	Real-world time to next treatment
SABCS	San Antonio Breast Cancer Symposium
SAP	Statistical Analysis Plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SSDI	Social Security Death Index
STORE	STandards for Oncology Registry Entry
UD	undocumented
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD Ph.D.	PPD	Syapse	PPD
PPD MPH	PPD	Syapse	PPD
PPD MD	PPD	Pfizer Oncology	PPD
PPD MA	PPD	Pfizer	PPD
PPD Ph.D.	PPD	Pfizer	PPD
PPD Pharm.D.	PPD	Pfizer	PPD
PPD Ph.D.	PPD	Pfizer	PPD

4. ABSTRACT

Title: Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving Palbociclib + AI Combination Therapy as First-Line Treatment

Rationale and Background: The treatment landscape for HR+/HER2- advanced and metastatic breast cancer (A/MBC) has changed with the advent of approval of CDK4/6i in combination with aromatase inhibitor (AI) approval for use in the first-line with palbociclib being the first to market in the US in February 2015. Treatment patterns and early clinical outcomes have been reported in real world use with limited follow up and cohort size. The present single-arm study is designed to describe patient characteristics, treatment patterns, and clinical effectiveness outcomes in patients diagnosed with HR+/HER2- A/MBC who received palbociclib combination therapy with AI as first-line treatment in the US community oncology setting.

Research Question and Objectives: The objective of this single-arm study is to describe the patient characteristics, treatment patterns, and clinical effectiveness outcomes for patients with a diagnosis of HR+/HER2- A/MBC who received palbociclib combination therapy with AI as the first-line therapy in the A/MBC setting.

Primary Objectives:

Objective 1 – Among patients with HR+/HER2- advanced/metastatic breast cancer (A/MBC) receiving palbociclib combination therapy with AI as first-line therapy:

a. Describe demographic and clinical characteristics.

b. Describe treatment patterns (eg, dose changes, discontinuations).

Objective 2 – Among patients receiving palbociclib + AI as first-line therapy, examine clinical effectiveness outcomes including real-world progression-free survival (rwPFS) and real-world overall survival (rwOS).

Study Design: This is a retrospective, observational database study that will document the treatment patterns and clinical outcomes of patients diagnosed with HR+/HER2- A/MBC who received palbociclib combination therapy with AI as the first-line therapy in the A/MBC setting in US community health systems participating in the Syapse Learning Health Network.

Population: The study will include adult patients 18 years or older, diagnosed with HR+/HER2- A/MBC who initiated palbociclib combination therapy with AI as the first-line therapy on or after 03 February 2015 up to and including 31 July 2019. Patients for this study will be identified from the Syapse Learning Health Network database.

Variables: Patient demographics, clinical characteristics, treatment patterns, and clinical effectiveness outcomes will be collected and analyzed.

Data Source:

The Syapse Learning Health Network consists of large community health systems based in the United States. These US providers manage care delivery networks that span the continuum of care in multiple regions. Syapse's point of care software platform ingests comprehensive real-world data on a daily basis and includes structured inpatient and outpatient, clinical and molecular data integrated from both health systems and molecular labs. Syapse Certified Tumor Registrars (CTRs) provide additional curation. This resultant database provides the basis for this study.

Study Size:

Study sample will include all eligible cases in the Syapse Learning Health Network database. Preliminary analysis identified up to 1,074 patients with evidence of key primary inclusion criteria: breast cancer diagnosis and palbociclib treatment. This population will be further examined and limited to those matching all inclusion criteria: patients with HR+/HER2- A/MBC with first-line palbociclib + AI treatment, on or after 03 February 2015 through 31 July 2019. Three to four hundred patients are expected to fulfill complete study inclusion criteria. Given the inclusion criterion requiring a qualifying treatment identification period between 03 February 2015 through 31 July 2019, and assuming a data cutoff date of 01 February 2020, the minimum follow-up available is therefore 6 months.

Data Analysis: Descriptive analysis will be conducted to describe patient demographics, clinical characteristics, treatment patterns (eg dose changes, discontinuations), and clinical effectiveness outcomes (rwPFS, rwOS).

Milestones:

Data analysis will be conducted once data/related variables are available, and the final study report will be completed September 2020.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
IRB approval of study protocol	April 2020
Start of data collection	April 2020
Interim statistical analysis	June 2020
End of data collection	August 2020
Final statistical analysis	August 2020
Final study report	September 2020

7. RATIONALE AND BACKGROUND

It is estimated that 42,260 people (41,760 female and 500 male) in the United States (US) will die of breast cancer in 2019. Breast cancer is the second leading cause of cancer death for women after lung cancer (Siegel et al, 2019). Currently, the average risk of a woman in the United States developing breast cancer sometime in their life is about 13% with 276,480 new cases of invasive breast cancer and 42,170 deaths from breast cancer expected this year in the United States. At this time there are more than 3.5 million women living with a history of breast cancer (BC) in the US including women who are still being treated (Miller et al, 2016) and in the US, women under the age of 50 comprise 20% of all breast cancers diagnoses. Metastatic breast cancer remains an incurable disease with 5-year survival rates of 27% (American Cancer Society Facts & Figures, 2020). About 71% of all breast cancers are HR+ and HER2- (American Cancer Society Breast Cancer Facts and Figures, 2018) HR+/HER2- A/MBC presents a challenge because patients with exposure to prior hormonal therapy, including aromatase inhibitor (AI) treatment, ultimately develop resistant disease (Ma et al, 2015). The treatment landscape for patients with HR+/HER2- A/MBC has changed with the approval of palbociclib in February 2015 as the first in class cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) indicated in combination with letrozole for the first endocrine therapy for patients with HR+/HER2- A/MBC and subsequently expanded to all AIs as well as for the treatment of male breast cancer. Palbociclib was approved in the US based on improved median PFS demonstrated in 3 pivotal clinical trials: PALOMA-1 and PALOMA 2 (initial endocrine-based therapy in combination with letrozole for advanced disease) and PALOMA-3 (in combination with fulvestrant after progression on or after prior endocrine therapy). Approval was granted based on findings from the Phase 2 PALOMA-1 trial (Finn et al, 2015) in February 2015. The OS results from that study demonstrated a HR of 0.897; 95% CI (0.623, 1.294); 1-sided p= 0.281 in a sample of 165 patients total (Finn et al, 2015). Palbociclib in combination with fulvestrant was approved 1 year later (February 2016) in pre or postmenopausal women with disease progression following endocrine therapy based on results from the PALOMA-3 trial (Turner et al, 2015; Cristofanilli et al, 2016). Final OS data from that study has been reported (Turner et al, 2018) demonstrating median of 34.9 months versus 28 months in the palbociclib + fulvestrant group versus fulvestrant alone (HR 0.81; 95% CI; 0.64, 1.03; 1-sided p=0.0249) which was not statistically significant. The safety profile from the PALOMA-2 and -3 trials were consistent, with no new safety signals identified across the Phase 3 studies. Long-term pooled safety analyses of the 3 randomized Phase 2 and 3 studies demonstrated no evidence

of specific cumulative or delayed toxicities with palbociclib plus endocrine therapy (Diéras et al, 2019). The primary toxicity of palbociclib is neutropenia, which can be managed with dosing interruption and/or dose reduction. Additional CDK4/6i therapies, ribociclib and abemaciclib, were approved in 2017 and 2018, respectively, for use in first-line therapy as well. All of the CDK4/6i therapies also received FDA approval for use in combination with fulvestrant for patients who progressed after prior endocrine therapy (Eggersmann et al, 2019).

Understanding the effectiveness of new treatments in a diverse clinical practice as a complement to RCT data is important as this provides evidence of the clinical benefit of these treatments in a more heterogeneous population with comorbid conditions and variations in care delivery seen in routine clinical practice. Real-world outcomes for patients with A/MBC who were treated with palbociclib in combination with AI or fulvestrant have been reported in several publications and at medical congresses. A comparative effectiveness analysis of palbociclib + letrozole versus letrozole alone was presented at the SABCS 2019 congress. Using the Flatiron Health Analytics Database, a total of 1,430 female patients with HR+/HER2-MBC in the first-line setting were included in the analysis demonstrating in an unadjusted HR for PFS of 0.59 (95% CI: 0.51, 0.67; p<0.0001) and an HR for OS of 0.63 (95% CI: 0.53, 0.76; p<0.0001) (DeMichele et al, 2019). Another study reported on the Ibrance® Real World Insights Study (IRIS) involving medical chart review of 652 US patients with A/MBC treated with palbociclib in combination with either AI (n=360) or fulvestrant (n=292) (Taylor-Stokes et al, 2019). The 12-month progression-free rate was 84.1% for patients treated with palbociclib + AI and 79.8% for those treated with palbociclib + fulvestrant. The 12-month survival rates were 95.1% for palbociclib + AI and 87.9% for palbociclib + fulvestrant (Taylor-Stokes et al, 2019).

This present study is designed to examine further real-world use of palbociclib and aromatase inhibitor combination therapy in both male and female patients with A/MBC as first-line treatment. All patients initiating palbociclib + an AI from the Syapse Learning Health Network dataset who meet the inclusion and exclusion criteria and initiated palbocicilb combination therapy between February 2015 and July 2019 will be evaluated. This study is designed to describe patient characteristics, treatment patterns, and clinical effectiveness outcomes in a cohort of patients diagnosed with HR+/HER2- A/MBC who were treated with palbociclib combination with AI in the US community oncology setting.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the patient characteristics, treatment patterns, and clinical effectiveness outcomes for patients with a diagnosis of HR+/HER2- A/MBC who initiated palbociclib combination therapy with AI as the first-line therapy in the A/MBC setting between 03 February 2015 and 31 July 2019.

Primary Objectives:

1. Among patients with HR+/HER2- A/MBC receiving palbociclib combination therapy with AI as first-line therapy:

    a. Describe demographic and clinical characteristics:

        - Demographic characteristics will include age, sex, race, insurance status, menopausal status, and region of residence at A/MBC diagnosis;

        - Clinical characteristics will include variables such as, stage of initial diagnosis, histology, Eastern Cooperative Oncology Group (ECOG) performance status (where ECOG score unavailable, Karnofsky performance status will be converted to corresponding ECOG score) and comorbid disease burden, HER2 and estrogen receptor (ER)/progesterone receptor (PR) status, number and sites of distant metastasis at A/MBC diagnosis; modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy) and disease free interval (time between completion of adjuvant therapy and diagnosis of A/MBC).

    b. Describe treatment patterns:

        - Distribution of regimens from the diagnosis of A/MBC through the end of the record;

        - Sequence of regimens across lines, through the end of the record of systemic therapy;

        - Description of the dosing will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), type of dose adjustment (dose modification, schedule changes, dose delay, hold, or discontinuation), discontinuation, reason, and time to dose adjustment (discontinuation).

2. Among patients receiving palbociclib + AI as first-line therapy, examine clinical effectiveness outcomes including:

    a. Real-world progression-free survival (rwPFS) will be assessed for the first-line therapy.

    b. Real-world overall survival (rwOS) will be assessed from the start of the first-line therapy.

9. RESEARCH METHODS

9.1. Study Design

This is an observational, retrospective cohort study. Eligible patients will be identified from the Syapse Learning Health Network database and medical chart review will be conducted by Syapse Certified Tumor Registrars (CTRs). All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care. This single-arm descriptive analysis will describe the patient characteristics, clinical attributes and treatment patterns of A/MBC patients with HR+/HER2- disease, who were treated with palbociclib + AI as first-line therapy. Additionally, clinical effectiveness outcomes for these patients will be evaluated between Feb 2015 and July 2019.

9.2. Setting

This study uses eligible patients identified from the Syapse Learning Health Network database.

9.2.1. Inclusion Criteria

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

1. Female or male sex.

2. Diagnosis (confirmed by clinical review) of A/MBC, defined as breast cancer at stage IIIB, stage IIIC, stage IV or identified as having distant metastasis.

3. Age ≥18 years at A/MBC diagnosis.

4. Initiated palbociclib in combination with an AI as first-line therapy after A/MBC diagnosis on or after 03 February 2015 through 31 July 2019. Note that the date of the start of the inclusion period reflects the month of palbociclib US FDA approval.

5. Evidence of ER or PR positive disease, or absence of any indication of ER and PR negative disease closest to A/MBC diagnosis (ie, patients are eligible without affirmative indication of ER/PR+ status as long as ER/PR- indication is not present).

6. Evidence of HER2 negative disease, or absence of any indication of HER2 positive disease closest to A/MBC diagnosis (ie, patients are eligible without affirmative indication of HER2- status as long as HER2+ indication is not present).

9.2.2. Exclusion Criteria

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

1. Enrollment in an interventional clinical trial for A/MBC during the study observation period.

2. Evidence of prior treatment with any CDK4/6 inhibitor in the adjuvant setting.

3. Evidence of another primary cancer within 3 years prior to the initial line containing palbociclib.

9.3. Variables

9.3.1. Regimens and Lines

Firstline regimen is defined as the first antineoplastic drug/s a patient receives after diagnosis of an advanced/metastatic breast cancer, including all drugs received within a 60 day window of the first antineoplastic agent received. For example, if an additional drug is added to the regimen within 60 days, it is considered part of the line of therapy. The end of the firstline regimen is defined as discontinuation of all antineoplastic drugs in regimen AND a gap of ≥90 days for each drug before evidence of next treatment; OR addition of a non-interchangeable new antineoplastic after the first 60 days of firstline regimen (if added before 60 day cut-off it does not trigger a new line of therapy). Switching between aromatase inhibitors does not trigger a new line. The end date of the firstline regimen is the date of last antineoplastic treatment in the regimen. Two parameters in the algorithm are: regimen window (currently 60 days) and treatment gap window (currently 90 days).

9.3.2. Curated Data

Patients will be identified and data will come from the Syapse Learning Health Network database which includes both inpatient and outpatient clinical and molecular data captured through manual abstraction and interoperative data feeds from a number of health system source systems, including:

- Electronic medical record (EMR), including inpatient, outpatient oncology, ambulatory, surgical, etc.

- Electronic data warehouse (EDW).

- Laboratory information system (LIS).

- Picture archiving and communication system (PACS).

- Hospital based cancer registries.

- Computerized physician order entry (CPOE):

    - Additionally, Syapse augments health system data with the Surveillance, Epidemiology, and End Results (SEER) national cancer registry, other regional registries, the Social Security Death Index (SSDI), digitized obituary data. In order to capture complete and accurate vital status and dates of death, Syapse brings together data from multiple sources to create a composite view of patients' mortality (including EHR, hospital registry, manual abstraction, digital obituaries (such as tributes.com and legacy.com), Social Security Death Index, and SEER). Syapse is in the process of validating the completeness and accuracy of the Syapse mortality composite score versus the National Death Index (NDI), a centralized database of death records. Initial analysis shows that the combined Syapse Data Sources are very accurate. More detailed information forthcoming in the data management document.

The following data elements will be extracted from feeds and/or curated by Certified Tumor Registrars (CTRs) for this study:

Data Elements	Description
Demographic characteristics	
Date of birth	Year, month, day (Availability of the exact date will depend on the Expert de-ID approach).
Date of initial BC diagnosis	Date of initial breast cancer (BC) diagnosis.
Date of A/MBC diagnosis	Date of advanced/metastatic breast cancer (A/MBC) diagnosis.
Patient sex	Male, Female, Transsexual, Other, Not Provided.
Primary race	American Indian/Alaska Native; Asian; Black/African American/Native Hawaiian/Pacific Islander; White; Not Provided; Other (Exact list will depend on the expert de-ID approach).
Secondary race	(if provided) (Exact list will depend on the expert de-ID approach).
Ethnicity	Non-Hispanic/Non-Latino; Hispanic/Latino; Unknown (Exact list will depend on the expert de-ID approach).
Region of residence	Northeast, Midwest, South, West. Captured at A/MBC diagnosis (Exact list will depend on the expert de-ID approach).
Insurance type	Medicare/Medicaid; Commercial; Commercial and Medicare/Medicaid; None; Not Provided. Captured at 1) date of A/MBC diagnosis; and 2) at initiation of palbo.

Data Elements	Description
Menopause status	Premenopausal; Postmenopausal; Perimenopausal; Unknown; Not applicable. Captured on date closest to but before: 1) A/MBC diagnosis; and 2) initiation of palbo. Menopausal status: captured if explicitly stated in clinician notes. Otherwise captured based on following definition of menopause from NCCN Guideline v.3.2019: • Prior bilateral oophorectomy (date of surgery); • Age >=60 years old; • Age <60 years old and amenorrheic for 12 months+ in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression. Additionally, type, name, and start/end date of ovarian suppression agent is captured.
Date of death	If patient vital status = deceased, date of death from the medical record (capturing from EMR, registries, third party integrations) (Availability of the exact date will depend on the Expert de-ID approach).
Last contact date	If patient is alive (not deceased), date of the last contact by a healthcare provider from the medical record (Availability of the exact date will depend on the Expert de-ID approach).
Clinical characteristics	
Breast cancer histology	List captured at initial breast cancer diagnosis including: Adenoid cystic; Cribriform; Ductal; Inflammatory; Intraductal; Lobular; Medullary with lymphoid stroma; Medullary, NOS; Mucinous; Paget's disease and infiltrating; Paget's disease and intraductal; Papillary; Secretory; Squamous cell; Tubular, and more.
ECOG/KPS performance score	Score captured on date closest to (with a ±60 day cutoff around) 1) A/MBC diagnosis; and 2) initiation of palbo.
Stage at initial BC diagnosis	0, I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IIIC, IV, Unable to stage, Not found, Not applicable.
Presence of distant metastasis	Yes; No. Note: this variable would be "yes" if patient is diagnosed with de novo metastatic breast cancer or if patient developed metastasis after initial breast cancer diagnosis.
Date of first distant metastasis	Same as initial BC diagnosis if de novo metastatic BC, otherwise captured as date that the patient developed distant metastatic disease.

Data Elements	Description
Site(s) of distant metastasis at MBC diagnosis	Bone; Chest Wall; Contralateral Breast; Distant Lymph node(s); Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion; Skin; Brain; Ovary; Undocumented; Other, Specify; Visceral sites; Bone only.
Comorbidities	List of comorbidities at time of A/MBC diagnosis (sourced from problem list encompassing entire patient journey and confirmed from clinician notes), including: anemia, heart arrhythmia, hypertension, **myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes with chronic complications, diabetes without chronic complications, renal disease, connective tissue disease such as rheumatoid arthritis or lupus, Alzheimer's or other dementia, cirrhosis or other serious liver disease, non-breast cancer malignancy (excluding sites of breast cancer metastasis and malignant neoplasm of skin), metastatic solid tumor (other than breast cancer), HIV/AIDS**, and other comorbidities of interest. Note: comorbidities in bold are in CCI; CCI listed in derived variables section.
Biomarkers	
ER, PR, HER2 status	Positive; Negative; Equivocal; Unknown.
ER, PR, HER2 test type	ISH, IHC, NGS, PCR, Other, Unknown.
ER, PR, HER2 sample collection date	Year, month, day.
ER, PR, HER2 report date	Year, month, day.
BRCA status	BRCA1 Mutation; BRCA2 Mutation; BRCA NOS Mutation.
BRCA sample collection date	Year, month, day.
BRCA report date	Year, month, day.

Data Elements	Description
Treatment modalities prior to A/MBC diagnosis	
Breast surgery	Yes; No.
Surgery type	Partial mastectomy; Lumpectomy/excisional biopsy; Segmental mastectomy; Subcutaneous mastectomy; Total mastectomy; Modified radical mastectomy; Radical mastectomy; Extended radical mastectomy; Mastectomy, NOS; Surgery, NOS. Note: if multiple, all will be listed (longitudinal data).
Surgery date	Year, month, day.
Breast radiation therapy	Yes; No.
Radiation therapy site	Whole breast; Partial breast; Chest wall; Regional lymph nodes; Unknown. Note: limited to primary breast cancer site. If multiple, all will be listed (longitudinal data).
Radiation start/end dates	Year, month, day.
Recurrence	
Patient had recurrence	Yes; No.
Recurrence date	Year, month, day (Captures first time locally, first time regionally, and first time distant; if multiple sites, hierarchy prioritizes most advanced site).
Recurrence site	Local; Regional; Distant; Unknown.
Recurrence test source	Biopsy; Imaging; Imaging confirmed by biopsy; Unknown.
Clinician confirmation of recurrence	Sources including: Medical oncology consult/note; Radiation oncology note; Discharge summary; Other.
Recurrence linked to therapy	Yes; No.
Progression	
Patient had progression	Yes; No.
Progression date	Year, month, day.
Progression test source	Biopsy; Imaging; Imaging confirmed by biopsy; Unknown.

Data Elements	Description
Clinician confirmation of progression	Sources including: Medical oncology consult/note; Radiation oncology note; Discharge summary; Other.
Clinician confirmation date	Year, month, day.
Progression linked to therapy	Yes; No.
Complete systemic therapy history	
Therapy name	Therapy name.
Administration route	Categories including: Oral; Infusion; Injection; Other; Unknown.
Therapy start date	Year, month, day.
Therapy end date	Year, month, day.
Start reason	Recurrence; Progression; Other reason not related to worsening disease.
Start reason source date	Year, month, day (can be linked to clinician confirmation date of recurrence/progression if start reason is recurrence/progression).
Stop reason	Categories including: Progression; Toxicity; End of planned therapy; Insurance changes; Treatment ongoing; Other.
Stop reason source date	Year, month, day (can be linked to clinician confirmation date of recurrence/progression if stop reason is recurrence/progression).
Treatment part of clinical trial	Yes; No.
Palbociclib-specific variables (captured in addition to above variables)	
Combination AI partner	Letrozole, Anastrozole, Exemestane.
Concomitant LHRH Agonists	Goserelin (Zoladex), Histrelin (Vantas), Leuprolide (Eligard, Lupron), Triptorelin (Trelstar).
Dose 1 (start dose)	125mg, 100mg, 75mg.
Dose 1 start date	Year, month, day.
Dose n (where n>=2)	125mg, 100mg, 75mg.
Dose n start date	Year, month, day.
Dose n adjustment type or reason	Categories include schedule change; dose delay; hold; cost; patient refusal; toxicity.

9.3.3. Derived Variables

Variables that will be derived from curated data will include the following:

Data Elements	Description
Age at A/MBC diagnosis	Age in years; age categories: <50, 50-64, 65 –74, ≥75 years (Exact list will depend on the expert de-ID approach).
Age at start of palbociclib treatment	Age in years; age categories: <50, 50-64, 65 –74, ≥75 years.
Date of death	If patient vital status = deceased, date of death from the medical record (capturing from EMR, registries, third party integrations) (Availability of the exact date will depend on the Expert de-ID approach).
Palbo dose change ever	Yes; No.
Disease Free Interval (DFI)	Months from the end of adjuvant/neo-adjuvant therapy to the date of disease recurrence. • ≤12 months, 13-24 months, 25-36 months; • >36 months; • Unknown.
Endocrine sensitivity	≥12 months without recurrence/progression after completion of endocrine therapy in the adjuvant setting.
Primary endocrine resistance	Relapse during first 2 years of adjuvant endocrine therapy or progressive disease within first 6 months of first-line endocrine therapy for metastatic breast cancer.
Secondary endocrine resistance	Relapse while on adjuvant endocrine therapy but after first 2 years of treatment, relapse within 12 months of completing adjuvant endocrine therapy, or progressive disease 6 or more months after starting endocrine therapy for metastatic breast cancer.
Charlson Comorbidity Index (CCI)	Calculated based on the presence of 17 Charlson comorbidities at A/MBC.
Line of therapy	Line number (1; 2; 3; etc.) in the A/MBC setting assigned based on Syapse line of therapy algorithm.
Regimen medication(s)	Systemic therapies included in line regimen defined by Syapse line of therapy algorithm.
Line start date	Year, month, day.
Line end date	Year, month, day.
Time to first dose change	Days from palbo dose 1 start date to palbo dose 2 start date, if applicable.

Data Elements	Description
Number of dose changes	Number of dose reduction(s) and number of dose increases over the calendar time (quarter since February 2015) and over treatment cycle since palbo dose 1 start date.
Bone only distant metastasis at MBC diagnosis	From sites of distant metastasis: bone only.
Visceral distant metastasis at MBC diagnosis	From sites of distant metastasis: visceral sites. Visceral sites defined as: Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion.
Disease burden at MBC diagnosis	Lesions in liver, bone, or lung metastatic sites: Single, Multiple, Unknown.
Effectiveness Outcomes	
Real-world Overall Survival (rwOS)	Length of time from the start of palbociclib + AI treatment to the earliest of the following: date of death, date of last contact, or the end of study period.
Real-world progression free survival (rwPFS)	Length of time from the start of palbociclib + AI treatment to the earliest of the following: clinician-assessed progression event, date of death, date of last contact, or end of study period. Progression identified from tissue/pathology or imaging/radiology **and** confirmed by clinician (in 2 separate data points), from MA guidance: 1. Medical Oncology Consult/Note (can also include medical oncologist history and physical (H&P). 2. Radiation Oncology note/consult/(can also include radiation oncology H&P). 3. Progress Note (can also include /H&P/Consult - use this option for physician of other discipline in the absence of numbers1and 2). 4. Discharge Summary. 5. Nursing Note. 6. Care Everywhere/Scanned Documents/External lab reports (for information diagnosed outside of facility for which patient is being abstracted). 7. Other.
Real world time to treatment discontinuation (rwTTD)	Length of time from the start of palbociclib + AI treatment to the earliest of the following: date the patient discontinues first-line treatment, date of death, last known usage of first-line treatment, or end of study period.
Real world time to next treatment (rwTTNT)	Length of time from the start of palbociclib + AI treatment to the earliest of the following: subsequent line of therapy initiation, date of death, date of last contact, or end of the study period.

9.4. Data Sources

The Syapse Learning Health Network includes patient-level data from large community health systems based primarily in the United States. These US providers manage care delivery networks that span the continuum of care in multiple regions across 25 states including California, Nevada, Oregon, Washington, Arizona, Nebraska, Minnesota, Michigan, Illinois, Indiana, Wisconsin, Kansas, Missouri, Oklahoma, Arkansas, Louisiana, Texas, Kentucky, Tennessee, Mississippi, Alabama, Georgia, Florida, Maryland, and New York. Identification of cancer cases at each health system varies but in general includes a combination of billing codes and provider specialties.

At each participating health system where Syapse is deployed, structured clinical data is ingested into the Syapse database for any patient meeting any one of the following criteria: 1) was seen by the health system's oncology department(s), 2) was seen by an oncology specialist, or 3) has documented evidence of cancer based on a neoplasm ICD code. Syapse leverages the health system's existing source system feeds wherever possible to utilize active feeds that are relied on for clinical care purposes. Additionally, Syapse Certified Tumor Registrars (CTRs) capture additional information and context directly from health system EMRs.

For cancer cases identified at each health system, Syapse obtains structured somatic molecular results through its direct integration with commercially available molecular somatic testing laboratories.

In addition, Syapse augments vital status and date of death for patients captured in (1) Surveillance, Epidemiology, and End Results (SEER) national cancer registry, as well as regional and institutional registries, (2) the Social Security Death Index (SSDI) from a third party vendor, (3) online obituary data from a third party vendor, (4) manually abstracted data from online obituaries and physician notes, (5) health system's electronic medical record (EMR), including hospital-based cancer registries for date of death and vital status.

The detailed data from Syapse Learning Health Network database enables insight into cancer care in routine clinical settings (real-world), for example, by permitting hypothesis generation and retrospective research. The database is fit for purpose for this objective due to the health systems distribution broadly across CCI the US CCI , the type and extent of patient-level data, the minimal lag time for data availability and the data QC and verification processes in place including 7 year record retention and direct access to source EMR. See Section 9.8 for more details on quality control processes.

9.5. Study Size

Study sample will include all eligible cases in the Syapse database. Preliminary analysis identified up to 1,074 patients with evidence of key primary inclusion criteria: breast cancer diagnosis and palbociclib treatment. This population will be further examined and limited to those matching all inclusion criteria: Patients diagnosed with HR+/HER2- A/MBC with first-line palbociclib + AI treatment, on or after 03 February 2015 through 31 July 2019.

Three to four hundred patients are expected to fulfill complete study inclusion criteria. Given the inclusion criterion requiring a qualifying treatment identification period between 03 February 2015 through 31 July 2019, and assuming a data cutoff date of 01 February 2020, the minimum follow-up available is therefore 6 months.

Structured diagnosis code for breast cancer (ICD9 174.x or 175.x or ICD10 C50.x).

Structured medication orders or administrations for evidence of treatment with palbociclib (generic/trade name: palbociclib/Ibrance, RXNorm: 1601374, 1601381).

Certified tumor registrars apply a protocol screening procedure during initial patient chart review involving the following inclusion criteria:

1. Patient has A/MBC.
2. Patient is HR+/HER2- (Patients are included in the absence of any indication of HR- or HER2+).
3. Patient is treated with palbociclib on or after 03 February 2015 through 31 July 2019.
4. Patient is treated with palbociclib in combination with an aromatase inhibitor.

Excluded:

1. Patient does not have A/MBC.
2. Patient has indicated HR- or HER2+ status.
3. No treatment with palbociclib, or treatment is not on or after 03 February 2015.
4. Palbociclib treatment is not in combination (ie, within 60 days) with an aromatase inhibitor.

Patient received palbociclib + AI in the first-line setting.

9.6. Data Management

Data curation procedure, logic, definitions, and normalization are developed in collaboration between qualified clinical informaticists, epidemiologists, clinical oncologists, and certified tumor registrars (CTRs) before data collection and reviewed for quality during and after collection. Collection practices are standardized across the team through rigorous training, a qualification process for each CTR, as well as having all collected records undergo a quality control (QC) review to ensure accuracy and uniformity of collection practices. Syapse CTRs utilize an Electronic Data Capture system to document the patient's medical history according to protocol. To enable consistent and effective analysis and interpretation of Real-World Data, Syapse manages a data dictionary of data elements and their definitions. Records are retained and secured according to HIPAA regulations, and as governed by specific provisions in customer contracts.

Data collection will begin following development of curation guidance, CTR training, and Institutional Review Board (IRB) approval of a study protocol. Data will be maintained in a secure database for analysis. The collected data will be de-identified based on expert recommendation for this specific dataset upon which a final data format and data types for the dataset will be determined.

Syapse will engage a third party for the purpose of obtaining a formal determination by a qualified expert to de-identify a dataset of breast cancer patients in accordance with the Expert Determination Method described in section 164.514(b)(1) of the HIPAA Privacy Rule. In order to deliver the Pfizer Regulatory Breast Cancer Real-World Dataset while fulfilling our responsibilities as a Business Associate to our Health System customers, this dataset must be de-identified while preserving a level of detail, especially around dates, that meets the research objectives. A general workflow for expert determination can take a few weeks or months and starts once the data dictionary is finalized in the protocol. The approach includes various steps. First, the expert will evaluate the extent to which the health information can (or cannot) be identified by the anticipated recipients. Second, the expert often will provide guidance on which statistical or scientific methods can be applied to the health information to mitigate the anticipated risk of re-identification. The expert will then execute such methods using some percentage of the actual data set. Finally, the expert will evaluate the identifiability of the resulting health information to confirm that the risk is no more than very small when disclosed to the anticipated recipients. This process may require several iterations until the expert and the recipients agree upon an acceptable solution.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Records

As used in this protocol, the term CRF/DCT 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.

A CRF/DCT is required and should be completed for each included patient. The completed original CRFs/DCTs 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. Syapse shall ensure that the CRFs/DCTs are securely stored at Syapse in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

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

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

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Syapse agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, eg, CRFs/DCTs and hospital records), copies of all CRFs/DCTs, 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 Syapse according to local regulations or as specified in the vendor agreement, whichever is longer. Syapse must ensure that the records continue to be stored securely for so long as they are retained.

If Syapse becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Syapse and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data Analysis

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

The primary and secondary objectives of the study are to describe patient characteristics, real-world treatment patterns and clinical effectiveness of palbociclib + AI as first-line treatment for A/MBC patients.

Descriptive analyses: For categorical variables (eg region, race, and stage at initial diagnosis), data will include the frequency (number of cases) and percentage (%) of total patients observed in each category; for continuous variables (eg, age and time from initial breast cancer diagnosis to metastatic diagnosis), variables will be presented as the mean, standard deviation (SD), median, 25th and 75th percentiles and ranges (minimum and maximum) in some cases. The calculation of percentages will always include the missing category in the case of missing values. Continuous variables may be categorized into intervals, with the distribution of patients (N, %) provided.

Kaplan-Meier curves and landmark analyses will be performed to estimate rwPFS, rwOS, rwTTD, and rwTTNT. Specifically, landmark time points are; 3, 6, 12, 18, 24, 30, and 36 months for rwPFS and 6, 12, 18, 24, 30, and 36 months for rwOS. For rwTTD and rwTTNT, landmark time points are; 3, 6, 12, 18, 24, 30, and 36 months. Ninety-five percent confidence intervals on the median rwPFS, rwOS, rwTTD, and rwTTNT will be reported. Censoring for each event will be defined in the SAP.

Cox proportional hazard models will be fit using age categories, ECOG performance, menopausal status, metastatic status (De novo, versus number of metastatic sites), number of disease sites (1, 2, ≥3), menopausal status, prior endocrine therapy, prior chemotherapy, prior surgery, prior radiation therapy as appropriate based on availabilities of the data and sample sizes. Potential interactions will be examined using survival trees for time to events.

9.8. Quality Control

9.8.1. Data Integration and Quality

Syapse acquires clinical structured data from a number of health system source systems including, but not limited to, electronic data warehouse (EDW)/North American Association of Central Cancer Registries (NAACCR) flat files, health level seven international (HL7) messages including HL7 version 2 and HL7 fast healthcare interoperability resource specification (HL7 FHIR), and JavaScript object notation (JSON) files. Syapse leverages the health system's existing source system feeds wherever possible to utilize active feeds that are relied on for clinical care purposes. Quality control measures include collaboration with clinical data analysts, informaticists, and EMR analysts employed by the health systems, who are familiar with the specific context of the source system, to validate the output of the structured data represented in the Syapse database appropriately matches the respective source system.

For cancer cases identified at each health system, Syapse obtains structured somatic molecular results through its direct integration with commercially available molecular somatic testing laboratories (eg Foundation Medicine, Tempus, Neogenomics, Caris CellNetix, Paradigm, among others). Molecular laboratories structure the molecular results according to Syapse's data schema standard for interoperability. Syapse ingests structured

molecular results as reported by each laboratory without any modification. Quality control measures include retention of the original and any addendum PDF reports for each patient. Syapse structured data was a part of an abstract describing normalization of structured outcomes presented at 2018 ASCO (Tittel, et al, 2018)

Additionally, demographic, clinical characteristics, testing, treatment, and outcomes data is abstracted from the participating health system's EHR by certified tumor registrars (CTRs) for cancer cases identified via Syapse's interop data feeds. Guidance for abstraction is based on the Facility Oncology Registry Data Standards, better known as FORDS, which was developed in 2003 by the Commission on Cancer (CoC) of the American College of Surgeons (ACS) for its CoC accredited programs. FORDS is considered a set of entities that have been well established and proven through years of collection and validation. The traditional way in which a CTR codes a core set of data has been redefined within the scope of Syapse. A separate guidance has been created to capture both Syapse core data elements and all other data elements needed specifically to support the protocols used. The Syapse redefining of data standards supersedes FORDS/STORE manual when appropriate to understand RWD in the context of insights and outcomes to meet research and regulatory purposes. During abstraction, the data is manually entered into defined fields controlled for source documentation and vocabulary. Quality controls include CTR training and testing, QC of 100% of cases, and use of inter-rater agreement applied at appropriate intervals during the abstraction process to pre-agreed data points.

9.8.2. Review and Verification of Data Quality

All cases will be re-reviewed at least once either from the CTR that completed the case or a review from another CTR ensuring high quality and accuracy from an Inter-Rater QC process. The abstraction tool itself also has various quality checks built in that would detect potential data entry errors at the time of abstraction, rather than allowing errors to perpetuate. After the dataset is curated by the CTRs, the data will be analyzed by a Syapse epidemiologist and the CTRs consulted to re-review sections of the data for overall data consistency and high quality.

All data abstracted from the Syapse Learning Health Network undergo an independent quality control review, with evaluation for consistency, completeness, and outlier values. This review is conducted by the Syapse Epidemiology and Syapse Clinical Analytics teams. Data queries generated as part of quality review are documented and resolved, with documentation of queries and resolution maintained in a complete query log.

Data housed in the electronic data capture tool will then be exported for data cleaning and preparation, creation of derived values, and preparation of analysis datasets using R statistical software. Data will then undergo initial statistical review, including examination of all fields for outlier values, and evaluation for internal consistency of study data. Values that are flagged as potentially anomalous during statistical review will be queried and resolved before analysis datasets are finalized. All study data also undergoes scientific review of study results prior to data lock.

9.9. Limitations of the Research Methods

Limitations of the Analysis

This study is subject to limitations of accuracy and completeness of the Syapse data. The data is derived from routinely collected clinical data; therefore data is subject to missing information for variables and errors in the source EMR data. Due to potential missing data in the EMR, certain variables may not be obtainable for the entire Syapse population, which will limit stratification and subgroup analyses. In addition, biomarker testing and result availability is variable across participating Syapse health systems.

Selection Bias

Since the database is limited to participating sites of care, if the populations that are treated at these centers are disproportionately represented relative to the total population in the United States, the results from the descriptive analyses may be biased. If, for example, more severe patients are referred to the larger specialty hospitals/academic centers, their treatment regimens, survival, and the distribution of tumor types may be different.

Measurement Error(s)/Misclassification(s)

Although it is expected that the quality of the data should be generally high, depending on missing variables and potential errors in abstraction of unstructured data, there is a possibility of challenges to the internal validity of the data. Syapse abstracted database will be used to support this study. We expect minimal measurement error and/or misclassification due to Syapse data collection process as Syapse has direct access to longitudinal patient records in the EMR detailing the full cancer progression. Furthermore, these data are collected by trained, experienced CTRs. Misclassification may result if the source EMR data has missing data where not all events or treatments are recorded.

External Validity of Study Design

The generalizability of this study will depend on the representativeness of the Syapse participating health systems compared to the US population. Syapse is deployed in urban hospitals in 25 states. Eligible cases are identified and slated for abstractions from those geographic regions.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. 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.

Patient personal data will be stored at Syapse in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Syapse 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, Syapse 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, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Syapse research agreement and applicable privacy laws.

Syapse is a third-party business associate to each health system utilizing the platform and operates under HIPAA quality improvement exception. Syapse platform is utilized by health systems partners for population-based activities relating to improving health, reducing health care costs, protocol development, case management, and care coordination. Syapse hosts health system data in compliance with HIPAA Privacy Rule as well as contractual obligations related to protecting the privacy and security of the PHI. Syapse has all policies and necessary protections in place for the protection of human subjects, as outlined in Data Use/Sharing Agreements between Syapse and its health system partners

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

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

No identifying information is released about any individual unless required by law. Under no other circumstances would any identifying information be made available to outside parties or be used for other purposes by the study team. To conduct this study, Syapse will submit this protocol for exemption to a commercial Institutional Review Board (IRB) prior to study start.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appears in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be completed by Pfizer and is estimated to be September 2020.

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 Syapse 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.

13. REFERENCES

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.